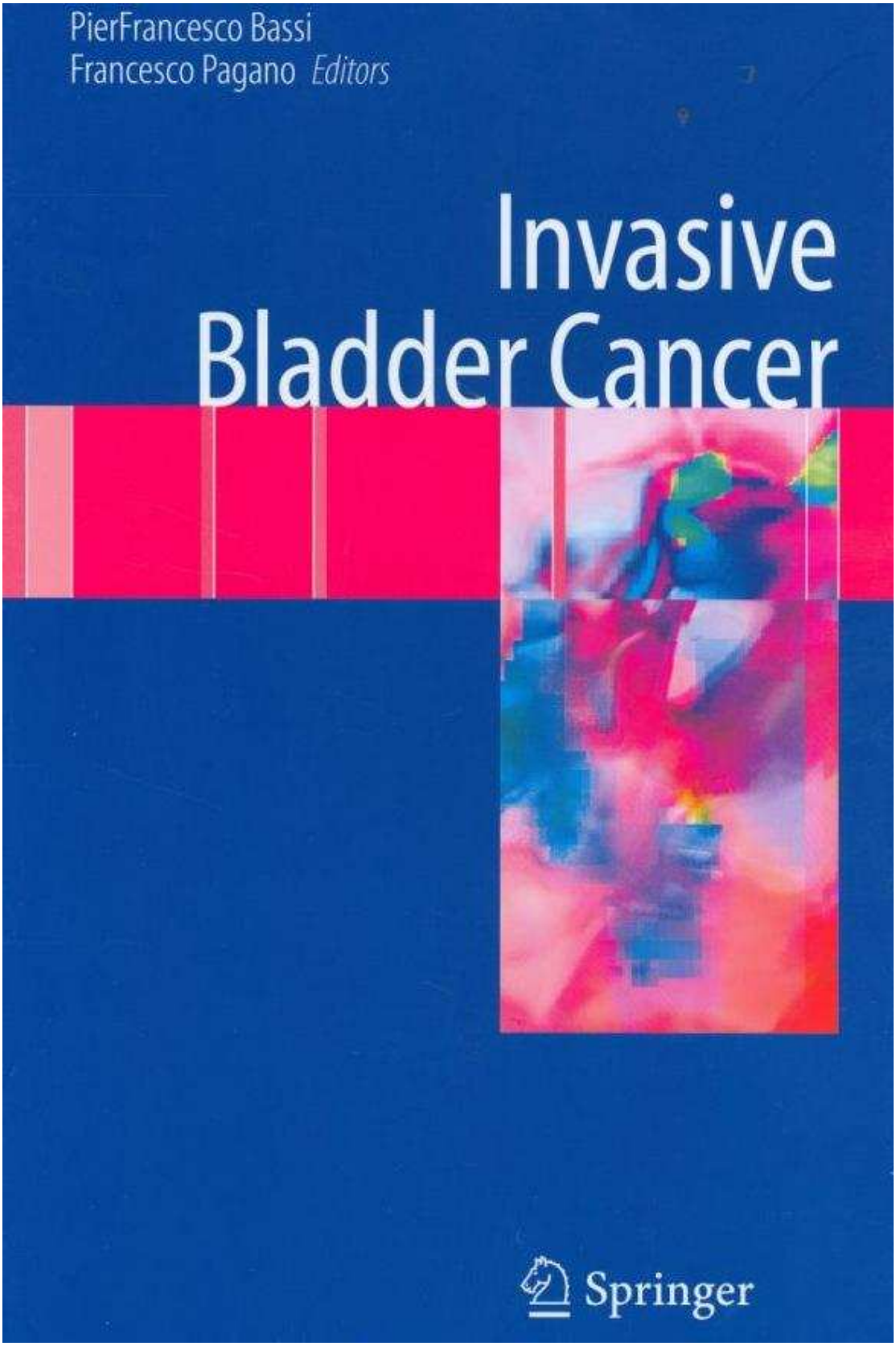

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Invasive Bladder Cancer

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Editors

Invasive Bladder Cancer

Springer

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British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Control Number: 2006931003

ISBN-10: 1-84628-376-0 e-ISBN-10: 1-84628-377-9
ISBN-13: 978-1-84628-376-5 e-ISBN-13: 978-1-84628-377-2

Printed on acid-free paper.

9 8 7 6 5 4 3 2 1

Springer Science+Business Media
springer.com

Preface

Advanced bladder cancer has always been a devastating disease: most patients still die of their disease and in the process suffer compromise in the quality of their existence.

Nevertheless, tremendous advances continue to be made in the understanding of the nature of this disease and in developing newer treatment approaches that may be more effective than was possible previously. Many of therapeutical measures can now be used with less morbidity to prolong survival, even obtain cure, while maintaining a good quality of existence.

Leading experts in bladder cancer have requested to critically evaluate the state of the art on this field.

PierFrancesco Bassi
Francesco Pagano
November 2006

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Chapter 1

Epidemiology and prevention of bladder cancer

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Introduction

In most populations, the occurrence of bladder cancer is 3–4 times more frequent in men than in women.[1] This reflects the more frequent exposure of men to tobacco-smoking and to occupations that imply contact with some chemicals, like aromatic amines, which are the two major recognized risk factors for bladder cancer.[2–5]

Transitional cell carcinoma (TCC) is by far the most frequent histotype, although the distribution of histotypes varies in different populations. In American whites, 93% of all bladder cancers were TCC, while this figure was 85% in American blacks and even lower in Egypt.[5] Tobacco and occupation, however, are also risk factors for non-TCC of the bladder.[6,7]

Most bladder carcinogens exert their action by direct contact with the bladder epithelium. Inhaled or ingested compounds, which are either directly carcinogenic or which can be transformed by the body in carcinogenic byproducts, are excreted via the urine, and in this way they reach the urinary bladder.[8] There is also evidence that chronic inflammation, caused either by infections or stones, has a role in the promotion of bladder cancer.[9]

Descriptive epidemiology

The interpretation of incidence rates of bladder cancer is difficult, since it is not easy to distinguish between papillomas and malignant tumour, and thus the rates recorded in various cancer registries may partly reflect different diagnostic criteria.[10,11] This caution notwithstanding, the highest incidence rates are recorded in Europe and North America, although Northern Africa and Western Asia are also high-risk areas.[1]

In Europe, the highest incidence rates for men were recorded in northern Italy, Spain, and Geneva, Switzerland, with rates of more than 30/100,000 men, while rates were intermediate in the UK, Germany and France, and low in several eastern and northern European countries, as well as in other Swiss registration areas.[12] The highest mortality rates in men were around 9/100,000 men in Denmark, Italy, Malta and Spain, while low rates (around 4/100,000 men) were recorded in Sweden, Finland and Iceland. In women, the highest mortality rates were between 2 and 3/100,000 women and were recorded in Denmark and the UK.[12]

As far as time trends are concerned, incidence rates tended to increase in both sexes in the United States between 1969 and 1990, whereas mortality tended to decline, particularly in men.[4] In Europe, mortality rates increased in southern and eastern Europe between the mid-1950s and late 1980s, while a decline has been observed in several northern European countries over the last two decades. This pattern was similar to that of lung cancer, and underlines the importance of tobacco-smoking as an etiologic factor.[13]

Risk factors

Cigarette-smoking and occupational exposure to aromatic amines are known risk factors for bladder cancer. Several other factors (Table 1) may influence bladder carcinogenesis.[2–5] Each factor is briefly discussed below.

Tobacco

The association between cigarette-smoking and bladder cancer has been known for several decades, and has been consistently observed in a number of case-control and cohort studies. The risk of bladder cancer in smokers is 2–4 times that of non-smokers, and increases with the number of cigarettes and duration of smoking.[14–17] In heavy smokers, the risk increased up to five

Table 1: Overview of potential risk and protective factors for bladder cancer

Risk/protective factor	Effect	Carcinogen or mechanism of carcinogenesis	Possible evaluation
Cigarette-smoking	Direct	Exposure to aromatic amines and other carcinogens (tobacco hydrocarbons, tar)	Real
Occupation 1 Aromatic amine manufacture 2 Dyestuff manufacture 3 Rubber industry 4 Painting 5 Leather industry 6 Aluminium industry 7 Truck drivers and other drivers	Direct	Exposure to aromatic amines and other chemical carcinogens. Diesel exhausts or reduced bladder voiding (drivers)	Real (for exposure to aromatic amines)
Fluid intake	Inverse	Dilution of carcinogens, increase of voiding frequency	Possible
Carcinogens in drinking water (chlorination byproducts, arsenic)	Direct	Direct carcinogenic action	Possible
Coffee	Direct	Carcinogenic metabolites in urine	Controversial
Artificial sweeteners	Direct	Undefined in humans	Inadequate
Diet Vegetables and fruit	Inverse	Antioxydant or other properties of vitamins, minerals or other compounds	Possible
Urinary tract diseases • *Schistosoma haematobium* • Cistitis • Other urinary tract infection • Kidney or ureter stones	Direct	Chronic inflammation/altered metabolism	Real for *Schistosoma haematobium*, possible for other
Drugs • Phenacetin/acetaminophen • Cyclophosphamide • Phenobarbital	Direct Direct Inverse		Possible
Family history of bladder cancer	Direct	Genetic predisposition	Possible
Genetic polymorphism of genes involved in detoxification of aromatic amines (NAT1/NAT2, GSTM1)	Direct when NAT2 deleted, inverse when GSTM1 deleted	Inefficient detoxification of aromatic amines with consequent increased production of carcinogenic metabolites	Possible

times, as compared to those who have never smoked. The risk is higher for smokers of unfiltered, high-tar or black tobacco cigarettes than for filtered, low-tar or blond-tobacco.[2,15,18,19] Former smokers have a 30–60% lower risk of bladder cancer than current ones, but published studies have not been totally consistent with respect to the relation of risk with time since quitting.[4,20] It is not clear whether exposure to tobacco other than cigarettes increases the risk of bladder cancer. Several studies reported an increased risk for pipe-smokers, while the relation with cigars, snuff and chewing tobacco is still undecided.[4]

It is not clear which among the several carcinogens contained in cigarettes are responsible for this association. In addition to aromatic amines, tar or selected tobacco hydrocarbons can also be carcinogenic for the bladder.[3,21]

Occupation

Several occupations have been associated with an increased risk of bladder cancer. Excesses of bladder cancer have been reported among workers employed in aromatic amine manufacture, dyestuff manufacture and its use, rubber manufacture, painting, the aluminium industry, the leather industry, and truck drivers and other drivers.[2,4,5,22–24] A number of other occupations have also been associated with increased risk of bladder cancer, although the evidence is less convincing.[4]

Exposure to some aromatic amines, and particularly 2-naphthylamine and benzidine, is the major determinant of the excesses of bladder cancer observed in workers in several types of industries, like dyestuff or rubber manufacture.[25]

In a study of 664 dyestuff factory workers in northern Italy, who were exposed to 2-naphtylamine, benzidine and other aromatic amines, 41 deaths from bladder carcinoma were registered, i.e. 46 times the expected number. The large number of cases in the cohort allowed the evaluation of the role of several time factors, according to different models of carcinogenesis.[26,27] According to these models, workers directly involved in the manufacture of aromatic amines had a higher risk than those with an intermittent exposure. Moreover, the risk was highest for workers exposed at younger ages, also after controlling for duration. This suggests that aromatic amines may act on one of the early stages of the carcinogenic process.[28,29] Thus, workers exposed to aromatic amines should also be monitored several years after cessation of exposure. However, the relative

risk, but not the absolute one, tended to decrease after exposure ceased, suggesting that aromatic amines may also have a late stage effect in the process of carcinogenesis.[27]

The presence of aromatic amines in hair-dyes may explain the increased risk found in hairdressers in some studies. This raised concern for personal use of hair-dyes, although the studies that investigated the issue failed to find an increase in risk of bladder cancer for personal use of hair-dyes.[30–32]

Fluid intake and water source

A higher amount of fluid intake may dilute metabolites in the urine and increase the frequency of voiding, thus reducing contact of carcinogens with the bladder epithelium. Consistent with this hypothesis, data from the Health Professionals Follow-up Study found that men in the highest fluid intake category had half the risk of bladder cancer as compared to those in the lowest category, and the protection was observed for water as well as for other fluid intake.[33] Epidemiologic results, however, are not totally consistent, perhaps also because of the difficulties in measuring total fluid intake, and the issue is still unresolved.[34–36,37]

The *source* of the drinking water may also be important. Some studies found that drinking tapwater containing chlorination byproducts following disinfection of drinking water with chlorine may increase the risk of bladder cancer.[38,39] Also, arsenic in drinking water has been associated with increased risk of bladder cancer in Taiwan and Argentina.[40,41]

Coffee

Caffeine and its metabolites, as well as several other compounds contained in coffee, are execreted in the urine, and thus the role of coffee in bladder carcinogenesis is biologically plausible. There is no clear evidence of a carcinogenic effect of coffee or caffeine in experimental animals.[42] In humans, a case-control study of bladder cancer published in 1971 reported an association with coffee consumption.[43] Since then, several studies (more than 30) have investigated the association between coffee and bladder cancer, and they have yielded remarkably consistent results. They generally reported a higher risk in coffee-drinkers as compared to non-drinkers, but no trend with dose or duration. Moreover, the risk was often reported in only one sex, with no clear association in the other one.[42,44] The largest study published to date is a case-control study conducted

in 10 geographic areas of the United States on 2,982 incident cases of bladder cancer and 5,782 population controls.[45] It reported risks of 1.6 and 1.2 respectively in male and female coffee drinkers with respect to non-drinkers, and the combined estimate was 1.4. Among drinkers, men in the highest consumption category had the highest odds ratio, but no evidence of any dose-response relation was noted for women. Thus, the results from epidemiologic studies exclude a strong association between coffee and bladder cancer risk, although a modest one cannot be ruled out. The question of whether this association is causal or due to residual confounding by smoking or an association between coffee-drinking and a yet unidentified risk factor is still unresolved. The epidemiological evidence on decaffeinated coffee is sparse and inadequate for evaluation.[44]

Artificial sweeteners

In 1977, a case-control study on 408 cases reported a 60% increase in risk of bladder cancer in men (but not women) who used artificial sweeteners.[46] Several other studies have since investigated the issue, and in general, failed to confirm the association. The largest and more informative study was a case-control study conducted in 10 areas of the United States on more than 3,000 cases and over 5,700 population controls.[47] In that study, the odds ratio for use of artificial sweeteners was 1.02 (95% CI, 0.92–1.11). No association was found in men (OR=0.99) or women (OR=1.07), nor according to type nor form of artificial sweeteners, and there was no dose-response relation. In general, the overall epidemiologic evidence does not suggest that there is an association between saccharin and other artificial sweeteners and bladder cancer, and the International Agency for Research on Cancer has recently changed the evaluation of saccharin from group 2B (possibly carcinogenic to humans) to group 3 (not classifiable as to its carcinogenicity to humans).[48]

Diet

Many compounds contained in food and their metabolites are execreted through the urinary tract, and thus a role of dietary factors in bladder carcinogenesis is plausible. Though there are some studies that have investigated the relation between diet and bladder cancer risk, epidemiological data from analytical studies are few, and most studies had a limited dietary questionnaire that did not allow assessment of total energy, macro- and micronutrient intake.[34,35,49–63] Most studies

that investigated fruit and vegetable intake reported a lower risk of bladder cancer in subjects with high consumption, although the Health Professional Follow-up Study, based on 252 cases of bladder cancer, found an inverse association between bladder cancer risk and intake of cruciferous vegetables, but no relation with other vegetables or fruit.[62,63] Thus, the possible protective effect of vegetables and fruit on bladder cancer is still controversial, and the evidence on other foods is even more limited. Some (but not all) studies suggested a possible direct association with fat intake, and some studies found an inverse one with vitamin A and carotenoids intake.[49,53,54,56–9] In general, epidemiological data collected to date are inadequate to allow any definite insight on the role of diet and specific dietary factors in bladder carcinogenesis.[63]

Urinary tract diseases

Several studies have found a higher prevalence of bladder cancer in areas with a high prevalence of infection with *Schistosoma haematobium* than in those where infection is less frequent, and the percentage of squamous cell carcinoma is higher in endemic areas.[64–7] Also, the few analytical studies conducted in endemic areas consistently reported an association between bladder cancer and schistosomiasis.[64,68] The relation has been explained through chronic irritation of the urothelium, or altered metabolism with consequent high urinary levels of carcinogenic metabolites.[2,64]

Other urinary tract infections and urinary tract stones may cause chronic irritation of the bladder epithelium, and may thus increase bladder cancer risk.[66,69–73] Although the association with cistitis and other urinary tract infections has been observed in several case-control studies, it is difficult to rule out recall bias as a possible explanation. In general, most studies are consistent with an approximately doubled risk in patients with (recurrent) urinary tract infections, and with a possible role of these on one of the later stages of the process of carcinogenesis.[5]

In a cohort of 61,114 Swedish patients who were hospitalized for kidney or ureter stones, and followed for up to 18 years by means of record-linkage, there were 46 cases of renal pelvis or ureter cancer and 319 cases of bladder cancer. The corresponding standardized incidence ratios were 2.5 and 1.4 respectively.[74] Thus, there is some evidence that kidney and urinary stones may moderately increase the risk of bladder cancer in humans, as they do in rodents.[5]

Drugs

Heavy consumption of phenacetin-containing analgesics has been linked to increased risk of bladder cancer, while results for acetaminophen are more reassuring.[4,75] Some studies found that patients treated with cyclophosphamide for non-Hodgkin's lymphoma had an increased risk of developing bladder cancer.[4] In a few studies, treatment with phenobarbital was inversely associated with bladder cancer risk, particularly among smokers.[76]

Family history of bladder cancer

First-degree relatives of bladder cancer patients have an approximately double risk of bladder cancer as compared to subjects with no family history of the disease.[77] The increase in risk appears bigger when the index case is young.[78,79]

Biomarker of cancer susceptibility

To exert their carcinogenic effect, aromatic amines, like most chemical carcinogens, require metabolic activation to reactive species that bind to DNA. The activation of aromatic amines is performed by some enzymes, whose polymorphic distribution in the population may give rise to a genetically determined different individual susceptibility. In particular, N-acetyltransferase (NAT) is an enzyme whose activity may result in detoxification of aromatic amines. In humans it is coded by two genes, NAT1 and NAT2.[80] The NAT2 enzyme is polymorphic, and in about 50% of Caucasians, the so-called 'slow acetylators', the activity of this enzyme is reduced. In a case-control study of bladder cancer, a large proportion of slow acetylators was observed among cases of bladder cancer occupationally exposed to aromatic amines, but not in smoking-related bladder cancer patients.[81] Other studies reported an excess of slow acetylators in bladder cancer patients with a history of smoking or occupational exposure to aromatic amines.[82,83]

The glutathione S-transferase M1 (GSTM1) is an enzyme involved in the detoxification of a number of carcinogens. The genetically determined deletion of two copies of the gene coding for GSTM1 has been reported in about 50% of caucasians. Individuals with no functional allele of the GSTM1 gene have been shown to be at higher risk of bladder cancer in several studies.[5,84–6]

Implications for prevention

There are several factors that are known to or suspected to influence bladder cancer carcinogenesis. The proportion of bladder cancer attributable to each factor (attributable risk) depends not only on the relative risk associated to a factor, but also on the frequency of exposure, and thus varies according to geographical area and calendar period.

Cigarette-smoking is the major identified cause of bladder cancer. The proportion of cases attributable to tobacco was about 80% in men and 30% in women in a study in the UK, about 50% in men and 30% in women in a study from the United States, around 70% in men and 30% in women in a study from Italy, and more than 70% in men (but very low in women) in Alexandria, Egypt.[15,87–9] Thus, reducing cigarette-smoking is an imperative for prevention.

Occupational exposure to aromatic amines and to other chemicals has been estimated to cause 5–10% of bladder cancers in the UK and North America.[87] In several developed countries, the control of occupational exposures to bladder carcinogens has probably led to a substantial decrease of the proportion of cases of bladder cancer due to occupational factors, and this reduction may become even more evident over the next decades, when the effects of exposures that happened decades ago will affect incidence rates to a smaller degree.[87,88] Less information is available for some other heavily industrialized areas of the world, where measures to reduce occupational hazard may still not be adequate.[5]

Reduction of infection by *Schistosoma haematobium* is an important preventive measure in endemic areas, such as Egypt and Tanzania.[89] It is difficult to quantify the potential for prevention of reducing urinary tract infections in other populations.

Selected aspects of diet may influence bladder carcinogenesis but – apart from a possibly favourable effect of vegetable consumption – available data are still inadequate to provide indications for prevention.

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Chapter 2

Early diagnosis and screening

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Introduction

Carcinoma of the bladder continues to be a common and serious healthcare problem. In 2001, 56,500 new cases of bladder cancer were diagnosed in the United States, and 12,600 people died of this disease.[1] Bladder cancer is the fourth most common solid tumour in men and the eighth most common in women, ranking seventh and tenth, respectively, among causes of cancer death.[1] The term 'bladder cancer' encompasses all primary malignancies of the bladder, but transitional cell carcinoma (TCC) is by far the most prevalent and well studied, and for these reasons is the focus of this chapter.

While TCC expresses a broad range of histologies and behaviours, most lesions fall into one of two groups at diagnosis.[2,3] The first is comprised of superficial, low-grade cancers that recur frequently but rarely invade beyond the lamina propria and almost never metastasize (Figure 1). The second consists of high-grade cancers that also recur but have usually invaded the muscularis propria, and may have already metastasized prior to diagnosis. Recurrences in patients with low-grade, stage Ta (mucosally confined) or T1 (confined to the lamina propria) tumours usually possess the histological and behavioural characteristics of the index lesion.[4] However, high-grade lesions with muscularis propria invasion (stage T2a or greater) are occasionally found late in the course of previously low-grade disease. Poorly differentiated superficial tumours also recur with lesions similar in histologic appearance to the primary cancer, but more rapidly, and with deeper infiltration, than their low-grade counterparts.[5]

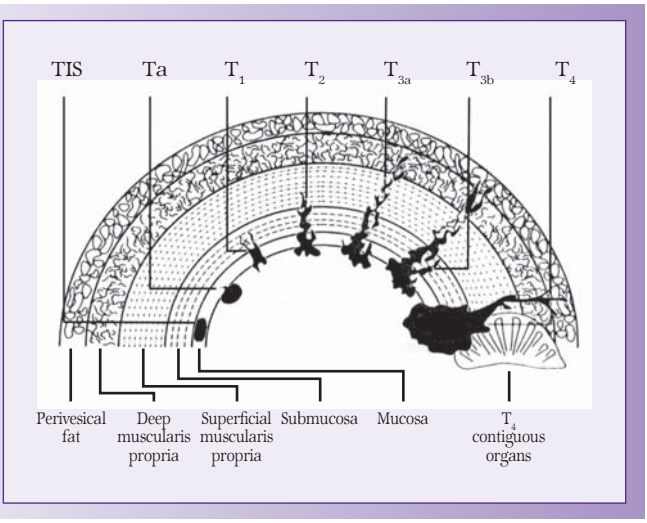


Figure 1: Tumour-nodes-metastases staging (1997 revision) of urothelial carcinoma of urinary bladder (from Bostwick DG and Lopez-Beltran A (1999) *Bladder Biopsy Interpretation*. United Pathologists Press: New York).

Two aspects of TCC's biology are important in understanding its suitability for early detection. First, very few TCCs that have not invaded the muscularis propria are ever associated with metastases.[6] This is confirmed by the observation that even frequently recurring, poorly differentiated stage T1 disease can almost always be cured with local therapies. Once penetration of the muscularis propria has occurred, however, the likelihood of metastasis is substantially increased (Figure 2; Table 1).[2,7] As deaths due to bladder cancer are caused by metastases, it is the muscle-invasive lesion and its subsequent metastatic spread that represents the major threat to survival.[2,7] Thus, a window of time exists in which tumours destined to become muscle-invading can be detected before they actually are, so that effective therapies can be administered before metastases occur. Second, almost 90% of muscle-invading bladder cancers present as index lesions; and do not arise from the pool of patients with recurrent, superficial tumours under surveillance.[8,9]

Efforts to reduce mortality from bladder cancer must focus on three areas: prevention, development of more effective therapies for muscle-invasive and metastatic disease, and early detection of potentially invasive lesions while they are still superficial and amenable to less morbid, but still effective, treatments. This last point represents the rationale for screening for bladder cancer.

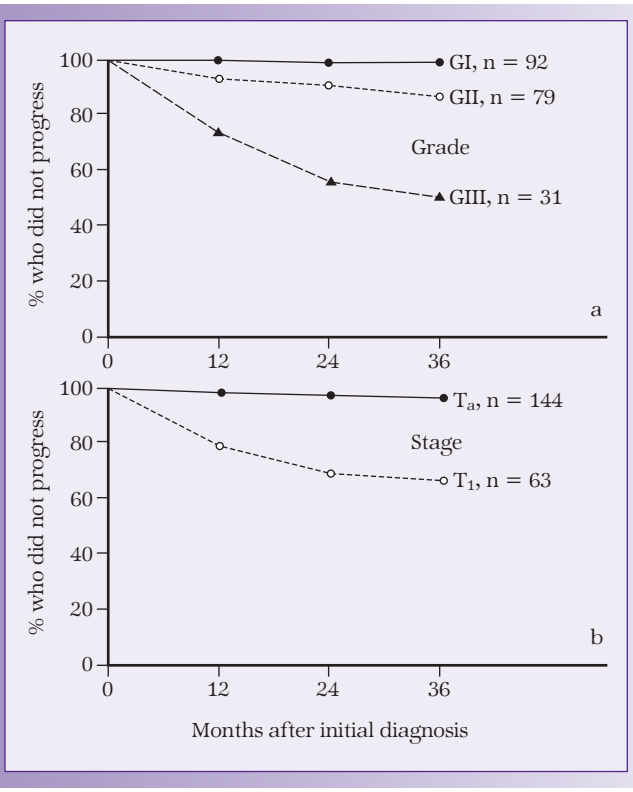


Figure 2: a: differences in interval free of progression between patients with grades I and II, and II and III tumour are statistically significant ($p<0.05$ and <0.001 respectively). b: differences in interval free of progression between patients with stages Ta and T1 disease is statistically significant ($p<0.001$).

Table 1: Progression of the disease.

Grade	*No. Pts*	*% Progression*
O	5	0
I	92	2
II	79	11
III	31	45
Stage	*No. Pts*	*% Progression*
Ta	144	4
T1	63	30
Nontumor abnormalities	*No. Pts*	*% Progression*
None, hyperplastic or mild dysplasia	11/146	8
Moderate to severe dysplasia	5/15	33
Tumor size (cm)	*No. Pts*	*% Progression*
<5	17/181	9
>5	7/20	35

Candidates for screening

Major risk factors for developing bladder cancer are age, gender, race and environmental exposures; very few cases are directly inherited.[10] TCC is not prevalent in people below 50 years of age with the median age of diagnosis being 69 years old in males and 71 years old in females.[11] Not surprisingly, incidence and mortality rise with increasing age. Bladder cancer occurs almost three times more frequently in males than females, but mortality is 35–50% higher in women than men. In the United States, Caucasians are twice as likely as African-Americans to be diagnosed with bladder cancer, but mortality in African-Americans is almost double that of Caucasians.[12] These differences between age, gender and race may be caused by a variety of factors: diagnostic delay due to psychosocial issues, healthcare access, provider bias, and/or co-morbidity issues, or the choices and intensities of treatments offered or accepted, or differences in the biological behaviours of TCCs in different populations. Indeed a combination of any or all of these may play a role.

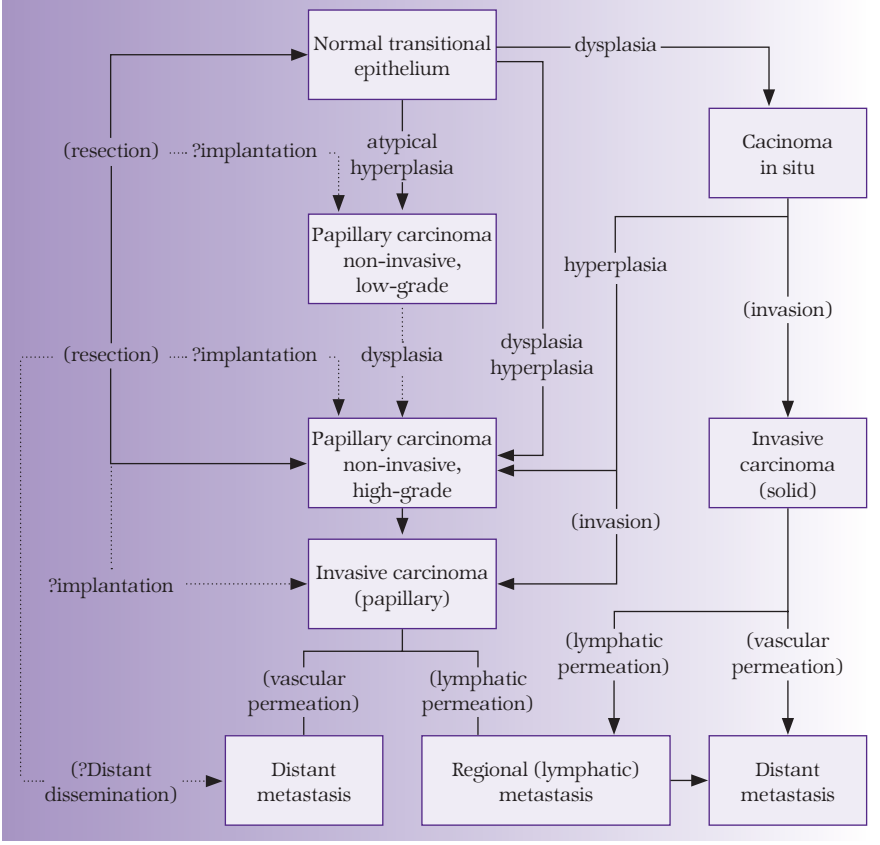
Bladder cancer has been associated with multiple environmental risk factors. The most significant, in the general population, is cigarette-smoking, with active smokers having four times an increase in incidence over people who have never smoked tobacco.[13] Risk correlates with the number of cigarettes smoked, duration of smoking, and degree of inhalation.[14] In the United States and Western Europe, approximately 70–75% of men over the age of 50 have significant smoking histories.[15] For those who have given up smoking, the risk decreases slowly over 10 to 20 years of abstinence.[2] Thus, former smokers are still at risk and should be included in bladder cancer screening programmes. Data on second-hand cigarette smoke exposure (so-called 'passive smoking') are less certain, although a recent report from Israel would indicate that such individuals are also at increased risk.[16]

Aniline dyes and coal combustion byproducts were associated with TCC in the past, and aromatic amines and inorganic chemicals in the workplace are currently a major source of exposure-related tumours. While it has been estimated that exposure to workplace chemicals accounts for 20% of bladder cancer in Caucasian males, this is probably a significant overestimation of modern circumstances.[6] Chronic cystitis associated with foreign bodies, pelvic radiation therapy and cyclophosphamide exposure

have also been linked to an increased risk of developing bladder cancer. Alternatively, with rare exception, the risk of developing bladder cancer has not been directly associated with inheritance.[10,17–18]

It is critical to remember that there are no data indicating that smokers and exposed workers preferentially develop one type of TCC over another (indolent vs. aggressive) when compared to the distribution in the general population.[19] This implies that the development of both low- and high-grade TCC probably shares a common pathway (Figure 3). Early detection

Figure 3: Multiple pathways in bladder development (modified from Droller MJ (1998) Bladder Cancer: State-of-the-Art Care. *Ca Cancer J Clin* **48(5)**: 274).



programmes should screen for both types of TCC, since the risks for each are similar.[2] Although the primary goal of screening is to detect high-grade cancers at pre-invasive stages, programmes that focus exclusively on these tumours may erode confidence in the entire screening effort as subjects at high risk become diagnoed with low-grade superficial TCCs that screening has missed.

Screening for cancer

Screening is the application of a test to an asymptomatic target population in which a positive result correlates with disease. The measure itself is not diagnostic, and the presence of disease must be confirmed by further diagnostic tests. The goal of screening is to identify disease early in its course, and offer therapy when it can be more effective and associated with lower morbidity.[6] The World Health Organization has established criteria for widespread application of a screening programme.[6] First, the disease must be a significant health risk in the target population. Second, the screening test must be safe, straightforward to apply and interpret, and meet minimum standards for sensitivity, specificity and predictive values. Third, large-scale application of the measure must be logistically and economically feasible. Fourth, effective therapeutic interventions should be readily available to the screened population. It is crucial to remember, however, that a successful screening protocol demonstrates prolonged survival and decreased disease-related mortality in the screened population compared to an unscreened population matched for demographics and co-morbidities, not simply a shift to earlier stages at diagnosis.

The reliability of a screening protocol depends on the validity of the measure and the characteristics of the target population. Screening tests are assessed on the basis of four descriptors. 'Sensitivity' and 'specificity' compare the ability of the screening test to assign a positive or negative result relative to the actual presence or absence of the disease (Table 2).

The criteria for positive and negative tests can be adjusted to increase or decrease these values. A test can be made more sensitive by decreasing the threshold for positivity, for example using three red blood cells instead of five per high-power field to define microhaematuria. This changes the test's specificity in the opposite direction, however. Because a bladder cancer diagnosis only can be made with cystoscopy and (usually) biopsy

Table 2: Progression of the disease.

Sensitivity =	n with a disease & a positive test / n with a disease & either a positive or negative test	=	true positives / true positives & false negatives
Specificity =	n without a disease & a negative test / n without a disease & either a negative or positive test	=	true negatives / true negatives & false negatives
Positive predictive value =	n with a positive test who have the disease / n with a positive test whether they have the disease or not	=	true positives / true positives & false positives
Lead time	= the interval from detection because of screening to the time at which diagnosis would have been made without that screening (i.e. when symptoms or signs would have provoked evaluation)		
Length bias	= the tendency of a screening test to preferentially identify indolent disease with a long preclinical sampling phase		

(with or without cytology), actual true and false negative rates cannot be ascertained unless all subjects undergo these procedures. Thus, sensitivity and specificity can only been measured in subjects who are cystoscoped regardless of the 'screening' test's results. This limits assessments of these tests to patients with haematuria or prior histories of TCC, in whom cystoscopy is mandatory.

The 'positive' and 'negative' predictive values describe the ability of the screening test to predict the correct diagnostic result (Table 1). These values are also dependent on the threshold for positivity of the screening measure. While a high positive predictive value (i.e. the absence of false positives) connotes an accurate screening modality, it says little about the test's sensitivity, since false negative tests are not considered in the calculation. To optimize the validity of the screening protocol, the target population should have a high prevalence of the disease. By selecting a population with multiple risk factors, such as males over the age of 50 with smoking histories, the likelihood that screening will have many false positives and false negatives are reduced.

Arguments against screening emphasize the consequences of unnecessary diagnosis and treatment. Some diseases, like prostate cancer, are often found incidentally at autopsy, but are not related to the cause of

death. Patients do not benefit from aggressive diagnosis or treatment of indolent disease. Bladder cancer, however, is almost never an incidental post-mortem finding because it causes symptoms, leading to evaluation and diagnosis, prior to death.[2] This implies that bladder cancer has a brief presymptomatic latency period, and diagnosis before symptoms occur is not a disservice to patients who would have eventually presented at a later time, and possibly later stage, with bladder cancer symptoms.

Potential screening methods

Painless haematuria is the most common presenting sign or symptom of bladder cancer.[20] Unfortunately, neither the degree nor the frequency of bleeding (i.e. persistent vs. intermittent) correlates with the seriousness of its underlying cause. For these reasons, if a screening protocol to identify haematuria is developed, it should contain a sensitive test that is applied repeatedly. Once a positive test is identified, subjects should undergo a thorough evaluation. This includes upper tract imaging, cystoscopy and lavage cytology.[21] The most commonly used methods to detect haematuria are the chemical reagent strip for haemoglobin and spun sediment microscopy on voided urine.

Other assays under investigation focus on detecting in urine or exfoliated cells the genetic 'signature' of TCC, specific antigens on tumour cell surfaces, and molecules believed to be important in carcinogenesis. Most of the methods discussed here have been tested primarily in populations with bladder cancer histories who undergo cystoscopic examination as part of routine surveillance, rather than general populations at risk for bladder cancer. Current methods focus on clinical or molecular markers associated with active disease, but it is likely that future screening methods will assess genetic predispositions and premalignant alterations long before overt tumours develop (Tables 3 and 4).

Currently, the simplest screening tool is the reagent strip test for haemoglobin in voided urine. Studies comparing the reagent strip to microscopy have reported excellent sensitivity, specificity and predictive values for the strips in detecting microhaematuria.[22] More than three red blood cells per high-power field of centrifuged urinary sediment is the threshold for positivity in these studies. Because the intermittent nature of haematuria, even in the presence of serious disease, can result in negative tests, repetitive testing is needed to maximize the strip's sensitivity in detecting bladder

Table 3: Sensitivity.

	% Sensitivity (No.)								
	Overall*	Grade			Stage			Primary	Recurrent*
		1	2	3	pTis	pTa	pT1-pT3b		
Cytology	44 (54)	22 (9)	38 (24)	83 (12)	73 (11)	29 (24)	67 (12)	59 (17)	38 (37)
95% CI	31,59	3,60	19,59	52,98	39,94	13,51	35,90	33,82	22,55
BTA stat	74 (57)	33 (9)	77 (26)	100 (13)	82 (11)	60 (25)	100 (14)	89 (19)	66 (38)
95% CI	60,84	7,70	56,91	75,100	48,98	39,79	77,100	67,99	49,80
NMP22 (optimised)	53 (57)	44 (9)	62 (26)	62 (13)	45 (11)	48 (25)	79 (14)	74 (14)	42 (38)
95% CI	39,66	14,79	41,80	32,86	17,77	28,69	49,95	49,91	26,59
FDP	52 (52)	25 (8)	46 (24)	92 (12)	60 (10)	45 (22)	69 (13)	44 (18)	56 (34)
95% CI	38,66	3,65	26,67	62,100	26,88	24,68	39,91	22,69	38,73
Telomerase	70 (57)	56 (9)	85 (26)	85 (13)	91 (11)	76 (25)	71 (14)	79 (19)	66 (38)
95% CI	57,82	21,86	65,96	55,98	59,100	55,91	42,92	54,94	49,80
Chemiluminescent hemaglobin (optimised)	67 (57)	67 (9)	62 (26)	85 (13)	82 (11)	56 (25)	86 (14)	89 (19)	55 (38)
95% CI	53,79	30,93	41,80	55,98	48,98	35,76	57,98	67,99	38,71
Hemaglobin dipstick	47 (57)	11 (9)	46 (26)	77 (13)	55 (11)	28 (25)	79 (14)	68 (19)	37 (38)
95% CI	53,79	0.3,48	27,67	46,67	23,83	12,49	49,95	43,87	22,54

* Includes tumors fulgurated without biopsy.

Table 4: Bladder cancer detection.

Test	Sensitivity	Specificity	PPV	Low-grade detecxtion	Cost/ complexity
Home hematura	+++	–	–	+	++++
Cytology	——	+	+	–	+++
Flow cytometry	±	+	+	–	++
Immunocytologic staining with antigens	+	+	+	+	+
Growth factors and receptors	?	+	–	+	+
Bard tumor antigen test	–	+	–	–	+
NMP–22	–	+	–	–	+
FDP test	–	+	–	+	+
Microsatellites	++	+	+	+	—

+, favors use of this test in screening (the more+'s, the more favorable); –, favors not using this test in screening. PPV, positive predictive value; NMP, Nuclear matrix Protein.

cancer. Repetitive haematuria testing, at least five times, with a positive screening occurring if any of the tests are positive, has a sensitivity that approaches 100% for TCC visible at cystoscopy.[23] Because of the test's ease-of-use, even elderly populations can perform it at home quite reliably, thus enhancing its utility as a screening tool despite the need for multiple testing events.

Cytologic examination of exfoliated cells in both voided urine and saline bladder lavage specimens has been used to 'screen' patients with known bladder cancer histories for recurrence for many years. Using the method pioneered by Papanicolaou, urothelial cells are graded on the basis of nuclear size and atypia, and cytoplasmic granularity (among other features), and assigned a reading of 'benign', 'indeterminate' or 'malignant'. At times, identification of a single markedly abnormal cell is sufficient to make a cytologic diagnosis of malignancy. Microscopic cytology is more sensitive in patients with high-grade tumours or carcinoma *in situ*.[14] The sensitivity of cytology performed on voided urine was reported at 44% for all grades and stages of TCC combined, but for Ta and T1 lesions this falls to 22% and 38% respectively.[24] Intraobserver variability is common, especially for low-grade lesions, where sensitivities of 20–50% have been reported.[25] Bladder lavage improves the sensitivity of cytology primarily because many more cells are present for examination, but requires an invasive procedure to obtain the specimen. Because of limited sensitivity, frequent indeterminate results, and the better quality of specimens obtained through invasive procedures, cystoscopy is usually done in addition to cytology to identify missed lesions. Cytology alone is inadequate to detect urothelial cancers at an early stage with a simple, objective, non-invasive test.

Flow cytometry and quantitative fluorescence-image analysis (QFIA) report the proportion of diploid, hyperdiploid and aneuploid cells in a population of exfoliated urinary mucosal cells. Increased proliferation and aneuploidy are characteristics of neoplasia, and assessment of cellular DNA content of the spun sediment of voided urine or saline bladder lavage by these methods can accurately diagnose tumour recurrence in patients with known bladder cancer.[26] Flow cytometry involves staining nuclear DNA with a specific fluorochrome that is measured as the cells flow through laser excitation. In image analysis systems, the cells are deposited on a microscope slide, the DNA stained with fluorochromes or absorbing dyes, and images of the nuclear DNA are captured using a computer-controlled camera or other light detector. The hyperdiploid fraction is defined as the proportion of cells

with greater than diploid DNA content, and values above 8% for the slit scan method, or 15% for the standard one, are indicative of hyperproliferation or aneuploidy.[27] Aneuploidy correlates with high-grade malignancy, while low-grade/stage tumours tend to be diploid. Sensitivity and specificity can be affected by the presence of white blood cells, which are indistinguishable from urothelial cells by DNA staining alone. It is important, then, to ensure that protocols are adjusted to identify inflammatory cells and exclude them from the final counts.[27] Hemstreet demonstrated the potential of QFIA as a screening tool for bladder cancer in benzidine-exposed workers who displayed genetic abnormalities in sloughed urothelial cells months to years prior to diagnosis.[28] Results can be confounded by doublets or clumps of cells, by contamination by nucleated nonurothelial cells, and low cell counts, but automated or trained observer methods of image analysis permit recognition of these types of contaminants.

Cytometry's chief advantage over cytology is that it is a non-subjective, highly reliable assessment of DNA content, but it cannot identify the truly rare abnormal cell. Theoretically, image analysis can combine the objectivity of flow cytometry with cytology's ability to detect the truly rare event. The sensitivity of cytometry for all grades of TCC is 78%, according to Murphy *et al.*, but rises to 80–90% for high-grade lesions.[29] When combined with urine cytology, the sensitivity rises to 95% for high-grade lesions. However, the rate of false positive tests and the lack of sensitivity for low-grade tumours make it difficult to justify the use of cytometry for screening asymptomatic populations at this time.

Marker antigens

Surface antigen expression on urothelial cells is altered in malignant states, and abnormal expression of many antigens appears to correlate with recurrence and/or progression of TCC. Currently, however, none alone are adequate for screening, due to limited sensitivity (Table 5). Expression of a blood group substance, Lewis X antigen, is up regulated in the malignant urothelial cell independent of tumour grade and stage. These characteristics are preferable for a screening assay because they detect the presence of an abnormality not otherwise seen, and will have fewer false negative results in patients with low-grade cancers.[30]

Several monoclonal antibodies have been developed against a variety of antigens expressed by TCCs. M344, T138 and DD23, for example, are

Table 5: Sensitivity, specificity, positive predictive value, and negative predictive value of various tests on voided urine for the detection of bladder cancer.

Test	*% mean sensitivity* (range)*	*% mean specificity (range)*	*% mean PPV (range)*	*% mean NPV (range)*
BTA test[22, 40, 55, 60]	40.5 (28–65)	87 (78–96)	55 (33–80)	73.3 (52–94)
BTA Stat[45, 61 62]	68 (66–72)	33–95†	20‡	95‡
BTA TRAK[25]	72	73	NA	NA
NMP22[2, 59, 65]	62 (54–70)	78.5 (78–79)	63 (58–68)	76 (66–86)
F/FDP[40]	81	75	79	78
Lewis X antigen[33]	81§	85.5§	72§	91§
Telomerase[42, 43]	90 (89–91)	77	88	82

PPV = positive predictive value; NPV = negative predictive value; F/FDP = fibrinogen/fibrin degradation products; NA = not available, some figures based on data presented in abstract form only.
* Mean values calculated from all studies referenced for a particular test; ranges reflect individual values from all studies referenced.
† Higher specificity for healthy patients (95%) and those with nongenitourinary disease (93%) when compared to patients with benign genitourinary disease (72%), urinary tract trauma (33%), or other genitourinary malignancies (73%).
‡ Based on a 10% prevalence of bladder cancer in the population under surveillance.
§ Figures based on analysis of one voided urine specimen.

expressed on a significant number of TCC cells. M344 is predictive of recurrence, and is only rarely associated with invasive lesions, while T138 is usually found on aggressive and invasive tumours. Normal transitional cells do not express DD23, but tumours that do are less likely to recur. In preliminary studies, cancer detection with a combination of these antigens has been compared to cytology, and improvement in sensitivity over any one alone was shown.[31] The expression of cell adhesion molecules, such as E-cadherin and laminin, are associated with invasive behaviour, and probably are not in themselves suitable for screening populations in which less aggressive, but more prevalent malignancies require as accurate a detection as more aggressive ones.

Growth factors and receptors

Several proteins have been identified in the urine and bladder epithelium that have possible prognostic value in patients with TCC. The epidermal growth factor receptor (EGF-R) is normally expressed only on the basal

layer of transitional epithelial cells, but becomes abnormally abundant on malignant cells. The quantity of EGF-R expressed is directly related to the biological aggressiveness of the tumour, with high levels associated with a grim prognosis. Moreover, in malignant states the distribution of EGF-Rs in the urothelium changes; rather than being expressed exclusively on the basal layer of epithelial cells, they appear on cells throughout all layers of urothelium, both within the tumour and on dysplastic and normal-appearing urothelium remote from that site. The utility of aberrant EGF-R expression as a screening test is low, however, as it appears to be better detected in fresh-frozen sections than either paraffin-embedded, formalin-fixed tissue or exfoliated cells.[14] Epidermal growth factor (EGF), which binds to the EGF-R, is normally excreted in high concentrations in urine. Reduced concentrations of EGF have been found in voided urine from patients with TCC, possibly reflecting increased levels of EGF-R expression throughout the urothelium and binding of urinary EGF with subsequent internalization and degradation of the ligand receptor complex.[32]

Transforming growth factor-beta is an inhibitor of cell proliferation, and high urinary and tissue concentrations are predictive of less aggressive tumours. Malignant cells secrete abnormally high amounts of an autocrine motility factor (AMF), which has been shown to influence motility, invasion and metastasis, and concentrations are particularly increased in aggressive TCCs. High levels of AMF receptor expression may also predict future tumour recurrences. Angiogenic factors, such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) are also generated in significantly higher concentrations in TCC cells compared to normal bladder urothelium.[33] Elevated concentrations of these factors in the urine of patients followed for bladder cancer surveillance are associated with recurrence. For example, elevated VEGF has a sensitivity of 75% and a specificity of 62% for the initial diagnosis of bladder cancer, and 83% and 43%, respectively, for its recurrence. For both diagnosis and recurrence, investigators found results for VEGF superior to cytology for detection of low-grade TCCs.[33]

Other molecular tests

NMP-22 is a nuclear matrix protein that can be measured via immunoassay of voided urine. A sensitivity of 67% for TCCs of all grades was reported, but the subjects enrolled in this study were undergoing follow-up for

recurrent superficial bladder tumours.[34] Another study described increasing specificity and positive predictive values to above 90% with awareness and exclusion of certain categories that incur high false positive results.[35] Thus, extrapolation of these data to an asymptomatic population is difficult. BLCA-4 is another nuclear matrix protein that appears to be specific for bladder cancer. It is expressed in 75% of tumour tissue and 100% of normal-appearing bladder epithelium for patients with bladder tumour elsewhere.[36] While this level of sensitivity is significantly better than urine cytology, evaluation of this test in at-risk patients without a history of bladder cancer is needed to judge its potential in mass screening projects.

The bladder tumour antigen (BTA) assay quantifies degradation products of substances within the basal lamina and lamina propria of the bladder, presumably resulting from tumour-derived enzymatic destruction and/or erosion of the bladder wall. The original BTA test was an agglutination strip assay on voided urine. It was replaced by the STAT, and then the TRAK assays as revisions were made to improve sensitivity and specificity. The sensitivities for the Bard BTA test were 38% for grade I and 71% for grade III TCCs, while those for the BTA TRAK, a sandwich enzyme immunoassay, were 55 and 66% for grades 1 and 2 respectively, and 86% for grade 3 cancers.[37,38] False positives were noted in both assays in patients with benign prostatic hypertrophy, ureterolithiasis and lower urinary tract infection. No specificity or predictive values were noted, and it is not clear at this stage whether this test is a good predictor of progression.

Telomerase is a nuclear enzyme that regenerates the terminal ends of chromosomes normally broken off with each mitosis, and is found at high levels in malignant cells. Expression of this enzyme, and hence regeneration of the telomeric DNA which would otherwise be lost, is responsible for the *in vitro* immortality characteristic of malignantly transformed cells. The TRAP assay can measure telomerase activity in exfoliated urothelial cells, and sensitivities have been reported to be about 80% for each grade of TCC, although other studies have shown the sensitivity of the test to be much lower than that.[39,40] Other assays can now detect messenger RNA for this enzyme and may be even more sensitive. While occasionally normal white blood cells can express small amounts of telomerase, in general the specificity and positive predictive value of this assay is very high, since few other non-malignant cells will express it. Because of their complexity and lack of sensitivity, assays for the telomerase message or activity are not suitable for primary screening of large populations at this time.

Hyaluronic acid (HA) has multiple functions in facilitating tumour growth and protecting malignant cells from immunologic surveillance. It, and the products of its breakdown by hyaluronidase, are found in significantly higher concentrations in the urine of bladder cancer patients, regardless of tumour grade. Hyaluronidase levels are also increased in TCC tissue, particularly of grade 2 or grade 3 cancers, when compared to normal bladder or grade 1 TCC tissue.[41] Lokeshwar *et al*. demonstrated a sensitivity of 92.2% and a specificity of 85.1% when both molecules were measured simultaneously using a biotinylated binding protein assay on urine from patients with known bladder cancer. At this point, the greatest utility of these tests appears to be in non-invasive surveillance for recurrent bladder cancer.[41]

Survivin is an apoptosis inhibitor, expressed in many tumours, and detectable in voided urine using a polyclonal antibody ELISA assay.[42] In a preliminary report, Smith *et al*. detected survivin in all of 46 patients with transitional cell carcinoma (100% sensitivity), but only a small proportion of non-bladder cancer pathologic conditions. However, 60% of patients with haematuria also had positive tests. Since almost all patients with bladder cancer have haematuria, this lack of specificity is not a trivial issue for using survivin as a screening tool. In addition, few patients had superficial cancers and none had well-differentiated ones in this study.[42] Thus, as currently assayed, survivan's suitability for screening is unknown.

Chromosomal anomalies and genetic aberrations

Analysis of genetic material is useful in predicting recurrence and prognosis in bladder cancer, and may have a future role in screening practices. Fluorescence in situ hybridization (FISH) is used to identify loss of parts or all of chromosome 9, the most frequent chromosomal abnormality in TCC. In the most frequently used assays, cells from saline bladder lavages are incubated with a fluorescent probe specific for the centromere of chromosome 9. Quantification of copy number is done by direct visualization with a fluorescent microscope, and compared with the modal number of chromosomes (based on flow cytometry or image analysis). Loss of a copy of chromosome 9, when combined with DNA ploidy analysis, can detect over 80% of all TCCs, relatively independent

of tumour grade, with over a 95% specificity.[43] A recently approved commercially available assay using DNA probes to the centromeres of chromosomes 3, 7 and 17, and a separate probe to the 9p21 region of chromosome 9, to which increased copies of 3, 7 or 17, or a loss of copy of 9p21 are considered positive, have been reported to be positive in 36% of grade 1 cancers, 67% of grade 2 cancers, and 97% of grade 3 tumours with a specificity of 96%.[44] While the lack of sensitivity for low-grade tumours is worrying, if sensitivity for high-grade cancers and excellent specificity are confirmed, this test holds promise in a screening paradigm.

Microsatellite markers on free DNA in urine and blood are another potential minimally invasive screening option for the detection of bladder cancer. Tandem repeat sequences of two, three or four nucleotides (DNA microsatellites) are present throughout the genome in patterns that are quite unique for each individual. In most malignant cells, variations in microsatellite DNA occur, presumably due to altered DNA repair mechanisms. Using DNA probes to target areas of interest, the DNA of urothelial tumour cells has been compared to that of presumably normal cells (such as circulating white blood cells), looking for alterations in the microsatellite pattern present in genomic DNA. Theoretically, by using informative DNA markers, alterations of microsatellite repeats can be identified in a single cell mixed with thousands of normal ones.[45] Results have been correlated with histologic findings and recurrence in several studies.[45–8] Specimens analyzed have included tissue and voided urine, and reported sensitivities are as high as 91%.[46,49] As with telomerase and chromosome 9 FISH/DNA ploidy, false positive tests appear to be quite rare.

Another high technology modality used as a screening option for bladder cancer is 'virtual cystoscopy', whereby axial images under computerized tomography are analyzed for wall thickness and the presence of cancer, although this option appears costly to date and might have more relevance in those individuals for whom there is a high risk of carcinoma.[50]

As noted earlier, these (and other) assays have primarily been tested on specimens from patients with active bladder cancer, or a history of bladder cancer, and patients whose bladder cancer status was presumed negative. The normal controls were often much younger, and not race- or gender-matched with typical bladder cancer patients. In general, these assays have not been tested in the general or high-risk populations without bladder cancer histories, so their performance in a true screening

setting is unknown. Moreover, very few of these tests have been performed on the same specimens, except when compared with cytology. In those circumstances, the cytologic analysis has usually been done by each individual institution participating in the trial, rather than by a central laboratory expert in urinary cytologic examination.[51] As a result, the comparable performances of each assay are uncertain. Furthermore, whether multiple assays can additively improve sensitivity without seriously decreasing specificity is not clear.

Another issue that is pertinent to screening is that surveillance cystoscopy in patients with prior bladder cancer tries to detect cancers when they are both less invasive and smaller. Boman *et al*. recently demonstrated quite elegantly that several marker tests (NMP22, BTA stat, UBC antigen) failed to detect 25–37% of superficial recurrent grade 3 cancers, primarily because of their small size.[52] Yet it is precisely this type of early stage, high-grade lesion that these tests have to detect reliably it they are to be used for screening. Whether other tests can improve on this inadequate sensitivity for small, high-grade cancers is uncertain. Thus, the utility of these tests alone or in combination, either simultaneously or sequentially, in screening scenarios remains unexplored. Currently only data for repetitive haematuria testing in the general population, and cytology and DNA image analysis in industrially exposed populations, have been reported.

Screening in general populations

Four prospective cohort studies of home haematuria screening have been published. Messing and Britton *et al*. recruited men over the age of 50 or 60 years without a known history of genitourinary disease from primary care practices in Wisconsin, USA and Leeds, UK respectively.[22,23,53–8] Each participant repeatedly tested his urine at home with a haemoglobin-sensitive reagent strip according to a protocol. Any man with any positive test was offered a full haematuria workup. Both studies found a 15–20% prevalence of microhaematuria in the screenees. Approximately 6–10% of these men actually had a bladder tumour on evaluation, yielding an overall incidence of bladder cancer of 1.1–1.3% of screened participants in both locales. To determine if haematuria screening could reduce bladder cancer mortality, presenting tumour stages and grades, and outcomes from disease of screenees in the Wisconsin study were compared with

those of age-and-geography matched men with newly diagnosed bladder cancer reported to the State of Wisconsin tumour registry in 1988 (Table 6).

Similar proportions of grade 1 and 2 superficial (stage Ta and T1) TCCs occurred in unscreened (56.8%) and screened (52.4%) men. The percentage of high-grade tumours was also similar in each population, comprising 43.2% of the standardly diagnosed and 47.6% of screening-detected bladder cancers. However, a significantly higher percentage of muscle-invasive lesions was found in the unscreened compared to the screened group (23.9% vs 4.9%) bladder cancers. In essence, screening had not altered the grade distribution of newly diagnosed bladder cancer, but by enabling early detection, had shifted the diagnosis of tumours likely to become muscle invading – the high-grade TCCs – to pre-invasive stages. As a result, none of the men diagnosed with bladder cancer in the screened group succumbed to their malignancy with a follow-up of four to nine years, whereas 16.4% of the unscreened group (36% of those with high-grade lesions) had died of their disease within two years of diagnosis.

Table 6: Mortality from bladder cancer in all Wisconsin men age 50 and older with bladder cancer diagnosed in 1988 versus those with bladder cancer detected by hematuria home screening.

	Unscreened: Mortality		*Screened: Mortality*	
	Within 24 months of diagnosis		*Anytime after diagnosis (30 to 102 months follow-up)*	
Bladder cancer	*Number of deaths*		*Number of deaths*	
Grade and stage	*All cases*	*%*	*All cases*	*%*
Low-grade (1.2) superficial (stage Ta, T1)	5/290	1.7	0/11	0
High-grade (3) superficial (stage Ta, T1, TIS)	12/99	12.1*	0/9	0*
Muscle invasive or greater (stage T2-4 or N+ or M+)	67/122	54.9	0/1	0*
Overall rates	84/511	16.4†	0/21	0†

* Disease-related mortality in men with high-grade or invasive bladder cancers in unscreened (35.7%) versus screened (0) p = 0.014.
† Disease-related mortality in all bladder cancer cases unscreened (16.4%) versus (0) p = 0.025.

It could be argued that the screened men only appeared to have a better outcome because of lead time bias, which artificially extends the survival time by diagnosing the disease earlier in its course without changing the ultimate results. However, considering that the pre-clinical phase of bladder cancer is relatively brief, that the follow-up of screened men was four to nine years, and that most patients who succumb to aggressive bladder cancer do so within two to three years of diagnosis, it is unlikely that lead time bias can explain these survival differences. Length time bias, which skews screening results by detecting clinically insignificant tumours, was also unlikely due to the similarities in the proportions of low- and high-grade malignancies between the screened and unscreened populations. It is possible that the screened men with bladder cancer may have selected themselves to participate based on an unstated suspicion that they harboured this disease or an unusually great concern for their own health status, but again, the incidences of bladder cancer (1.2–1.3%) was essentially identical in the Wisconsin and Leeds studies, in men with prostate cancer or benign prostatic hyperplasia who undergo cystoscopy simply as part of a pre-treatment protocol, and in men solicited for the Wisconsin screening study who declined to take part.[55,56,59] Thus, self-selection on the part of screenees was unlikely to explain either the incidence of TCC found, or the patients' outcomes. Finally, differences in quality and availability of healthcare might have caused these divergent survival statistics between screened and unscreened men with bladder cancer, but the similarities in outcomes between the Wisconsin registry group and national death rates from bladder cancer, as well as contemporary survival results reported from academic centres, make it unlikely that unscreened Wisconsin men with bladder cancer received suboptimal care. However, a prospective, randomized trial is the only way to clarify these issues.

Screening in high-risk populations

Several investigators have screened high-risk populations with industrial exposures to carcinogens. A group of aluminium workers exposed to coal-tar derivatives in Québec were screened for TCC with cytology of voided urine between 1980 and 1986, and the patients diagnosed via screening were compared to those diagnosed via symptomatic presentation in the 1970s.[60] There was a non-significant decrease in stage at presentation and

no significant survival advantage was displayed. The analysis was limited, however, by the use of publicly available information for follow-up, as opposed to interview or examination of the patients themselves.

Hemstreet *et al*. screened a total of 1,892 risk-stratified Chinese male workers exposed to industrial carcinogens using QFIA on voided urine specimens, and demonstrated earlier diagnosis of TCC compared to standard cytology.[61] Criticisms of this work include a failure to correlate a diagnosis of bladder cancer with a positive QFIA test, and a failure to provide details regarding the incidence of TCC in individuals not at high risk (according to their risk-assessment algorithm). In separate work, case studies presented by Frumin *et al*. Support screening workers exposed to known bladder carcinogens with standard urinalysis, as none of the diagnoses made in their cohort were detected by cytology, but rather by microscopic haematuria.[62]

Conclusions

Bladder cancer has multiple characteristics that make it ideal for screening. First, it is a common, serious malignancy and a significant cause of death in industrialized societies. Second, there is a pre-clinical phase during which the disease is asymptomatic, but detectable if an evaluation is done. Symptomatic presentation is correlated with advanced stage and poorer outcomes than detection by asymptomatic microhaematuria. Third, there are several well-defined populations with significant risk factors for bladder cancer that would likely benefit from early diagnosis and treatment. Fourth, treatment of pre-muscle invading disease is relatively inexpensive, well tolerated, non-morbid, very successful and widely available. Fifth, since the disease is virtually always diagnosed and treated prior to demise, early detection would not be a disservice to screening participants. Sixth, there are several non- or minimally invasive tests that are potentially available alone, in combination, or in sequential use as screening instruments. Currently all these tests have less than ideal sensitivity and specificity profiles for screening both the superficial well-differentiated tumour and the potentially metastatic poorly differentiated invasive tumour. The superficial low-grade cancers are important because, although they are rarely a risk to a patient's life, the failure to diagnose this common type of bladder cancer would hurt the perception of the test as an effective screening tool. With regard to the high-grade and/or invasive

type of TCC, a sensitivity of 80–90% would miss 10–20% of tumours, and this compromises the major goal of screening, which is to reduce bladder cancer mortality. The advent of newer tests, along with prospective, randomized, appropriately powered trials are needed to demonstrate that earlier detection, promoted by screening, reduces mortality from this disease. For now, the roles of markers and new tools for screening and detection, even as complements to cystoscopy, have yet to be defined.

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Chapter 3

Non-invasive diagnosis

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Introduction

Non-invasive testing for bladder cancer has been carried out for many years by means of urine testing for blood, the presence of malignant cells on cytological examination and assessment of DNA ploidy in voided urine or bladder washings.

The ideal non-invasive test would detect bladder cancer of all grades and stages with 100% sensitivity and specificity. No such test yet exists – not even cystoscopy is completely accurate. In addition, the ideal test would be easy to do and would be reproducible by different investigators and on different occasions. Many new tests are being assessed and most studies have been done on patients with haematuria or those being followed up for known bladder cancer.

Non-invasive tests might in theory be offered to individuals with newly presenting haematuria, to those patients being followed up for known superficial disease, and also to those at increased risk because of occupational exposure. Commercial developments include the use of the BTA stat and TRAK tests, measurement of NMP22, fibrin degradation products (FDPs) and telomerase. The immunocyt test measures high molecular weight forms of CEA and mucins and has also been used to detect transitional cell carcinoma. More recent developments include molecular techniques to detect known genetic alterations in bladder cancers. These include assessments of micro-satellite alterations in the urinary sediment, the use of staining for p53 to supplement conventional cytology, and the measurement of oncogene products such as E-cadherin, CD 44 and ß hCG in urine. Previous studies have not yet been large enough to be sure whether these tests differ significantly in their clinical utility.

Table 1: Non-invasive tests in current use.

- Hb dip-stick
- Cytology: urine or washings
- Imaging: USS
- Flow cytometry
- BTA
- BTA stat
- BTA TRAK
- NMP-22
- Fibrin/FDPs
- Telomerase (TRAP)
- Microsatellite analysis
- CA 19-9
- MMPs
- Soluble E-cadherin
- CEA
- CA125
- CD44
- CYFRA 21-1: cytokeratin 19 and 20
- Lewis X
- B-5
- M344
- Hyaluronic acid/hyaluronidase
- IL-6, IL-8
- bFGF

Background

Each year in England and Wales, around 8,000 men and 3,000 women develop cancer of the bladder; it is the fourth most common cancer after lung, colo-rectal and prostate/breast cancer.[1] In the developed world, transitional cell carcinoma (rather than squamous or adenocarcinoma) is responsible for most bladder carcinoma. The incidence is around 20 to 25 per 100,000 of the population each year. About 25% of newly diagnosed cancers are muscle invasive (T2–T4); the remainder (70%) are superficial – classified as limited to the mucosa (pTa), lamina propria (pT1) or being *in situ* changes (Tis – 5%).

Presentation of bladder cancer

The most common symptom is painless macroscopic haematuria. Irritative symptoms such as frequency, urgency and pain may signify the presence of carcinoma *in situ* or invasive bladder cancer. Less common complaints include loin pain from ureteric obstruction, lymphoedema owing to nodal metastatic disease and non-specific symptoms from metastatic disease.

Microscopic haematuria and screening

Microscopic haematuria detected by urine strips is associated with bladder cancer in 10% of patients over 50 years, and it should be investigated. However, it does not follow that widespread screening for microscopic

haematuria will improve death rates from bladder cancer. People who have occupationally exposed to carcinogens are currently followed up by means of regular urine cytology.

Conventional diagnosis

Open access haematuria clinics in which patients can be seen and assessed without delay have been set up, but we do not yet know if they have survival benefit.[2] A full history is taken, including potential exposure to carcinogens, and a physical examination is performed. Intravenous urography is used to image the upper tract (or KUB plus ultrasound), and flexible cystoscopy under local anaesthesia is carried out. Investigation includes blood tests and a fresh mid-stream sample of urine for culture and cytological examination. Imaging of the upper tracts is important because it may detect upper tract tumours or dilatation caused by muscle invasion or growth into the intra-mural ureters.

Non-invasive methods

Urine cytology

This is the original non-invasive test. It requires a person skilled at interpreting urinary cytology and care in collection and interpretation.

Table 2: Sensitivities and specificities of the different non-invasive tests.

	Sensitivity total vs (invasive)	*Specificity total vs (invasive)*
Cytology	35% (55%)	85%
Bard BTA test	40% (64%)	60% (80%)
BTA stat	65–70% (80–90%)	60% (80%)
BTA TRAK	60% (80%)	80% (80%)
FDPs	65% (90%)	86%
NMP-22	70% (90%)	80%
Quanticyt	65–70%	85%
Telomerase	80% (85%)	80%

Early morning urine samples are prone to artefact and the presence of infection, inflammation and urinary stones can give false positive results. Care is also needed in the interpretation of bladder washings because clumps of normal urothelium may be dislodged, replicating the appearance of a well-differentiated transitional cell carcinoma (TCC). In most studies, cytology is good at diagnosing high-grade disease and carcinoma *in situ* (*tis*).[3,4] Overall, about 30–40% of bladder cancers are detected by urine cytology, though the sensitivity is greater for patients with high-grade disease. Specificity is around 80–90%.[5]

The Bard BTA test

This was a qualitative test that involved the detection of high molecular weight fragments of basement membrane in the urine. It was a latex agglutination assay that used strips containing modified IgG coated latex particles and complexes of yellow and blue dyes. A positive test was the presence of a yellow line on the strip.

The first two major studies were those reported by Sarosdy *et al*. and the European Multicentre trial.[6,7] In the Sarosdy study there were 499 patients with a past history of TCC. The BTA test was compared to voided urine cytology. There were 151 recurrences, 121 of which were confirmed histologically. The BTA test detected 61/151 of the tumours (40%), whereas voided urine cytology detected only 25 (17%). For patients with invasive tumours, the BTA test detected 64%, versus 43% for cytology. In the European Multicentre trial there were 401 patients. Of these, 140 (35%) had a past history of TCC and 225 (56%) had symptoms of haematuria. There were 84 tumours, 67 of which were proven histologically. The BTA test was compared with cytology. The BTA test detected 64% of the tumours, whereas cytology detected 28%. In patients with invasive tumours, the BTA test detected 89% compared with 39% for cytology.

On the other hand, Murphy *et al*. studied 67 patients with previous TCC, and there were 28 tumours.[3] Voided urine cytology had a sensitivity of 61% compared with 46% for the BTA test – and cytology was more specific. In general, both techniques were more sensitive and specific in the detection of high-grade and high-stage tumours. The UK and Republic of Ireland bladder tumour antigen study group adopted a different policy and stratified prospectively 272 patients with a history of TCC into two groups depending on the result of the BTA test.[8] Those with a positive test had a GA cystoscopy, those with a negative result underwent a flexible

cystoscopy under local anaesthesia. In total, 188 patients underwent a flexible cystoscopy, and of these 145 were truly negative and 43 were falsely positive on the BTA test. Of the 126 patients who underwent a GA cystoscopy, 43 were falsely positive. It was estimated that the potential global savings per year in these 272 patients was £20,500.

The BTA stat and BTA TRAK tests

Though BARD also markets these tests, they are based on a quite different underlying premise. The antigen detected is a member of the human complement factor H family (hCFHrp). The antigen – C3b/CFH – blocks the alternative complement pathway activation and prevents cell lysis. It is suggested, therefore, that the production of CFH by tumour cells confers a selective growth advantage. The BTA stat test is an immuno-chromatographic assay that utilizes monoclonal antibodies to hCFHrp that are conjugated with colloidal gold. It is a one-step point of care qualitative test and provides a result within five minutes. It requires the use of fresh or frozen urine. The BTA TRAK test is based on the same antigen and antibodies, but is a qualitative test.

In a multicentre trial in Europe, there were 107 patients with TCC.[9] The sensitivities of BTA stat and cytology were 65% and 33% respectively. For tumour grades I, II and III, the sensitivities of BTA stat were 39%, 67% and 83% respectively. Those of cytology were 4%, 20% and 69%. The specificities of BTA stat and cytology in the 124 subjects without bladder cancer were 64% and 99% respectively.

Another study from America evaluated the BTA stat. The BTA stat test detected 147 (57%) of 220 recurrent cancers. In some patients, results of the conventional BTA was also available. In these patients, cytology had a sensitivity of 23%, the BTA test 44%, and the BTA stat test 58% for detection of recurrent cancer. The specificity of the BTA stat test was 72% for benign genitourinary disease, and 95% in healthy volunteers.[10] Another recent study looked at the sensitivity and specificity of the BTA stat test for the detection of TCC. Of the 250 patients studied, 71 had a tumour. The overall sensitivity of the BTA stat test was 83% (specificity 69%). The sensitivity of urine cytology was 40% and specificity was 95%.[11] For invasive tumours, the sensitivity of the BTA test was 100% and the sensitivity of cytology was 70%.

The UK and Republic of Ireland BTA study group looked at 64 patients with new bladder tumours. The sensitivity of the BTA stat test for patients

with grade 3 TCC was 88%, and for muscle-invasive disease it was 100%.[12]

In the recent comparative study reported by Ramakumar, there were 14 patients with T1–T3b tumours.[5] The sensitivity of cytology was 67%; for BTA stat it was 100%; for NMP22 it was 79%; for telomerase it was 71%; for Hb it was 89%; and for Hb using a stick test it was 68%.

The large multicentre European trial compared BTA trak to cytology in 220 patients (155 men, 65 women; mean age 64.2 years).[13,14] In the 100 patients with TCC, the sensitivities of BTA trak (with a cut-off of 14 kU/L) and cytology were 66% (66 of 100) and 33% (33 of 100) respectively. The specificity of BTA trak was 69% (83 of 120) compared to 99% for cytology.[13] For muscle-invasive disease and cis the sensitivities of BTA trak were 88% and 56% compared to 60% and 80% for cytology.

Fibrin and Fibrin Degradation Products (FDPs): Auratek®, AccuDx®

Most tumours are associated with increased expression of various tissue proteases and their inhibitors. These enzymes result in increased degradation of fibrin to FDPs. In bladder cancer, these substances can be detected in the urine. The commercial assays use a lateral flow immunoassay involving mouse monoclonal antibodies. They assess qualitatively urinary fibrin/FDPs and are a rapid (<7 minutes) point-of-care test, a purple spot indicating a positive result.

In a study reported by Schmetter and colleagues, there were 192 patients with a prior history of TCC.[15] The sensitivity of Auratek FDP in the detection of recurrence was 68%, compared to Hb dipstick (41%) and voided urine cytology (34%). For G1 tumours, the detection of FDPs was 62% sensitive, whereas for T2–T4 tumours it was 100% sensitive. Using healthy controls, the test was 96% specific, compared to a specificity of 86% in patients with benign GU disease.

Nuclear Matrix Protein 22 (NMP-22: Matritech)

This family of nuclear matrix proteins forms the structural framework of the nucleus. One of the family – the Nuclear Mitotic Apparatus Protein (NuMA) is increased 25 fold in TCC cell lines. NMP-22 is a protein that forms part of the NuMA complex. The test marketed by Matritech is an ELISA kit containing a monoclonal antibody Mab to the NuMA. It detects

urinary NMP-22. The urine requires stabilization by protease inhibitors and usually involves the collection of three samples over 24 hours, or the use of one sample between 12.00am and 12.00pm.

Soloway *et al.* reported a study of 90 patients who had a previous bladder tumour within the previous 18 months. A urine sample was taken 3–60 days after TURT and a check cystoscopy was done between 30 and 180 days post-TURT. Patients who had recurrent disease (50 of 125 check cystoscopies) had an increased level of NMP-22 (21 U/ml) compared to those whose bladders were clear (6 U/ml). Using a 10 U/ml as a cut-off to detect recurrence, the sensitivity was 70% and the specificity was 79%. For muscle-invasive disease, the sensitivity was 100%.[16] In a later study by Stampfer *et al.*, NMP-22 was compared to voided urine cytology. There were 231 patients with previous TCC. The sensitivity of NMP-22 was 67% (for patients with greater than T1 disease it was 83%), the sensitivity of urine cytology was 31%.[17] Landman and Sharma reported similar results.[18,19] However, Sharma noted the use of exclusions and inclusions – such as avoiding testing patients with stents or bowel segments and defining 'atypical' cytology as positive. They found that such protocols enhanced the sensitivity of all tests considerably – particularly urine cytology.

Modern molecular techniques (telomerase, detection of micro-satellites)

The use of the polymerase chain reaction allows the amplification of DNA (or RNA after reverse transcription) found in very small amounts in body fluids. Very sensitive detection can be achieved of the presence of particular genes or gene transcripts (such as telomerase) or the presence of micro-satellite markers that can be associated with cancer.[20–24]

Sidransky's group, in particular, have pioneered the use of such techniques in urine to detect bladder tumours and recurrences with great sensitivity and specificity – but the tests are time consuming and seem unlikely to be adopted widely at present.

Several groups have reported that the detection of telomerase may be useful clinically. Telomeres are found at the specialized ends of chromosomes. Because their position does not allow DNA replication by conventional DNA polymerases, they require a special enzyme called telomerase to enable them to be replicated during cell division. Most normal adult differentiated cells do not contain telomerase, whereas cancer cells do. It is thought that telomeres shorten with successive cell divisions and eventually very short telomeres are associated with apoptosis.

The detection of telomerase in urine is associated with the presence of bladder cancer.

Standardized techniques using PCR technology (TRAP – telomerase amplification protocol) have enabled the test to be applied to patients with bladder cancer.[24] In one study, urine samples were obtained from 63 patients with a history of bladder cancer. Cytology was compared to the TRAP assay. The test was not very sensitive, but was specific in this study. In more recent reports, the sensitivity of the TRAP assay was better – in the order of over 80%.[5,18] The presence of gross haematuria can decrease significantly the sensitivity of the TRAP assay.

Other modern tests

Other recent studies have evaluated other markers.[25–28] These include ßhCG, CD44, p53 positivity to target cytology, and the Immunocyt test. The Immunocyt test measures high molecular forms of CEA and mucins and has been used to detect transitional cell carcinoma.

Conclusions

Many different types of urine-based tests have been developed. In principle these are very exciting because if they could be developed to be as sensitive and specific as cystoscopy, then they will reduce the number of invasive procedures. The patients who will benefit include the following:

1 Patients with gross haematuria
2 Patients with microscopic haematuria
3 Patients with lower urinary tract symptoms
4 Patients undergoing follow-up cystoscopy for a diagnosis of TCC
5 Patients with invasive tumours who have been treated by bladder preserving techniques who are under regular follow-up.

As yet, none of the tests is good enough to replace cystoscopy.[29] The best of the tests include BTA stat and TRAK, FDP measurement, NMP-22, Immunocyt and telomerase. On average the sensitivity is 70–80% and the specificity is about the same. For muscle-invasive or high-grade disease the sensitivity is greater – in the region of 80–90%. However, the urologist should be aware that gross haematuria can interfere with the tests. In

addition conditions causing inflammation, such as stones, infection, bowel segments and stents, can cause false positive results.

In the near future, the urologist will want to see more head-to-head comparisons of the tests in large enough groups of patients to determine accurately which are the better tests.

Another variable is the ease of carrying out the tests, how reproducible they are, and whether the urologist can do them easily in the office. True cost and cost-effectiveness need to be determined. The type of healthcare system in which the urologist practises is also important in terms of how the costs of the test can be reimbursed.

In the future it would be good to see some large-scale trials of people with low-risk superficial bladder cancer.[30,31] The trial could address the question of whether the frequency of cystoscopies could be reduced by the use of tests carried out by the patient or GP (or urologist).

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Chapter 4

Molecular pathology of tumour progression and metastasis

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Introduction

About 30% of all patients with newly diagnosed bladder cancer will present with muscle-invasive disease and about half of them will eventually die from the disease, despite mutilating surgery or polychemotherapy. The steps underlying tumour progression are invasion and metastasation. Thanks to the achievements of molecular biology, these processes are increasingly better understood. The new results arising will be eventually translated and incorporated into our current clinical knowledge. They form the basis for future strategies to manage locally advanced or metastatic bladder cancer.

Since the entire knowledge on tumour biology can hardly be summarized in one article, the aim of this manuscript is to provide some insight into the molecular biology of bladder cancer using selected examples which should help in understanding the basic concepts underlying invasion and metastasis. The examples chosen within this paper represent some of those alterations that might gain clinical relevance within the near future.

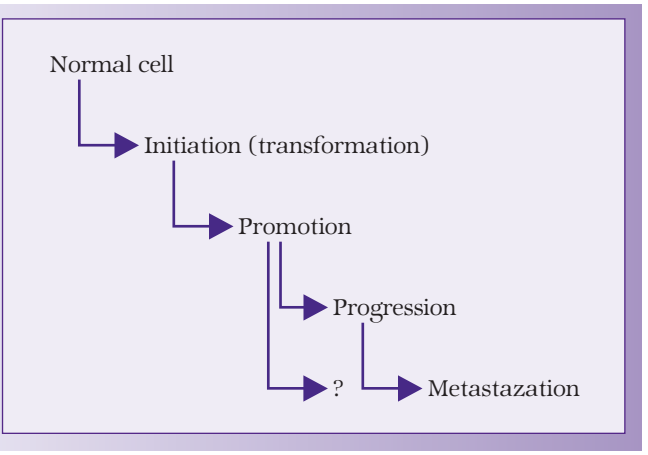

Figure 1: From a normal to a metastatic cell: tumour progression.

Carcinogenesis and tumour progression represent events consisting of multiple steps that may occur sequentially (Figure 1). Today, some of these steps can be related to cytogenetical or molecular alterations. Through the course of disease the tumour cell may subsequently aquire several new (with regard to a terminally differentiated cell) properties finally making it capable to metastasise (Figure 2). Within this manuscript the following steps are discriminated:

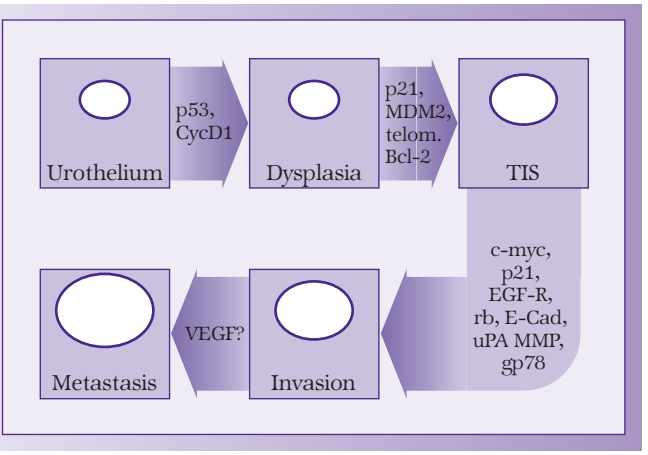

Figure 2: Molecular events related to the steps of tumour progression.

- Immortalization
- Proliferation
- Apoptosis
- Angiogenesis
- Decreased Cell Adhesion
- Invasion
- Metastasation.

Immortalization

Immortalization remains a fundamental step in carcinogenesis. Physiologically, every cell that has reached terminal differentiation is prone to senescence and will subseqently undergo cell death. One of the key reasons for this is the abundance of telomerase expression in terminally differentiated cells. Telomerases guarantee the integrity of the telomers, the ends of the chromosomes, by compensating for losses occurring through proliferation and differentiation. Once the cell has reached the stage of terminal differentiation, telomerase activity will be shut down. This yields a consistent loss of genetic material at the ends of the chromosomes (Figure 3).

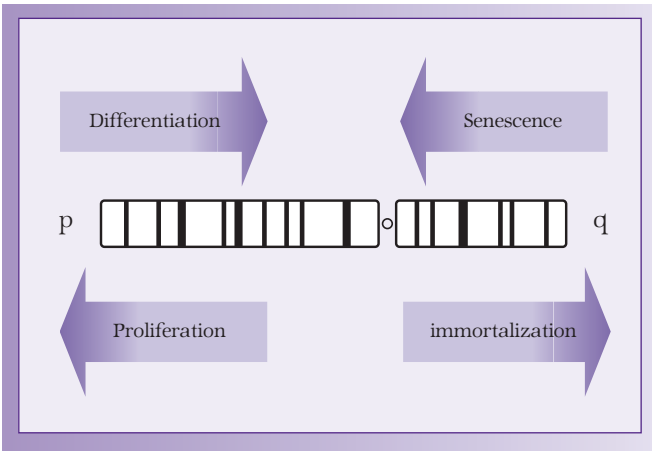

Figure 3: Telomerase activity: against the natural clockwork.

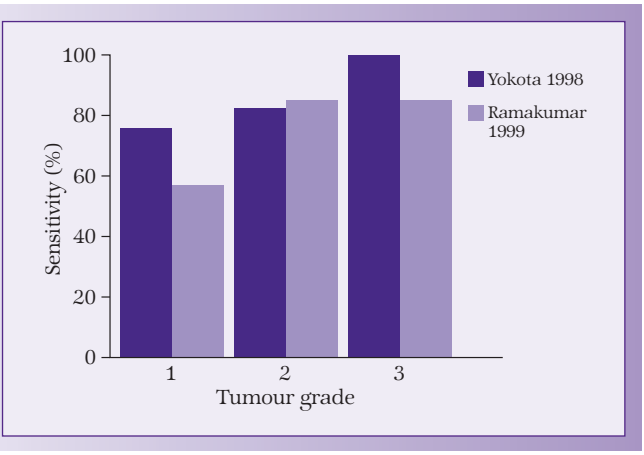

Figure 4: Telomerase activity in voided urine. Diagnostic sensitivity related to tumour grade.

Investigation of tumour cells, however, showed that carcinogenesis is paralleled by a reconstitution of telomerase activity. In bladder cancer, even high-differentiated tumours have been found to be positive for telomerase activity as determined by the TUNEL assay. As a consequence this observation has been translated into a diagnostic use.[1–6] Several studies on the diagnostic use of telomerase activity in bladder cancer have demonstrated a high sensitivity and specificity of this assay (Figure 4). Current prospective studies are aiming at the determination of the definitive role of the detection of telomerase activity in urine as a diagnostic tool in clinical routine.

Proliferation

Physiologically, cell division and cell death are subject to a multiplicity of regulatory pathways, yielding a delicate balance. In cancer cells this balance is disrupted. Proliferatory pathways are activated, resulting in a net growth of the respective tissue. Among others, Shiina *et al*. and Clasen *et al*. have investigated bladder cancer proliferation by examining the immunohistochemical positivity for Ki67, a marker of cell proliferation.[7,8] Ki67 was clearly increased in bladder tumour specimens, as compared with normal mucosa, and correlated with tumour stage and tumour grade, demonstrating a faster cell-cycle transition.

Cell-cycle control is the key step underlying cell division and proliferation (Figure 5). Rb phosphorylation regulated by complexes of Cyclin E and Cyclin Dependent Kinase (CDK) 2 or Cyclin D and Cyclin Dependent Kinase (CDK) 4 decreases G1/S transition and thus controls for this paramount checkpoint. This complex formation is decreased by two other molecules, designated p21 and p27. Increased p21 and p27 concentrations prevent Cyclin/CDK complex formation and thereby result in increased pRb concentrations. These increased pRb levels are responsible for a delayed G1/S transition. Notably, p21 transcription is under the control of another key cell-cycle regulating molecule, the p53 gene product.

The p53 tumour suppressor gene, termed as 'guardian of the genome', is one of the key molecules responsible for the integrity of the genome (Figure 6). Physiologically, p53 transcription is increased in response to genomic damage, e.g. caused by UV-radiation, DNA alkylation or other agents.[9] Through p21 activation and pRb a G1 arrest is achieved, permitting the DNA repair mechanisms to restore genomic integrity and thus providing the basis for adequate cell division and two intact genomes in the subsequent cell generation. As an alternative pathway, p53 may trigger apoptosis in the case of failure of DNA repair, thus preventing multiplication of cells with a defect genome. Considering this important role of p53, it is easily conceivable that a functional loss of this gene has significant impact on cell proliferation. The observation that more than 50% of all tumours have p53 alterations is, therefore, hardly amazing.

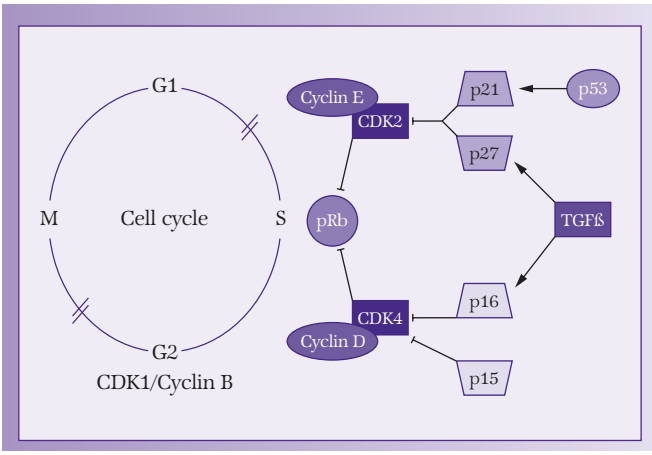

Figure 5: The cell-cycle regulating network (simplified).

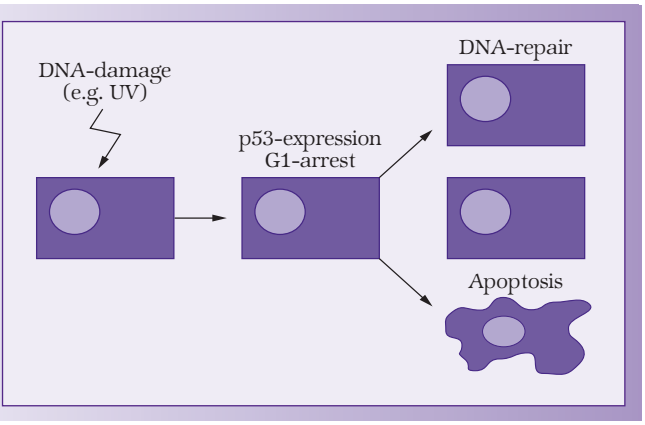

Figure 6: DNA integrity: the role of p53.

Inactivation of tumour suppressor genes as p53 and Rb represent crucial steps in tumour progression and metastazation. Molecular biology has provided some insight into the events underlying tumour suppressor gene inactivation. The loss of one allele either inherited or aquisited through carcinogen exposition usually represents the first of two hits. Subsequent mutational events may inactivate the remaining allele. Since Rb and p53 are involved in cell-cycle regulation, a functional loss of the gene products increases the speed of G1/S transition, thus resulting in an increased cell proliferation.

In bladder cancer, functionally impaired Rb and p53 gene products, as well as an altered expression of WAF1/p21, are frequently observed, suggesting that insufficient cell-cycle regulation is involved in tumour progression.[7,8,10–17,18] Based on these considerations, genes involved in cell-cycle regulation appear to be interesting candidate genes to provide information on the tumour biology and to be used as prognostic marker molecules (see Chapter 7), but they could also serve as therapeutic targets for future gene therapy.[19–21]

Apoptosis

An altered regulation of the programmed cell death (apoptosis) is another way to overcome the physiological balance between cell proliferation and cell death. Several previous investigations have shown altered apoptotic rates in bladder cancer tissue.[22–24] Key genes regulating apoptosis are the

pro-apoptotic bax gene and the anti-apoptotic genes bcl-2 and bcl-X. Gazzaniga *et al*. investigated these genes in a series of normal bladder tissues and tumours of different stage and grade by RT-PCR technique.[25] They observed a correlation of bcl-2 expression with tumour stage while the expression of bax was decreased in bladder cancer. Bcl-X, only found in the large isoform bcl-XL, was variably expressed in the different tumour stages. These observations suggest a putative role of these genes as predictors of tumour recurrence and tumour progression.

Ye *et al*. studied the correlation between bcl-2 and bax expression and early recurrence in 43 patients with superficial bladder after resection and intravesical chemotherapy.[26] A bcl-2/bax ratio of greater than and less than 1 was found in 50% of the relapsing patients, but only in 11% of the patients without tumour recurrence within one year after initial TUR. Interestingly, the bcl-2/bax ratio correlated with immunohistochemical p53 accumulation, suggesting a crosstalk among bcl-2, bax and p53, potentially affecting drug-induced apoptosis and regulating resistance to chemotherapy.

Angiogenesis

In the 1970s, Folkman *et al*. showed that new capillary blood vessels are necessary for a cancer to expand beyond a diameter of 2mm.[27] Therefore, neovascularization is a prerequisite for both the progression of the primary tumour and for the growth metastatic lesions. This process is designated as tumour angiogenesis. The quantitative determination of angiogenesis, microvessel density, has been demonstrated to be a useful prognostic parameter in a variety of tumours, e.g. in prostate and bladder cancer, thus underlining the role of angiogenesis in tumour progression.[28–31]

New vessel growth is tightly regulated by angiogenic stimulators, such as vascular endothelial growth factor (VEGF), fibroblast growth factors (FGFs) and angiogenic inhibitors, such as thrombospondin-1 and angiostatin. Recently, Crew *et al*. demonstrated a correlation between urinary VEGF levels and tumour recurrence in superficial bladder cancer (Figure 7).[32]

Thrombospondin-1 is an extracellular matrix glycoprotein which has been shown to be a potent angiogenesis inhibitor. The correlation between tumour recurrence and thrombospondin-1 expression has been studied by Grossfeld *et al.* in 163 patients with invasive bladder cancer.[33]

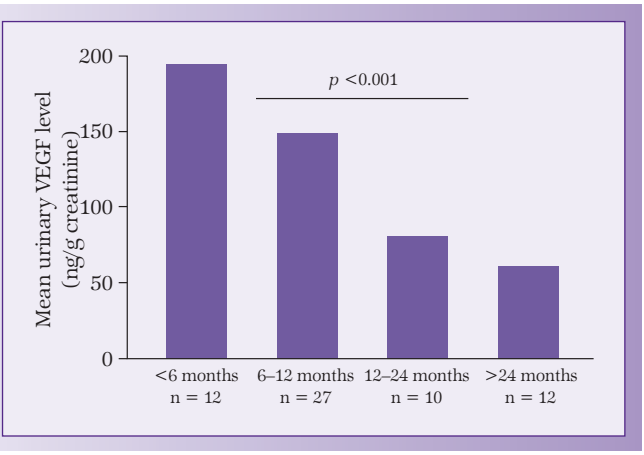

Figure 7: Urinary vascular endothelial growth factor (VEGF) as prognosticator of tumour recurrence[32].

Patients with low thrombospondin-1 expression had higher recurrence rates and decreased overall survival compared to those with moderate or high expression. Interestingly, thrombospondin-1 expression remained an independent prognostic factor of tumour recurrence and overall survival in the presence of tumour stage and tumour grade. Thrombospondin-1 expression was significantly associated with microvessel density in this study but also correlated with nuclear p53 accumulation.[33] These results suggest that p53 may also affect tumour angiogenesis by regulating thrombospondin-1 expression.

With regard to these observations, molecules involved in tumour angiogenesis may not only be promising predictors of disease outcome, but also serve as interesting targets for gene therapy. As several angiogenesis inhibitors are currently investigated in a variety of solid tumours in phase I/II trials, these concepts approach clinical reality.[34]

Decreased cell adhesion

Decreased cell adhesion and motility of the tumour cell are other fundamental requirements for the aquisition of invasive properties. Selectins, integrins and cadherins are those substances responsible for cell/cell contact and interaction. Thus, a subsequent loss of adhesion molecules will be associated with an increased capability of a given cell to leave the cellular formation and invade the surrounding tissue.

A group from Nijmegen in the Netherlands analysed the loss of E-cadherin expression in bladder cancer.[35] E-cadherin is a calcium-dependent adhesion molecule of the cadherin supergene family. According to the investigations by Bringuier *et al*. in 49 patients with bladder cancer, decreased E-cadherin expression is significantly correlated with tumour stage, tumour grade and survival in this series.[36] Further investigations revealed that the structural and functional integrity of the E-cadherin-catenin complex is important for cell adhesion. Besides an impaired E-cadherin expression, abnormal expression of α- or ß-catenin were found to be of prognostic relevance.[35,37]

In addition to a loss of adhesion molecules, the expression of motility factors may further contribute to mobilize the tumour cell from its surrounding. Otto *et al*. reported an inverse relation between E-cadherin and autocrine motility factor receptor (gp78).[38] The autocrine motility factor is a tumour-derived cytokine able to induce direct and randomized cell migration via a receptor-mediated signalling pathway.[39,40] In a retrospective analysis of 83 patients with bladder cancer, reduction of E-cadherin expression and increased gp78 staining were both significantly correlated with tumour progression.[38] Those patients with a reduction in E-cadherin concomitantly with an increase of gp78 expression (n=30) had a 71% risk of tumour progression and 32% of these patients died of disease at a median of two years after initial diagnosis. This contrasts to a 15% progression rate in those patients with normal E-cadherin/gp78 expression. These data underline the important role of cell adhesion and cell migration within the process of tumour invasion and metastazation.

Invasion

Tumour invasion requires destruction of the extracellular matrix in general, and particularly the degradation of the basal membrane. Laminin, a component of the basement membrane, is known to be sensitive to several proteases, including plasmin. Plasmin, a serin protease, is derived from its precursor, plasminogen, through the enzymatic action of urokinase, also termed plasminogen activator (uPA). In colorectal cancer, it was found that the degree of invasion was correlated with the amount of cell surface receptor-bound uPA (Figure 8). In-vitro experiments demonstrated that antibody-mediated inhibition of PA binding significantly reduced the invasive capacity of the tumour cells.

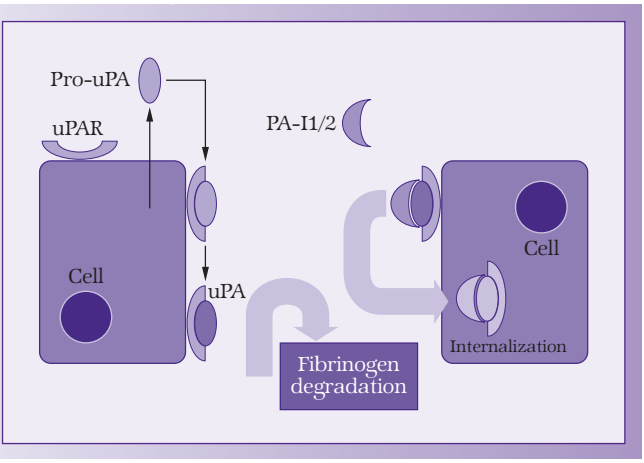

Figure 8: The interaction of plasminogen activator (uPA), plasminogen activator receptor (uPAR) and plasminogen activator inhibitors 1 and 2 (PA-1, PA-2) in the degradation of extracellular matrix proteins.

Also in bladder cancer, the plasminogen activator (uPA)/plasminogen activator inhibitor (uPA-I) system represents an important pathway in the protease remodelling of the microenvironment.[41] Hudson *et al*. demonstrated the different invasive and metastatic potential of bladder cancer cell lines according to their differences expressing uPA or the uPAR.[42] These observations were confirmed in a clinical trial by Hasui *et al*. in 52 patients with primary bladder cancer.[43] In this study, high uPA expression was found to be the most important risk factor as compared with tumour stage, grade, multiplicity and tumour size with regard to patient survival.

Metalloproteinases (MMP) represent another group of proteases used by the tumour cell to invade the surrounding tissue. MMPs belong to the superfamily of Zn^{2+}-dependent endopeptidases, having a broad spectrum of proteolytic activity for several components of the extracellular matrix. The expression of one the members of this family, type IV collagenase, is positively correlated with tumour grade in prostate cancer.[44] The activity of metalloproteinases is regulated through natural inhibitors, e.g. the tissue inhibitor of metalloproteinases (TIMP). In animal experiments, transfection of the TIMP gene into tumour cells yielded an inhibitory effect on the invasive and metastatic capacity of tumour cells expressing high levels of metalloproteinases.[45]

These finding are in contrast with observations by Kanayama *et al*. in 41 patients with bladder cancer examining the impact of the MMP-2/TIMP-2 system on patient prognosis.[46] Furthermore, the MMP-2 activator

membrane-type matrix metalloproteinase (MT1-MMP) was studied. Notably, it was found that high expression of all factors was significantly correlated with decreased survival. Although this underlines the relevance of the MMP/TIMP system for tumour progression, further investigations are required to obtain more insight into the complex interactions between the proteins involved in the degradation of the extracellular matrix.

Destruction of the extracellular matrix by the invasive tumour cell requires prior attachment to the target structures, e.g. the basal membrane. Within this context integrins appear to play an important role. Integrins are essentially receptor proteins, transmembrane glycoprotein heterodimers consisting from alpha and beta subunits. The composition of the heterodimer determines the component of the basal membrane to which the cell becomes attached. The α3,ß1-receptor recognizes an epitope of fibronectin, while other heterodimers would recognize other molecules, e.g. laminin. Increased integrin expression has been related to the malignant potential of a given tumour.[47]

Obviously degradation of the extracellular matrix after prior attachment e.g. to basement membrane components can be achieved through several pathways. Besides uPA/uPAR the cathepsin-D system is another option

Metastazation

Many factors are involved in tumour metastasis, with a decreased cell–cell adherence, an increased cell motility and the potential of tissue invasion being prerequisite for the metastatic process. Degradation of the basal membrane finally permits the tumour cell to enter lymphatic or blood vessels. Cell adherence to the capillary bed at the invasion site in the target organ, and migration into the perivascular tissue, are more or less the reversed process of cell invasion within the primary tumour.

Despite significant progress in the investigation of local tumour progress, the clinical observation of a preferential metastazation to tumour-specific target sites is still poorly understood. However, there is some evidence that the specific metastatic growth may be regulated through distinct carbohydrate ligands and their respective binding sites.[48] Buszello *et al*. demonstrated that carbohydrate-binding sites, mainly for Maltose and N-acetylgalactosamine, are present on the primary tumours and the respective metastases, but not in normal renal tissue.[49]

Shirahama *et al.* investigated the expression of binding sites of fucose-binding proteins in patients with invasive bladder cancer.[50] Overall, actuarial and cancer-specific survival was significantly worse in patients with strong expression of fucose-binding protein-binding sites. Furthermore, autopsies revealed that fucose-binding protein-binding sites were strongly expressed in all primary tumours and in most of the metastatic tissues.

Conclusion

It should be clear to the readers that the examples chosen and reported in this manuscript are far from being complete, but should rather highlight the complex molecular steps from transformation of a mucosal cell to metastasis. It is evident that we are still far from a complete understanding of carcinogenesis. However, it remains a major concern of the authors to demonstrate the fast progress of basic and translational research in disclosing the molecular pathways underlying cell transformation or tumour progression and to provide suggestions on how these findings can be used in the future clinical management of bladder cancer.

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Chapter 5

Staging: Past, present and future

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Introduction

Bladder cancer is a heterogeneous disease. The extent of this malignancy is highly correlated with its prognosis and with the options to treat it. Clinicians can only decide the appropriate therapy if they are informed as completely as possible how bladder cancer has affected the parent organ and its surroundings, the lymph nodes and the distant organs by possible metastases. Therefore an adequate staging system is necessary. Such a staging system should be adopted by a majority of clinicians, radiologists and pathologists. The system should provide clear-cut, standardized methodology for the classification of the extent of the disease. Only then is it possible to predict prognosis, to adequately decide treatment and to compare treatment results on an international basis. International clinical trial organizations such as EORTC (European Organization for Research and Treatment of Cancer) cannot perform their work without having an appropriate staging system.

The past

The first classification of bladder cancer was reported by Jewett and Strong in 1946.[1] Even in those days it was already noted that infiltration of bladder

cancer more than halfway through the muscle wall was associated with poor prognosis. This conclusion is still valid today.

Later on the TNM clinical classification was developed. The tumour, nodes and metastasis (TNM) system provide pre-treatment clinical staging by biopsy (transurethral resection), radiological techniques (IVU, ultrasound, CT-scan and MRI) and histopathologic staging. The TNM system has been accepted as the international staging system by European, American and Japanese investigators. The TNM classification has been modified substantially in the last two decades (1987, 1992 and 1997).[2] In total there have been five versions so far. Five International Bladder Cancer Consensus Conferences have been organized in 1983, 1987, 1989, 1993 and 1997 respectively, during which the modifications were discussed intensively.[3] It is expected that new modifications will be necessary in the future, especially with regard to the addition of molecular and serum markers as valid prognostic factors.

The present

The 1997 TNM classification (Table 1) was agreed upon by the American Joint Committee on Cancer (AJCC) and the Union Internationale Contre le Cancer (UICC).[2,4]

Substantial changes in the 1997 fifth edition, compared to the 1992 fourth edition were made.

This means that the classification for *invasive bladder* tumours was changed. For superficial bladder tumours and for the N and M categories of regional node and distant metastases no modifications have been made.

In the 1992 TNM system (Table 2), bladder tumours invading the bladder wall (*muscularis propriae*) were divided into T2, T3 and T4.

The assessment of the depth of tumour invasion is so crucial for the prognosis of the patient that this is recognized in a subdivision of T2 and T3 tumours in the 1997 version.

For the clinician it is important to know whether a bladder tumour is invasive and, if so, how deep. Similarities and differences between the 1992 and the 1997 version of TNM are as follows:

Table 1: Urinary bladder TNM classification (1997): rules for classification

The classification applies only to carcinomas. Papilloma is excluded. There should be histological or cytological confirmation of the disease.

The following are the procedures for assessing T, N, and M categories:

T categories	Physical examination, imaging and endoscopy
N categories	Physical examination and imaging
M categories	Physical examination and imaging

Regional lymph nodes

The regional lymph nodes are the nodes of the true pelvis, which essentially are the pelvic nodes below the bifurcation of the common iliac arteries. Laterality does not affect the N classification.

TNM clinical classification

T-primary tumour

The suffix (m) should be added to the appropriate T category to indicate multiple tumours. The suffix (is) may be added to any T to indicate presence of associated carcinoma *in situ*.

TX Primary tumour cannot be assessed
T0 No evidence of primary tumour
Ta Non-invasive papillary carcinoma
Tis Carcinoma *in situ*: 'flat tumour'
T1 Tumour invades subepithelial connective tissue
T2 Tumour invades muscle
- T2a Tumour invades superficial muscle (inner half)
- T2b Tumour invades deep muscle (outer half)

T3 Tumour invades perivesical tissue:
- T3a microscopically
- T3b macroscopically (extravesical mass)

T4 Tumour invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
- T4a Tumour invades prostate or uterus or vagina
- T4b Tumour invades pelvic wall or abdominal wall

N-regional lymph nodes

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single lymph node 2cm or less in greatest dimension

Table 1: *Continued*

N2 Metastasis in a single lymph node more than 2cm but not more than 5cm in greatest dimension, or multiple lymph nodes, none more than 5cm in greatest dimension
N3 Metastasis in a lymph node more than 5cm in greatest dimension

M-distant metastasis
MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

pTNM pathological classification
The pT, pN, and pM categories correspond to the T, N, and M categories.

G histopathological grading
GX Grade of differentiation cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3–4 Poorly differentiated/undifferentiated

Urinary bladder
Ta Non-invasive papillary
Tis *In situ*: 'flat tumour'
T1 Subepithelial connective tissue
T2 Muscularis
- T2a Inner half
- T2b Outer half

T3 Beyond muscularis
- T3a Microscopically
- T3b Extravesical mass
- T4a Prostate, uterus, vagina
- T4b Pelvic wall, abdominal wall

N1 Single ≤2cm
N2 Single >2–5cm, multiple ≤5cm
N3 >5cm

Table 2: TNM classification for invasive bladder cancer: version 1992.

T2 Tumour invades muscle (superficial)
T3a Tumour invades muscle (deep)
T3b Tumour invades through bladder wall
T4a Tumour invades prostate, uterus or vagina
T4b Tumour invades pelvic or abdominal wall

- Muscle invasion: T2 versus T1 (unchanged)
- Invasion in innerhalf or outerhalf detrusor: T2a versus T2b (previously T2 versus T3a)
- Extravesical extension: T3a and T3b (previously T3b).

Accuracy of staging

Staging of bladder cancer is performed by a combination of modalities: transurethral resection (TUR), bimanual palpation before and after TUR, radiological imaging techniques and pathohistological examination.

Despite these combinations and the improvement of all methods available, the inaccuracy of staging in bladder cancer is 30–50%.[3] This is especially true in those patients for whom bladder preservation is pre-empted. Once the cystectomy specimen and the removed lymph nodes after radical cystectomy are available, the staging and grading is much more complete and reliable.[5] However, in many cases, radical cystectomy is avoided and patients are treated by radiation therapy, chemotherapy or combinations, whether or not preceded by a thorough, full-thickness TUR.[5] In these cases only biopsy material is available and not the whole tumour.

Role of TUR

Although it is possible to remove macroscopically papillary tumours which are superficial (Ta, T1), it is known that in many cases a second TUR reveals that tumour has been left behind after the first operation.[6] A muscle-invasive tumour might or might not completely be removed by a TUR. Theoretically a T2a tumour invading the superficial part of the bladder muscle wall could be removed completely. Resecting an invasive tumour requires the skill of an experienced urologist. Accurate pathologic staging requires the delivery of adequate separated samples of the exophytic part of the tumour, the 'invading' part of the tumour, and in some cases the perivesical part tissue to the pathologist.

However, in the urological community there is no consensus on how deeply a bladder-invasive tumour should be resected. If the urologist is inclined to perform the latest state-of-the-art treatment, radical cystectomy, he will not undertake a 'radical' TUR, risking bladder perforation and

cancer dissemination. In such cases the pathologist might be able to diagnose muscle-invasive cancer, but s/he will not be able to distinguish between superficial or deep invasion (T2a versus T2b). Furthermore s/he will not be able to distinguish between extravesical extension (T2b versus T3a), and such distinctions are crucial for the patient's prognosis.[5]

The distinction between T1 and T2 tumours is much easier because here the surgeon can provide easier reliable samples to diagnose correctly.[7] If no radical cystectomy is planned, the patient is availed of a full-thickness TUR for correct staging, as well as the chance to make the bladder sparing therapy successful.[8] The more tumour tissue that is resected, the more successful the adjuvant therapy will be.

Bimanual palpation

The role and significance of bimanual palpation is controversial. At the 4th International Consensus Meeting on Bladder Cancer, some investigators indicated that ultrasound or CT-scan was more accurate than bimanual palpation under loco-regional or general anaesthesia.[9] Others, taking into consideration the low sensitivity and specificity of imaging techniques, have emphasized that bimanual palpation before and after TUR might help in correct staging and predicting the prognosis of the patient.[10] The findings of bimanual palpation depend on how complete the resection of an invasive tumour has been performed. Furthermore it is clear that, as for digital examination of the prostate, bimanual palpation of bladder tumours is a subjective method of investigation, certainly less reliable in obese patients and in those who have had previous abdominal or pelvic operations resulting in scarring of the abdominal wall.

Ultrasound

Bladder tumours can be visualized by abdominal, transrectal or transurethral probes. Of these, transabdominal ultrasound is used most frequently.[11] Subject to the individual skill of the radiologist, the overall sensitivity and specificity is 90% and 76% respectively. Superficial papillary tumours are overstaged in 24% and T2 tumours are understaged in 10%. Nearly 30% of tumours extending beyond the bladder are not detected by

ultrasound.[11] Scars in the bladder wall caused by previous TUR procedures increase false positive assessments. Most investigators do not rely on ultrasound in the staging of bladder tumours.

CT-scan

Computed tomography (CT) is used by many investigators once the diagnosis of invasive (≥T2) bladder cancer is made. It is of no relevance for superficial bladder tumours. However, CT-scanning has not proved to be very accurate for staging for invasive bladder tumours either.[12]

Up to 67% of T1 tumours are incorrectly overstaged, 30% of T2 tumours are understaged and 20% overstaged. False results may be expected if the CT-scan is made just after transurethral resection because inflammation and oedema of the bladder wall cannot be distinguished from tumour. CT-scanning is also performed for the detection of pelvic lymph node metastases.[13] Although enlarged pelvic nodes (≥2cm) can be detected, it does not mean that the enlargement is caused by lymph node metastases *per se*. The TUR procedure causes inflammatory reactions which are reflected to the pelvic nodes, as with the site of the primary tumour.

MRI

Magnetic resonance imaging (MRI) has advantages over CT-scanning (these advantages are extensively reviewed by Barentsz in Chapter 6). Separation of tumour and healthy tissue is more accurate, and images are possible in multiple planes. In the hands of experts, MRI might be very successful in staging, but this expertise in not available in daily practice in most clinics, and so most clinicians currently do not feel that MRI is highly superior to CT.[14]

It can be concluded that although the TNM classification allows the use of multimodal techniques to provide correct staging, this staging is limited by the accuracy of the techniques used. In addition to this there remains criticism on the classification itself.

Urologists are not satisfied with the TNM classification of bladder cancer involving the prostatic urethra, prostate ducts and the prostate

stroma.[5] Transitional cell cancer may develop in the prostatic area as the lining of the prostate consists of urothelium. However, invasive bladder tumours developing in the bladder neck or trigone may grow continuously into the prostate. Many investigators support the view that the staging of transitional cell cancer arising in the prostatic ducts and urethra or invasion in the prostate stroma from these sites should be separated from those neoplasms invading the prostate by direct extension from the bladder.[15] The TNM system does not allow for this distinction, although the prognosis is considerably different. Transitional cell cancer involving the prostate is currently classified either as a prostate cancer or as a urethral cancer and is not mentioned specifically in the TNM system. The issue above remains controversial and should be subject to consideration when the next TNM version is discussed.

The future

Reviewing the therapeutic results of patients treated for invasive bladder cancer during the last half of the 20th century, the outcome is rather disappointing. This is due in part to incorrect staging.

Despite the improvement of surgery, imaging and post-operative care, about 50% of patients with invasive bladder cancer have died after five years. Improvement of radiation therapy, the use of neo-adjuvant and adjuvant chemotherapy and the combinations of these have not created a major step forward. Prognostic factors derived from clinical, histopathologic and imaging techniques are apparently not able to distinguish sufficiently the 'good' from the 'bad' cancers.

Molecular markers, such as p53, bcl-2, Ki-67, RB and p21 have been added to the diagnostic tools.[16] It is believed that they represent for a major part the true identity and behaviour of bladder cancer. At the 5th International Consensus Conference on Bladder Cancer in 1997 it was felt that p53 has already been showed to have prognostic impact and should be incorporated in the next TNM system.[3] The current problems with the molecular markers are twofold.

Using different thresholds and determination methods' results are not comparable and more standardization is needed. Although proven to be successful in the hands of some investigators, these markers have not been tested using large cohorts of patients in randomized prospective clinical trials.

Once validated, it is expected that molecular markers will have to be added to the TNM system. Consequently patients will benefit from a more refined TNM system in the future.

It is expected that staging will improve in the future. This improvement will come from basic research, clinical investigations, imaging techniques, clinical trial organizations, and national and international urological societies. To combine their findings and views, international consensus conferences, like the five so far held for bladder cancer, will be needed, not only for bladder cancer but for all other malignant urological tumours as well.

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Chapter 6

Magnetic resonance imaging

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Introduction

In the Western world, the most frequently encountered pelvic diseases are neoplasms. Urinary bladder and prostate cancer are the most common diseases of the male pelvis seen by radiologists. This paper focuses on these diseases. MR (magnetic resonance) imaging is the most promising technique in visualizing these tumours, and the emphasis of this paper is on this imaging modality.

Urinary bladder carcinoma

Benign tumours of the urinary bladder are rare, more than 95% of all bladder neoplasms are malignant.[1] These lesions are rarely encountered even in large radiological practices.

About 90–95% of urinary bladder malignancies are transitional cell carcinomas, and 5–10% consist of squamous cell and adenocarcinoma. The remainder include sarcomas, metastasis from other primary tumours, and urachal adenocarcinomas. In children, embryonal rhabdomyosarcomas are the most common bladder neoplasm. About two-thirds of the malignant tumours are superficial and are usually papillary. One-third of the tumours show infiltration in or beyond the muscular layer of the bladder wall.[2,3]

Bladder cancer is responsible for 4.5% of all new malignant neoplasms and 1.9% of cancer deaths in the United States. In 1993, approximately 52,000 new cases were registered in the United States. The mortality was about 10,000. Malignant tumours of the bladder are predominantly seen in the sixth and seventh decade of life, however, increasing numbers of patients under 30 years of age present malignant bladder disease. These malignancies occur more commonly in males than in females, with a ratio of about 4:1.

Because the bladder is the most common location of urinary tract, radiologists are frequently called on to participate in the diagnostic work-up and staging of patients with bladder cancer. Appropriate use of the different available imaging techniques is crucial for an accurate assessment of prognosis and for the development of appropriate treatment planning. In this chapter, clinical aspects, including staging, treatment, and prognosis of patients with urinary bladder cancer, will be described.

As MR imaging is the most accurate imaging technique, its role will be reviewed and illustrated. The appearance on MR images of the normal urinary bladder and carcinoma will be shown. Patient handling, the choice of pulse sequences, and contrast agents will be discussed. The role of MR imaging in staging urinary bladder carcinoma will be evaluated and compared with clinical staging and CT-scanning. Finally, future developments, such as new sequences, the role of surface coils and MR-guided biopsy will be considered. Also, the preferred radiological approach will be discussed.

MR anatomy

The bladder wall has, as does skeletal-muscle, an intermediate signal on T1-weighted images. On T1-weighted images the urine has low signal intensity, whereas the perivesical fat has high signal intensity. As urinary bladder carcinomas have intermediate signal intensity, as does muscle on T1-weighted images (Figures 1a, 1b and 1c), these are used for determination of tumour infiltration in the perivesical fat, and to show the endoluminal tumour component. T1-weighted images are also suitable for imaging lymph nodes, which have a signal intensity lower than the surrounding fatty tissue. However, normal and abnormal lymph nodes show no difference in signal intensity. Lymph nodes are considered to be pathologically enlarged, but in round nodes the shortest axial diameter

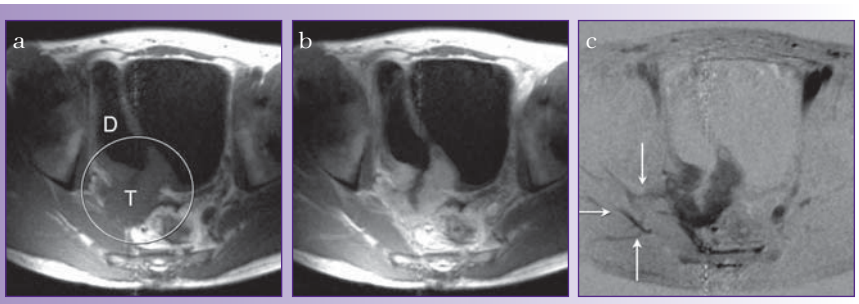


Figure 1: Patient with bladder diverticulum (D) and invasive cancer (stage T4B). (a) Axial T1-weighted GRE image shows tumour extending into the perivesical fat (circle). (b) Same image two minutes post-contrast injection shows more enhancement of tumour compared to wall. (c) Subtraction of a and b shows tumour enhancement in between the pelvic muscles (arrows). This infiltration is not visible on the T2-weighted images (see Figure 4). Reprinted with permission from Springer Verlag.[10]

is 8mm or more, and in oval nodes the axial diameter is 10mm or more (Figures 2a, 2b, 3a and 3b). Also, an asymmetrical cluster of small lymph nodes should be considered pathologic. Bone marrow metastases have signal intensity equal to the primary tumour, and thus are best recognized on T1-weighted images, on which there is a good contrast between these metastases and the surrounding fatty bone marrow.

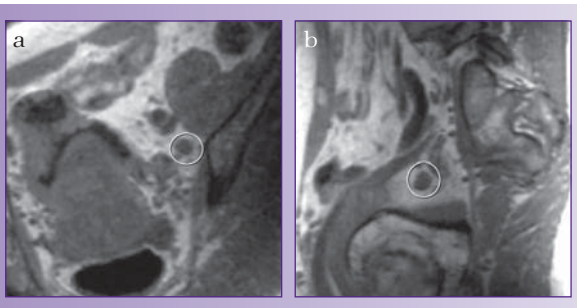


Figure 2: Three-dimensional MP-RAGE in round enlarged lymph node metastases. Three-dimensional MP-RAGE reconstructed images in (a) angulated sagittal plane, and (b) angulated axial plane perpendicular to long-axis of node show nodal size to be 1.1 x 0.9 x 0.9mm (circle) which is pathologically. Surgery confirmed metastasis. A node is considered pathologically enlarged if an oval node has minimal axial diameter of 10mm or more, and/or if a round node has a minimal axial diameter of 8mm or more. A node is round when the longitudinal axis/short axis ratio is more than 0.8 (see Figure 3). Reprinted with permission from Springer Verlag.[10]

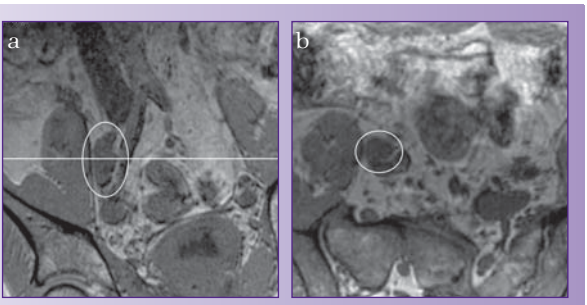


Figure 3: Three-dimensional T1-weighted MR images in oval enlarged lymph node metastases. Three-dimensional MP-RAGE reconstructed images in (a) angulated coronal and (b) angulated axial plane, perpendicular to long-axis of node (presented by line in a), allows nodal size evaluation in three dimensions (size = 3.2 x 1.3 x 1.2mm, circle). Also shape of node can be determined. Surgery confirmed metastasis. Reprinted with permission from Springer Verlag.[10]

On T2-weighted images, the bladder wall has low signal intensity. Perivesical fat has low or high signal intensity, depending on the type of T2-weighted sequence used. Urine has high signal intensity (Figure 4). Bladder cancer has intermediate signal intensity, which is higher than bladder wall or late fibrosis and lower than the urine. T2-weighted images are used for determination of depth of tumour infiltration in the bladder wall, to differentiate tumour from late fibrosis, to assess invasion into the prostate, uterus or vagina, and to confirm bone marrow metastases seen on T1-weighted images.

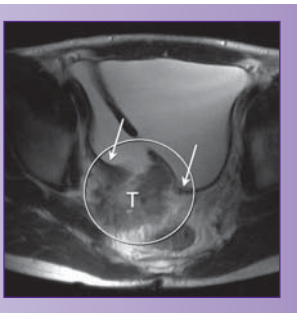


Figure 4: Same patient as in Figures 1a, 1b and 1c. On axial high-resolution T2-weighted MR images disruption of the normal low signal intensity bladder wall is present (arrows), which argues for at least deep muscular invasion of the wall. Also there is invasion in the perivesical fat. Reprinted with permission from Springer Verlag.[10]

Contrast agents

Urinary bladder carcinomas develop neovascularization, therefore this malignant tumour shows on contrast-enhanced MR images early and more enhanced compared to normal wall.[4] As urinary bladder cancer enhances to a greater extent the bladder wall and most surrounding structures, contrast enhanced T1-weighted images facilitate determination of muscular invasion and perivesical tumour extension. However, differentiation between post-biopsy tissue and malignancy remains difficult when using slower techniques, that is, one image every 30 seconds.

Fast, dynamic MR imaging, using at least one image every two seconds, provides the best separation between post-biopsy effects and urinary bladder cancer.[5] With this technique, early enhancement of urinary bladder cancer can be displayed. The enhancement of urinary bladder starts about six seconds after arterial enhancement, which is about four seconds earlier compared to other, benign tissues, such as post-biopsy tissue. When the beginning of enhancement is used as a criteria, the accuracy in differentiating post-biopsy effects from tumour improves from 80–90%, and staging accuracy from 67–84%.[5] This fast technique also facilitates visualization of early enhancement of metastatic lymph nodes and bone marrow metastases (Figures 5a, 5b, 5c and 5d).

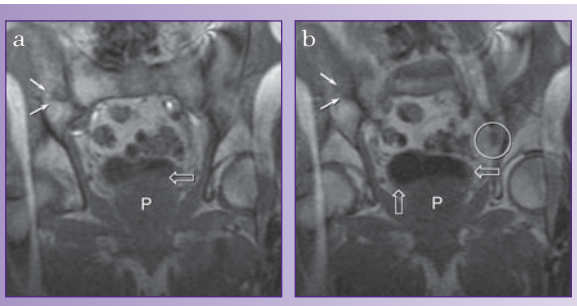
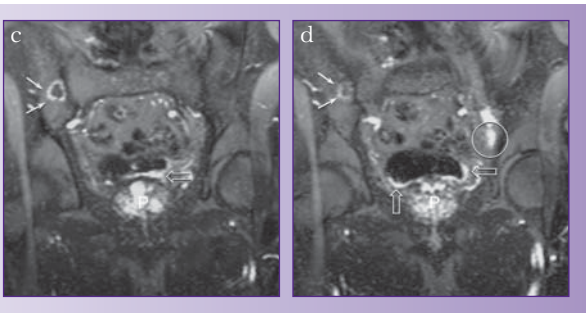


Figure 5: Patient with invasive bladder cancer (stage T3B), with nodal and bone marrow metastases. (a) and (b) Coronal T1-weighted fast Flash images show enlarged prostate (P), enlarged node (circle) and bone marrow lesion (arrows). Also thickening of bladder wall (open arrows). (c) and (d) Dynamic images (identical to a and b) acquired eight seconds after beginning of arterial enhancement is projected in red. Bladder tumour (open arrows), enlarged node (circle), and bone marrow lesion (arrows) show early enhancement, which argues for malignancy. Very ring-like enhancement of bone marrow lesion is highly suggestive for metastasis, and can be recognized on both slices. Histology and follow-up confirmed nodal and bone marrow metastases. Reprinted with permission from Springer Verlag.[10]

Figure 5: *Continued*



Staging

Local tumour extension, the degree of lymph node and distant metastases, and the histologic tumour type largely determine treatment and prognosis. Therefore, exact staging is imperative. To determine local tumour extension (T), presence of lymph node (N) and distant metastases (M) the Union Internationale Contre le Cancer (UICC) proposed a uniform clinical staging method (Table 1, Figures 6a and 6b). As well as this classification the American Jewett-Strong classification is used.[2]

In superficial tumours, that is, tumours without muscle invasion (Ta and T1), patients are treated with local endoscopic resection followed by adjuvant intravesical installations. Attempts will be made to cure patients with a tumour invading the muscle layer of the bladder wall or with only minimal perivesical extension (T2a–T3a) by radical cystectomy and lymphadenectomy. However, if the tumour is in an advanced stage (T3b–T4b), or if there are nodal or distant metastases, the patient will receive palliative chemo- or radiation therapy.

As clinical staging is not reliable to determine tumour extension beyond the bladder wall, other methods are needed. CT-scanning is a valuable addition, but since the introduction of pelvic MR imaging in 1983, several reports have attested to the superiority of this technique for staging urinary bladder carcinoma.[1–3]

MR imaging appears to be superior to CT scanning for staging carcinoma of the urinary bladder. Multiplanar imaging allows better visualization of the bladder dome, trigone and adjacent structures, such as the prostate and seminal vesicles. The accuracy of MR imaging in staging bladder cancer varies from 73–96%. These values are 10–33% higher than those

Table 1: TNM classification and Jewett-Strong staging system for urinary bladder cancer

Jewett-Strong	TNM	Histopathological findings
O	T0	No tumour
O	Tis	Carcinoma *in situ*
O	Ta	Papillary tumour, confined to epithelium (mucosa)
A	T1	Tumour invades subepithelial connective tissue (*lamina propria*)
B1	T2a	Tumour invades superficial muscle (inner half)
B2	T2b	Tumour invades deep muscle (outer half)
B2	T3a	Tumour with microscopical invasion of perivesical fat
C	T3b	Tumour with macroscopical invasion of perivesical fat
D1	T4a	Tumour invades surrounding organs
D1	T4b	Tumour invades pelvic or abdominal wall
D1	N1–3	Pelvic lymph node metastases
D2	M1	Distant metastases
D2	N4	Lymph node metastases above the bifurcation

obtained with CT-scans.[6] Several reports have recently been published on the staging of urinary bladder carcinoma with the use of IV-Gadolinium contrast. A 9–14% increase in local staging accuracy has been reported using these contrast agents. Furthermore, when using contrast agents,

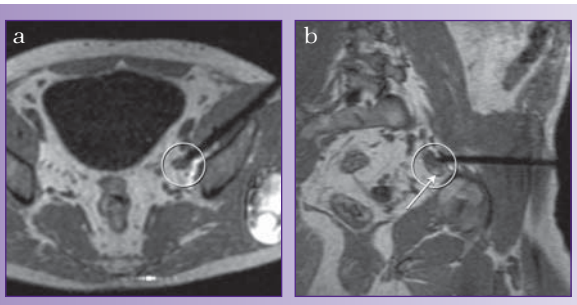


Figure 6: MR-guided nodal biopsy. Patient with lymph node metastasis. (a) Axial and (b) semi-sagittal T1-weighted three-dimensional MP-RAGE images during MR-guided biopsy. Needle is visible as black line. Tip of needle is situated at edge of enlarged node. On b, internal structure of node can be recognized. Caudal a small area of high signal intensity (arrow) represents fat in node. Biopsy at this site would have resulted in false negative finding. Now needle was directed more cranially and biopsy was positive. Reprinted with permission from Springer Verlag.[10]

visualization of small tumours (>7mm) will be improved. Best staging results using IV-Gadolinium contrast material are obtained with very fast T1-weighted sequences.[4,5] This can be explained by earlier enhancement of tumours compared to surrounding tissues. Although contrast-enhanced MR imaging has advantages over the use of unenhanced T2-weighted sequences, such as higher signal-to-noise ratio and shorter acquisition time, it is advised not to skip the T2-weighted images. Large prospective studies in this regard are necessary.

The role of MR imaging in nodal and bone marrow staging will be discussed below, together with prostate cancer.

In summary, based on published reports and our own experience, Table 2 offers an overview of the value of the several staging techniques for urinary bladder carcinoma.[2,3,6,7] MR imaging and clinical staging complement each other. MR imaging is the most accurate technique for differentiating the various stages of deeper infiltrating tumours (stages T2 and higher), whereas clinical staging is the best technique for differentiating

Table 2: Accuracy of different staging techniques

Stage	*Clinical staging including transurethral resection*	*CT*	*MR imaging*
T0–T+	++	–	+
Tis–Ta	++	–	–
Ta–T1	++	–	–
T1–T2a	++	–	0
T2a–T2b	0	–	+
T2b–T3a	–	–	–
T3a–T3b	–	++	++
T3b–T4a	–	+	++
T4a–T4b	–	+	++
N0–N+	–	+	+
M0–M+	–	0/+	++

Note:
M+ = bone marrow infiltration
T0 = no malignancy, e.g. scar, fibrosis, granulation tissue, hypertrophy
T+ = malignancy
++ = highly accurate + = accurate 0 = not accurate – = not possible

between acute oedema, early granulation tissue, and the various stages of superficial tumours (stages Ta and T1). When MR imaging is available, CT-scanning is no longer needed.

Future developments

Technological improvements are being introduced rapidly. With the new generation MR-scanners, faster sequences with a higher resolution can be applied. With the new MR-units it is possible to perform a high-resolution T1-weighted 3D MP-RAGE sequence with isometric voxels (1.4 x 1.4 x 1.4mm) in five minutes. Also, ultra-fast, multislice dynamic imaging becomes possible. At present, seven slices can be made with a time resolution of two seconds, allowing evaluation of urinary bladder cancer and its metastases with high specificity at multislice. The high signal-to-noise ratio, obtained with new phased array-coils, facilitates the use of a fast T2-weighted sequence with a 1024 x 1024 matrix. For evaluation of the extent of muscle invasion, the combination of an external with an endorectal-phased array-coil and these sequences seems promising.

Fast dynamic imaging

The behaviour of urinary bladder cancer after IV injection of a Gd-containing contrast agent as documented with fast dynamic MR imaging and time-images are a reflection of its neovascularity. Microvessel quantification is reported to be an independent predictor of survival in patients with invasive bladder cancer and might be useful in selecting those who would benefit from adjuvant therapy.[8] Fast dynamic MR imaging is more accurate compared to conventional unenhanced MR imaging in the follow-up of chemotherapy.[9]

MR guided biopsy

MR imaging has advantages over other imaging modalities for biopsy guidance. As MR imaging is a three-dimensional imaging technique, it facilitates multiple-angulated biopsy and can best be performed under MR-guidance. A good example in bladder cancer is the three-dimensional visualization of (enlarged) lymph nodes and the subsequent MR-guided biopsy (Figure 7). In a preliminary study we performed MR-guided biopsies in 13 patients with slightly enlarged nodes, and in 10 of them biopsy was true positive.[9]

Another advantage of (contrast-enhanced) MR imaging is the higher specificity and sensitivity in showing urinary bladder cancer and possible metastases compared to ultrasonography or CT-scanning. Based on the enhancement pattern of the tumour, with MR-imaging, the part of the tumour that contains the most pathologic vessels, and thus the most viable part of the tumour, can be localized and biopsied. At present specially designed MR-units are being developed in order to simplify localization under MR-guidance and to reduce biopsy time. With regular MR-machines, biopsies must be performed in the way it is done with CT-scanning. Special non-magnetic needles are available, but efforts must be made to further reduce susceptibility artifacts of these needles.

In the near future fast, high resolution, dynamic contrast-enhanced MR imaging of the urinary bladder will further improve the diagnosis, staging and follow-up of patients with urinary bladder cancer. Therefore, this technique will be used more and more frequently in these patients. MR-guided biopsy will contribute to a less invasive diagnosis, resulting in better treatment planning.

Preferred radiological approach

At present, MR imaging is the first mode of choice in imaging the urinary bladder and its cancer. However, due to limited resources in the healthcare system, this technique should only be used to obtain information that directly influences therapeutic management and outcome. To achieve this, the expertise of both urologists of MR imaging and radiologists of clinical handling is needed. Therefore, continuous education and communication between these two specialities is vital.

Detection of bladder cancer should be performed by cystoscopy and histology. Once bladder cancer is diagnosed, the following step should be staging. For superficial tumours, clinical staging, which includes transurethral resection, is the best technique. In addition, an IVU can be performed to rule out multifocal carcinoma in pyelum or ureter. Superficial tumours, without muscle invasion (stages Ta-T2) are treated with local endoscopic resection with or without adjuvant intravesical installations. Follow-up will be performed by means of repeated cystoscopy every three to six months. No further radiological imaging is needed in these patients.

If, however, there is muscle invasion, further staging should be performed with MR imaging. Attempts will be made to cure patients with

muscle invasion (stages T2a and T2b), perivesical infiltration (stages T3a and T3b) or invasion into prostate, vagina or uterus (stage T4a) by radical cystectomy and lymphadenectomy. In cases of pelvic sidewall or abdominal wall infiltration (stage T4b), or metastases in pelvic lymph nodes or bone marrow, palliative chemo- or radiation therapy will be given. Follow-up of these therapies can be best monitored with fast dynamic MR imaging.

Acknowledgement

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Chapter 7

Prognostic factors

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Introduction

Bladder cancer is a heterogeneous disease with considerable variations of its natural history, with five-year survival rates ranging from 97–98% of a monofocal, well-differentiated and small papillary tumour to 0% of an invasive bladder cancer extending throughout the bladder wall and with gross nodal metastases.[1] Among superficial bladder cancers, tumour recurrence after initial therapy varies from 30% in patients with a solitary papillary tumour to more than 90% in patients with multiple tumours.[2] Most tumours recur in six to 12 months but remain non-invasive and pose little risk to the patient.

The desire to predict which superficial bladder cancer will recur or progress to invasive cancer, and which invasive bladder cancer will metastatize has lead to the evaluation and identification of several prognostic factors. In this chapter we will provide a contemporary review of invasive bladder cancer prognostic factors related to the tumour, the host as well as the environment: a particular emphasis will be on the effective role in the clinical practice.

Classical prognostic factors

For many years ittle data, and of that unreliable data has been available about the factors predictive in survival of invasive bladder cancer. The major part of the published series has evaluated small patient cohorts undergoing different therapeutic modalities in a non-contemporary setting and with unsatisfactory statistical methods. More recently the problem has been

clarified by two wide-ranging studies.[3,4] A large and non-contemporary series of patients encompassing 21 years was retrospectively evaluated to establish a hierarchy of predictive variables of cancer specific survival. On multivariate analysis only tumour stage and grade, nodal involvement, positive surgical margins and patient age at surgery were independent predictors of poor cancer specific survival in the Frazier series.[3] Different results have been reported by Bassi *et al*. in a homogeneous cohort of patients undergoing radical surgery at a single institution as monotherapy for bladder cancer.[4] Only tumour stage and grade were independent predictors of survival; other variables, such as age at surgery, sex, tumour grade, perineural, lymphatic and vascular invasion, ureteral obstruction and previous superficial bladder cancer history were shown to be unable to predict the prognosis.

The anatomical extent of the tumour, or the depth of wall invasion, is universally accepted as the most important prognostic factors from large patient series. The five-year survival ranges from 70% for T2 tumours to 10% for T4 tumours. The prognosis is substantially related to the presence of organ confined or extravesical disease respectively.[3–7]

Nodal involvement has been universally associated to a poor outcome.[3–12] Nodal involvement is an independent predictor of survival in patients with invasive bladder cancer.[4,8,11,12] Furthermore, the prognosis of invasive bladder cancer is directly related to the extent of the nodal involvement, namely the number and size of the positive nodes. Patients with N1 disease seem to benefit from pelvic node dissection and radical cystectomy, as evidenced by similar outcome in those with node negative disease and similar P stage of the primary tumour. However, the observed benefit quickly disappears when more than one node is involved. Additional therapy, other than surgery, seems appropriate in the latter group.

The presence of obstructive uropathy has been reported by some authors as an ominous prognostic factor, but in a most recent series the independent predictive value of such variable hasn't been confirmed.[4,13]

Positive surgical margins have been shown in the Frazier series to be associated with a poor outcome and to be an independent predictor of survival.[3] No further information about this important finding is available in the literature.

Transitional cell carcinoma encompasses more than 90% of all bladder cancers. The remaining proportion of patients have pure squamous cell carcinomas or adenocarcinoma, rarely mixed histotypes.[14] Even though

a direct relationship between tumour extent and survival has been demonstrated for such histotypes, no reliable information is available regarding the comparative impact of histological type on outcome.[15,16]

Tumour differentiation, namely grade, has been considered an important prognostic factor for invasive bladder cancer for several decades. Several reports claim grade to be also an independent predictor of survival.[17–19] Bassi *et al.*'s recent series on a homogeneous cohort of patients undergoing radical cystectomy as a definitive and single treatment for invasive bladder cancer clearly showed that grade is a significant prognostic factor at the univariate analysis but without independent prognostic value at the multivariate analysis.[4] This observation is explained by the fact that in all the major published literature most of the invasive bladder tumours have been graded 3, according to WHO classification.[4,14,19]

Newer prognostic factors

Next to tumour properties and the former history of an individual patient, which can be recorded easily, a more sophisticated procedure may be used to evaluate the likelihood of recurrence or progression by DNA ploidy measurement, immuno-histochemical staining of the basement membrane components, evaluation of cell adherence molecules, growth factors, proteases, cell surface antigens and blood group antigens, as well as by the determination of cell-cycle related proteins in bladder carcinoma. All of these are experimental and none have reached clinical significance or become part of clinical routine.

Aneuploidy, as determined by FCM, has been associated with decreased survival in both low- and high-stage transitional cell carcinoma, although the correlations are better and more consistent for low-stage tumours.[20] Aneuploidy correlates well with histological grade and with lymph node metastasis.[20] Nuclear morphometry, an image analysis technique for evaluation of nuclear shape, correlates with metastasis.[21]

One potential option is to estimate the proliferative activity of tumour cells as an indicator of prognosis by cell-cycle-related proteins such as Ki-67 and PCNA (proliferating cell nuclear antigen). These proteins are detected in higher stage tumours and are associated with reduced survival, although this association is stronger with lower stage (Ta/T1) than invasive bladder cancers.[22–24] This may also be accomplished by specific labeling of S-phase cells with bromodeoxyuridine. Unfortunately, these sophisticated

techniques have added little further prognostic information than that obtained from standard prognosticators.[20,24]

Cell division is regulated by cell-cycle-associated proteins, including cyclins and their associated kinases. Loss of regulation of proliferation is an early and essential step in cancer development. Several genes and gene products associated with regulation of the cell-cycle have been the subject of recent intensive investigation. Two of these, the p53 and Rb tumour suppressor genes have been shown to be important prognostic factors for patients with bladder cancer.

The retinoblastoma tumour suppressor gene was the first such gene identified through the study of patients with retinoblastoma. Inactivation of the Rb gene is thought to be an important step in bladder cancer progression. The results of two small studies have suggested that loss of expression of the Rb protein may be of prognostic significance in transitional cell carcinoma of the bladder. Logothetis *et al*. studied 43 patients with locally advanced bladder cancer (T2–T4a) and found that patients whose tumours had lost Rb expression had a shorter three-year survival ($p=0.01$) suggesting that loss of Rb expression is a prognostic factor in patients with advanced cancer.[25] Cordon-Cardo *et al*. reported that patients with muscle-invasive bladder tumours that had lost Rb expression had a shorter five-year survival ($p=0.001$) than those patients whose tumours expressed normal Rb protein.[26]

The p53 tumour suppressor gene mutations are thought to be the most common genetic defect in human tumours.[27] This protein has an important role in preventing cell-cycle progression by delaying cell division, allowing time for DNA repair. Molecular analysis has shown that abnormal nuclear accumulation of p53 protein in bladder tumours, as detected by immunohistochemical staining, correlates closely with gene mutations detected by DNA sequencing.[28] Large series have shown that abnormal p53 expression is found more frequently in higher grade and higher stage bladder tumours and is a predictor of poor outcome.[29,30] Mutations in p53 have been associated with progression of superficial bladder cancer.[31–35]: Sarkis *et al*. showed that progression of patients with Ta, T1 and CIS correlated with p53 mutation.[31] Nuclear over-expression of p53 was an independent predictor of death from bladder cancer for patients with CIS and T1 tumours.[31,38] P53 status has been evaluated as a predictor of response to BCG in patients with superficial bladder cancer.[34] Although pre-treatment p53 over-expression was an independent predictor for

progression, it did not predict response to BCG. However, in patients with residual disease after BCG treatment, post-therapy p53 over-expression was predictive of disease progression. Esrig *et al.* investigated the role of p53 over-expression in 243 patients treated by radical cystectomy for transitional cell carcinoma of the bladder, and found that p53 over-expression was the sole independent predictor of relapse (75% versus 40%, $p<0.001$) in the entire cohort.[29] When patients were stratified by stage, nuclear p53 accumulation was associated with an increased risk of disease for patients with stage pTl, pT2 and pT3a, but was not significant for stage pTa or extravesical disease (pT3b, pT4 or lymph node metastasis). Lipponen investigated the role of p53 over-expression by immunohistochemistry in 212 patients treated by a variety of different modalities, and found a 29% incidence of p53 mutations in the entire cohort.[30] Over-expression of p53 protein was an adverse prognostic factor in patients with muscle-invasive disease. However, p53 over-expression was not an independent prognostic factor and provided no more predictive information than could be obtained from tumour stage and mitotic index.

Both p53 and Rb have been evaluated as predictors of response to therapy for muscle-invasive bladder cancer. Pollack *et al.* recently re-evaluated the role of pre-operative radiation therapy in patients with stage T3b transitional cell carcinoma.[35] They found that p53 mutations predicted a poor response to pre-operative radiation, while Rb status was the only independent predictor of response to radiation. Logothetis *et al.* looked at the prognostic significance of Rb status in patients with advanced transitional cell carcinoma treated with MVAC chemotherapy and cystectomy: in this study altered Rb expression predicted a poor response to therapy.[25] Sarkis *et al.* conducted a similar analysis and evaluated the significance of altered p53 expression in patients with muscle-invasive transitional cell carcinoma treated with neoadjuvant MVAC.[36] They reported that patients with p53 mutations had a significantly higher proportion of cancer deaths, so that p53 mutations predicted a poor response to MVAC chemotherapy. However, Cote *et al.* presented conflicting results related to p53 expression and response to chemotherapy.[37] In their study, p53 mutations predicted a positive response to chemotherapy.

An alternative pathway to disrupt p53 function without mutation of p53 is through amplification of MDM2, which inhibits the function of p53 and may contribute to progression in tumours that are immunohistochemically negative for p53. Amplification of the MDM2 gene or over-expression of its

product has been reported in some bladder cancer tissues.[38,39] Although Lianes *et al*. suggest that this pathway may be more important in low stage tumours, Habuchi *et al*. hypothesize that this pathway is involved in genetic instability and oncogene expression in higher stage tumours.[40,41] Further work is necessary to clearly identify the role of MDM2 in bladder cancer progression.

P21 is a negative cell-cycle regulator transcriptionally regulated by p53 that also prevents the inactivation of Rb. Abnormal immunohistochemical staining of p21 is reported to be a risk factor for progression of TCC in patients with wild type p53 expression.[42]

Interestingly, two preliminary reports examining the prognostic importance of the combination of altered p53 and Rb expression suggest that patients whose tumours exhibit both p63 and Rb dysfunction have the poorest prognosis, and patients whose tumours exhibit dysfunction of one gene have an intermediate prognosis.[43,44] Although it is impossible to predict which tumours with mutations in both genes will progress, no tumours that had wild type p53 and Rb expression progressed. These results suggest that mutation of the p53 and Rb genes have independent and synergistic roles in the development of bladder cancer.

Recently, two other genes, p15 and p16, which encode proteins that also regulate the activity of cyclins, have been studied in bladder cancer.[45] These two genes are localized to chromosome 9, at 9p21, and are putative tumour suppressors which may be lost early in the pathogenesis of TCC.

Neoangiogenesis, the neovascularity associated with tumours, may facilitate the transition of cells from the local tumour bed into the circulation, resulting in metastasis.[46] High tumour vascularity in invasive bladder cancers was reported to be a strong predictor of lymph node metastasis and an independent prognostic indicator for survival in two other reports conveying a 2.5-fold greater risk of dying of bladder cancer for those patients with high microvessel counts.[47–49] However, there are conflicting reports in the literature regarding the prognostic value of vascular density in bladder cancer. Babkowski *et al*. evaluated the prognostic significance of microvessel density in 54 patients with stage T1 bladder, and found that vascular density did not correlate with prognosis using any of the three antibodies.[38] The risk of progression to metastatic disease was relatively low in this study, compared to those in which microvessel density was found to be prognostic. Therefore this study does not eliminate the possibility that microvessel density could be a marker for metastasis in bladder cancer.

Specific antibodies to cell surface antigens from human bladder cancer have been produced. Two of these antibodies, developed by Fradet *et al.*, M344 and I9A211, are expressed preferentially on low-grade transitional cell carcinoma.[39] One or both of these markers are present on approximately 80% of low-grade, non-invasive TCC, and approximately 10% of muscle-invasive tumours. Their presence may enhance the detection of bladder cancer, in combination with cytology. The expression of both these markers has been associated with an increased recurrence rate. Two other antibodies developed by Fradet's group are the T138 and the T43 antibodies.[50] These antibodies preferentially react with higher stage tumours and in several studies of locally invasive bladder cancer have shown some prognostic value.

Loss of expression of blood groups A, B and H antigens in bladder cancer have long been recognized as prognostic indicators for patients with bladder cancer.[51–53] However, in carefully performed studies, the loss of ABO antigens was found to be relatively common and provides no prognostic information.[51–53] More recently, a group of antibodies reactive with the Lewis X blood group determinant have been studied, including 486 P3/12, and E7.[52] These antibodies were useful for detecting recurrence in low-stage bladder cancers, with a reported sensitivity of 81% and a specificity of 86%. The Thomsen-Friedenreich (T) antigen is another blood-group antigen that is expressed in bladder cancers but not in normal urothelial cells.[53] The T antigen is associated with recurrence in low-stage bladder cancers, but offers no prognostic information for invasive bladder cancers.[53,54]

E-cadherin, an epithelial cell adhesion molecule associated with differentiation, is lost in many types of cancers.[55] E-cadherin appears to act as a tumour suppressor. Several recent reports have shown an association between a decrease in E-cadherin expression at the cell border and increased bladder cancer stage.[56] In two of these studies, decreased E-cadherin expression was also associated with a poorer survival rate.[57,58]

Integrins function as receptors for extracellular matrix proteins.[59] Liebert *et al*. noted a progressive loss of a2ß1 expression with increasing bladder cancer stage.[60] This finding could result in a loss of cell–cell adhesion similar to E-cadherin loss. The loss of a2ß1 expression was observed in low-stage bladder cancers, suggesting that the loss of this expression occurs early in bladder cancer progression. The expression of another member of the integrin family, the a6ß4 heterodimer, is associated

with a basal anchoring structure in normal epithelial tissues, including the urinary bladder.[61] However, in invasive bladder cancer, the association between a6ß4 and the anchoring structure is lost. In many cases the a6ß4 integrin is over-expressed, suggesting that the cancer cells use this receptor to move through the basement membrane.

The epidermal growth factor receptor (EGFr) is found on most epithelial cells, including transitional cells. Clinically, over-expression of EGFr correlates with tumour stage and is associated with a poor prognosis, especially for lower stage bladder cancers.[62–64] In a subset analysis, Neal *et al.* found that EGFr did not predict survival for patients with higher stage tumours.[64] Similar results in high-stage tumours were obtained by Lipponen *et al.*, whose observations, combined with observations that high levels of EGFr are observed in normal-appearing urothelium distant from the tumour, suggest that increased expression of EGFr is an early event and may occur in pre-cancerous cells or is supported by changes in the bladder environment.[24,63]

The c-erb-B2 oncogene encodes a cellular surface protein. However, many bladder tumours that show strong staining for the c-erb-B2 product do not have gene amplification. Several studies report that high expression of c-erb-B2 protein is associated with higher stage increased metastasis and poorer outcome.[65–67]

Fibroblast growth factors (FGFs) are a large family of polypeptide growth factors, and contribute significantly to the induction of angiogenesis by their effects on endothelial cell migration and growth.[68] Since angiogenesis correlates with poor prognosis in bladder cancer, it is expected that expression of FGFs in the urine would be valuable predictors of disease state. Furthermore, FGFs affect many cell types, and treatment with FGFs induce a highly motile, fibroblastoid cell type in a rat bladder cancer epithelial cell line.[69] Two members of the FGF family, FGF-1 (acidic FGF) and FGF-2 (basic FGF) have been identified in the urine of patients with bladder cancer.[70–72] Levels of expression of FGF-2 correlated with higher stage and metastasis. Patients with higher stage tumours were more likely to have a positive urinary test for FGF-1.[70] Bladder cancer cells in tissues were also shown to express FGF-1: a greater number of high-stage tumours expressed FGF-1 and expression was also related to metastasis.[70–72]

Since penetration of the basement membrane is thought to be an essential step in the progression of bladder cancer, expression by cancer

cells of enzymes capable of destroying the basement membrane should correlate with metastasis. Several families of proteases have been evaluated in bladder cancers.[73,74]

One group of proteases are the metalloproteinases that degrade collagen IV (also called type IV collagenase or MMP2 and MMP9). Slightly contradictory results were obtained in two reported studies. In the first, the urinary levels of 72 kilodalton type-IV collagenase (MMP2) were found to be higher in patients with invasive cancers, and immunohistochemical staining revealed that the tumour cells were producing collagenase.[69] In contrast, in the other study, both the 72 and the 92 kilodalton type-IV collagenases were studied.[74] Again, increased levels were observed in invasive bladder cancers, but *in situ* localization showed that stromal cells produced the collagenase.

A second type of protease, the urokinase plasminogen activator (uPA), is a serine protease that is associated with fibrinolysis. Presence of active uPA may activate other cellular components, including metalloproteinases, and may also directly contribute to matrix degradation. Low-stage bladder cancers with low expression of uPA had significantly better survival that high expressors, although these differences were not independent of grade.[75]

A final group of proteases, the cathepsin family of cysteine proteases, has been the subject of preliminary analysis in bladder cancer. The T24 invasive human bladder cancer cell line showed high level of expression of cathepsin B, while the non-invasive human bladder cancer cell line RT4 had low expression.[76] However, in a clinical study of cathepsin D expression in bladder cancers, Dickinson *et al.* observed the opposite association: a decreasing expression of cathepsin D with increasing bladder cancer stage; invasive bladder tumours expressing cathepsin D had a better outcome than those not expressing it.[77,78] Cathepsin D expression was not an independent predictor in multivariate analysis. The authors noted that normal urothelium expressed high levels of cathepsin D, and that loss of expression might be related to loss of differentiation in higher stage tumours.[78]

The intact basement membrane, composed of collagen-IV, proteoglycans, laminin and other extracellular matrix components, presents a physical barrier to tumour cell invasion and metastasis. The dissolution of this barrier is one pathologic criterion for disease progression. Although the presence of the basement membrane may be evaluated in routine

histological staining, advanced techniques to specifically identify the integrity of this barrier may be useful in determining invasion. A number of investigators have evaluated immunohistochemical staining for extracellular matrix components of the basement membrane, including collagen-IV and laminin.[79–81] In general, increasing defects in basement membrane integrity are noted with increasing stage of tumour. Daher *et al.* noted the development of gaps in collagen-IV in the basement membrane, and divided their patient cohort into two groups based on intact or defective collagen-IV.[80] Of the invasive bladder cancer patients in this study, 29 were observed for a three-year follow-up period. Of the 16 evaluable patients with intact collagen-IV, 11 were still alive at three years; of the 13 patients with defective collagen-IV, none were alive at three years. These data suggest that even within high-stage tumours, evaluation of basement membrane integrity may be of prognostic significance. Laminin immunohistochemical staining has also been used to evaluate basement membrane integrity.[81] Disrupted basement membrane laminin was associated with metastasis. This same group detected the presence of laminin p1, a laminin degradation product, in the blood and urine of patients with invasive cancers.[82] The blood tests were neither highly sensitive nor discriminatory.[81,82] Of the non-cancer patients, 31% showed a positive result, and of bladder cancer patients, 57% of those with intact basement membrane were positive while 82% of patients with interrupted basement membrane were positive. The urine tests showed promise for following patients with invasive bladder cancers, demonstrating 58% sensitivity, 96% specificity and 87% positive predictive value.[82] Unfortunately, no follow-up of these patients was provided.

Host-related prognostic factors

In nearly all populations, men are 2.5–5.0 times more likely to develop bladder cancer than women. Incidence of bladder cancer rises monotonically with age: the disease is rare prior to age 35 and two-thirds of the cases occur in people aged 65 or older.[1,83]

There is a marked racial-ethnic variation in bladder cancer incidence: in the United States, non-Latino white men show the highest incidence of bladder cancer among all races. Their rate is twice that for Latino and African-American men, and 2.5 times higher than males in the Chinese and Japanese-American community. A similar pattern is observed in women,

even though within race the male rate is about 3–4 times higher than the female rate.[83,84]

As far as hereditary bladder cancer is concerned, numerous case reports document the clustering of transitional cell carcinoma in families, several of which demonstrate an extremely early age of onset of disease, which argues in favour of a genetic component to familial transitional cell carcinoma. The results of large epidemiological studies also suggest the existence of familial bladder cancer, and first-degree relatives appear to have an increased risk for disease by a factor of 2: familial clustering of smoking does not appear to be the cause of this increased risk. However, further studies are required to identify candidates' genes that may be responsible for this form of bladder cancer.[1,85]

Age has been reported as a prognostic factor of outcome in superficial and invasive bladder cancer.[17] Contradictory results have been observed in two large patient series treated with radical surgery.[3,4] Also, performance status has been shown to be an ominous variable of survival in patients undergoing systemic chemotherapy for advanced bladder cancer.[86] No reliable information on this variable has been reported in patients undergoing definitive surgical therapy for invasive disease: in fact, in such cases the anaesthesiological risk has been taken more frequently into account. Finally, anaemia has been found to be an adverse prognostic factor in patients treated with radiation therapy for muscle-invasive bladder cancer.[87,88] The opposite has been reported in surgically treated bladder cancer.[4]

Environment-related prognostic factors

Since the publication of a classic paper at the end of the 20th century postulating the higher incidence of bladder cancer among aniline dye-workers, multiple occupational, environmental and genetic factors have been identified: chemical dye exposure, 2-naphthylamine, 4-aminobiphenyl, benzidine, arylamines, cigarette-smoking, schistosomiasis, etc.[84,89]

Cigarette-smoking has been shown to be the single most important cause of bladder cancer. There is a good correlation between duration and severity of exposure to smoking and incidence of this tumour, and furthermore, continuing smokers experience worse disease-associated outcomes than quitters or ex-smokers.[90]

In contrast to Europe and the United States, in some regions of Africa schistosomiasis is the endemic bladder cancer and the most frequent tumour, with the majority of the patients being diagnosed with squamous cell carcinoma and one-third giving a history of bilharziasis.[16,84,89,91]

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Chapter 8

Surgical management

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Introduction

Surgery plays a major role in the treatment of all stages of invasive bladder cancer. The rationale for surgery in the case of invasive bladder cancer is based on the fact that the natural history of high-grade bladder cancer is to progressively invade through the lamina propria into the muscolaris propria, perivesical fat and adjacent pelvic structures.[1] Moreover, transitional cell carcinoma seems substantially resistant to radiation therapy, even though this therapeutical option hasn't been fully evaluated.[2,3] Finally, other treatment modalities, such as chemotherapy and bladder sparing techniques (partial cystectomy and/or extended transurethral resection), alone or in combination, seem not to provide the same results in terms of long-term disease-specific survival rate if compared to radical cystectomy, even though no comparative data in this regard are available.[2–6]

Partial cystectomy

The goal of bladder preservation, and partial cystectomy as a consequence, is to cure the cancer while maintaining a functioning bladder and the erectile function and continence with a less invasive procedure.[2]

Partial cystectomy remains a completely non-evaluated and controversial surgical option in the treatment of bladder cancer.[7] There have been no randomized studies in the literature comparing this form of surgical treatment, stage by stage, with current treatment modalities, mainly radical cystectomy. Most studies utilized partial cystectomy with no uniform indications, and incorporated a number of pre-operative and post-operative forms of adjuvant therapy (mainly radiotherapy), usually at the discretion of the surgeon and retrospectively evaluated patients undergoing this procedure at a specific medical centre over several decades by a variety of surgeons.[7] Some surgeons were relatively strict in their indications, while others included patients being treated with different indications.

While recognizing the inherent difficulties in analyzing studies using partial cystectomy in the treatment of bladder cancer, we attempted to summarize the data available to date.

Indications and contra-indications

Partial cystectomy is a questionable option for highly selected patients with a solitary, primary and invasive bladder cancer placed in a region that allows a complete excision with adequate margins (2cm) with proved absence of severe dysplasia or carcinoma *in situ* in the remaining parts of the vesical urothelium.[2,7,8]

Other reasons proposed for performing partial cystectomy included: inability to resect tumours adequately transurethrally because of their size or for adequate biopsy of radiation-induced ulcerations; the presence of tumour in a bladder diverticulum; tumour overlying ureteral orifice, necessitating ureteral reimplantation; palliation of severe local symptoms; patient refusal of urinary diversion; or a poor risk patient in whom urinary diversion was deemed inappropriate.[7,8]

Contra-indications that have been cited are the presence of multiple tumours, carcinoma *in situ*, prostatic invasion, or invasion of the trigone, the inability to resect with adequate margins, the need for ureteral reimplantation, prior radiation therapy, an inability to maintain an adequate bladder volume after resection, and evidence of extravesical tumour extension.[7,8]

Surgical procedure

A lower midline incision is used. The peritoneal cavity must not be opened in order to avoid intraperitoneal seeding during the procedure. The bladder

is then mobilized laterally, with ligation of the superior vesical boundle, if necessary, to expose a posterior tumour. Stay sutures are placed, and the bladder is opened; the tumour must be excised with a 2-cm margin. Ureteral reimplantation is recommended if necessary to obtain adequate margins, even though some authors consider this option a contra-indication to partial cystectomy. The full-thickness segment of bladder wall and tumour must be sent for frozen section to verify the tumour-free margins; then the bladder is closed in two layers. Transurethral catheter is left for bladder drainage, avoiding suprapubic tubes. Pelvic node dissection should complete the procedure.

Complications

Perioperative death has not been observed in several recent studies.[7–11] Common complications include myocardial infarction, pulmonary embolus, congestive heart failure, upper gastrointestinal haemorrhage, wound haematoma or infection, and significantly diminished bladder capacity.[7–12] Of additional note is the amount of functional bladder capacity remaining after segmental resection. As one of the cited goals of this procedure is to maintain physiologic bladder function, it is important to question the impact of the resection on normal micturition. Cummings *et al.* noted that 13% of their patients had a significant reduction in bladder capacity, 8% had significant irritative symptoms, and 3% ultimately underwent urinary diversion because of bladder dysfunction.[12] They also reported that this complication was observed more frequently in patients with multiple prior procedures involving the bladder or in those who had received adjunctive radiation therapy.[7–12]

Results

In their review, Sweeney *et al*. were able to demonstrate that only 6–19% of all patients with bladder cancer met the selection criteria for partial cystectomy.[7] In general, the overall five-year survival figures (Table 1) for patients submitted to partial cystectomy are quite similar to those of patients treated with radical cystectomy during their respective historical time periods.[7–12] Five- and 10-year survival rates were related to the grade and the stage of the tumour. Patients with grade I tumours had a 75–100% survival rate at five years, those with grades II and III tumours had 46–75% and 22–55% five-year

Table 1: Partial cystecomy and survival.

Reference	*Overall five-year survival*
Magri[10]	42%
Utz *et al*[9]	43%
Novack and Stewart[8]	50%
Evans[13]	59%
Long[14]	38%
Brannan[15]	58%
Resnick[16]	35%
Cummings *et al*[12]	60%
Cox[17]	42%
Merrell[18]	48%
Schoborg[19]	42%
Faysal[20]	40%
Lyndahl[21]	42%
Kaneti[22]	48%

survival rate respectively. Similarly, five-year survival rate decreased for increasing stages from 70–100% in the case of pTa cancers to 0–20% in the case of pT4 disease.[7]

Tumour implantation in the wound or suprapubic tract is the most dreaded complication, because it usually leads to the patient's death. Several studies report different wound recurrence rates.[7–12] However, it's clear that wound recurrence is associated to a dramatic outcome (Table 2). Transurethral drainage of the bladder alone and avoidance

Table 2: Partial cystecomy and wound recurrence.

Reference	*Wound recurrence*	*Five-year survival*
Magri[10]	11.5%	0%
Utz *et al*[9]	2%	0%
Novack and Stewart[8]	14%	0%
Peress *et al*[11]	11%	0%
Cummings *et al*[12]	1%	100%

Table 3: Partial cystecomy and local recurrence.

Reference	*Number of patients*	*With recurrence*
Magri[10]	102	22%
Merrel[18]	54	30%
Scholborg[19]	44	70%
Faysall[20]	117	78%
Resnick[16]	86	40%
Novack and Stewart[8]	50	20%
Lyndahl[21]	55	58%
Peress *et al*[11]	61	54%
Cummings *et al*[12]	101	49%
Kaneti[22]	56	38%

of a suprapubic tube post-operatively is highly recommended in order to minimize the risk of seeding the suprapubic tract.

The principal drawback of partial cystectomy is the higher rate of local recurrence (20–78%) (Table 3). Arund 50% of such recurrences appear in the first year and 75% by two years with a tendency for higher stage tumours to recur earlier than lower stage tumours.[7]

Radical cystectomy

Radical cystectomy is considered the standard treatment for muscle-invasive bladder cancer in the United States and Europe.[2,23] Radical cystectomy is indicated for suitable patients affected by bladder cancer invading beyond the muscolaris propria and those with superficial bladder tumours including TIS refractory to intravesical therapy.[2,24]

Surgical technique

This operation implies the en-bloc removal of the anterior pelvic organs: bladder with its peritoneum and perivesical fat, prostate and seminal vesicle in men, or the bladder, urethra, uterus, cervix, fallopian tubes, ovaries, anterior wall of the vagina and anterior pelvic peritoneum in women (the so-called 'anterior pelvic exenteratio').[25]

Intraoperatively the patient is positioned in a hyperextended supine position on the operative table with the legs abducted in a frog leg position or the modified lithotomic position if en-bloc urethrectomy is needed. A Foley catheter is placed in the bladder.

After a midline incision, the peritoneal cavity is entered above the umbilicus to consent the entire uracal remnant excision en-bloc with the bladder and the abdomen is carefully explored to rule out distant metastatic disease or any unrelated pathological abnormality. The parietal peritoneum is mobilized laterally off the inferior surface of the abdominal wall in a triangular form along the lateral umbilical ligament to the level of the vas deferent or round ligament in men and women respectively. Both ureters are dissected in the deep pelvis and divided in close proximity to the bladder wall in order to provide an adequate ureteral length; care should be taken to preserve the adventitia and surrounding tissue containing the blood supply to the distal ureter. Samples of the distal ureters should be sent to the pathologist for frozen section to assure tumour-free margins.

A lymphadenectomy is performed as the next step, although some urologists prefer to remove the bladder first and then perform the pelvic lymph-node dissection. The authors prefer this strategy so as to not lose any time in waiting for the frozen section of the ureter and the urethral stump. The lymphadenectomy is begun approximately 4cm distally to the bifurcation of the aorta. The dissection is extended laterally to the right and left genitofemoral nerves, removing all nodes surrounding the common, internal and external iliac vessels; the node of Cloquet, medial to the external iliac vein at the femoral canal is the distal limit of the dissection. Deep in the pelvis, the obturator fossa represents the posterior limit of the lymphatic dissection. The bladder is now retracted medially, exposing the lateral and posterior bladder pedicles. The first anterior branch off the internal iliac artery is the superior vesical artery, this is isolated and divided. The terminal branch of the internal iliac artery is the inferior vesical artery, which should also be divided. The complete dissection of the lateral bladder pedicles is then performed.

Subsequently, the bladder must be retracted anteriorly to obtain a good exposure of the Douglas pouch. The peritoneum is incised laterally to the rectum and in the mid-line over the rectal side to develop a plane between the posterior layer of Denonviller's fascia and the anterior rectal

wall. The rectum is then swept off the bladder, seminal vesicles and prostate in the man and the posterior wall of the vagina in the woman. Anteriorly the endopelvic fascia is incised (as in a radical prostatectomy) while the pubo-prostatic ligaments could be preserved if an orthotopic diversion is considered. Santorini plexus must be ligated before division of the dorsal venous complex. The levator ani is then bluntly dissected off the prostate and membranous urethra beyond the apex of the prostate. Urethra and Foley catheter are divided and if an orthotopic diversion is planned, the urethra is prepared as for a radical prostatectomy. The Foley catheter could be clamped, divided and retracted, the prostate is then peeled off the anterior surface of the rectum to the level of the prostatic pedicles, which are ligated and divided, and the specimen should be free to be removed from the pelvis. Frozen section of the urethral stump is recommended to assure tumour-free margins. In female patients, after division of the urethropubic ligaments, the vaginal incision is carried distal to the urethral meatus.

Complications

Radical cystectomy is considered a major surgical procedure.[25,26] The risk for a major complication with this procedure is about 5%, and the mortality rate is approximately 1–2.5% in the major series (Table 4). As a result,

Table 4: Mortality rates after radical cystectomy.

Reference	*Number of patients*	*Mortality*	*Diversion*	*Previous therapy*
Skinner[27]	531	1.9%	Contin.	xrt/cht
Montie[28]	229	0.4%	Contin.	xrt/cht
Frazier[29]	675	2.5%	Mixed	xrt/cht
Freiha[30]	100	2.0%	Contin.	No
Ghonheim[31]	185	0%	Contin.	No
Studer[32]	100	2.0%	Contin.	No
Benson[33]	73	1.4%	Mixed	n.s.
Elmajian[34]	295	1%	Contin.	xrt/cht

Table 5: Complications after radical cystectomy.

Complications		*Approximate incidence*
Minor	Ileus	12–20%
	Wound infection	2–7%
	Pneumonia	2%
	Mental status change	2%
	Urinary tract infection	1–3%
	Cardiac arrhythmia	1–2%
	Clostridium difficile colitis	1%
	Acute renal failure	1%
	Deep venous thrombosis	1%
	Intraoperative rectal injury	1%
	Ureterointestinal leakage	1–2%
Major	Return to operating theatre	2%
	Cerebrovascular accident	1%
	Sepsis	1%
	Respiratory failure	1%
	Pulmonary embolus	1%
	Myocardial infarction	1%
	Death	1-3%

Source: Cancer Control ©2002 H Lee Molfi tt Cancer Center and Research Institute, Inc.

various complications may occur during both the early and late post-operative period. It is important to know the factors that can increase the risk for complications: age, American Society of Anaesthesiologists score, pre-operative haemoglobin, smoking history, prior abdominal surgeries or external-beam radiation therapy, and type of diversion. Overall, the rate of minor complications for patients undergoing radical cystectomy is approximately 30% (Table 5).

Results

The significant improvements in clinical outcomes over the past 25 years can be attributed to advances in surgical technique and in medical and anaesthetic care.[23,25]

Overall, recurrence-free and survival rates vary among institutions.[25] Less than 50% of patients with locally advanced or node-positive bladder cancer will survive if treated by surgery (cystectomy) alone.[25,26]

Recently, Herr *et al*. reviewed a cystectomy series in over 2,000 patients.[35] The 10-year relapse-free survival rate was 77% with pathologic organ-confined tumours, 44% with extravesical tumours and 34% in cases with positive lymph nodes.

However, the larger series have agreed that higher pathological stage and increased lymph-node status are generally associated with increased recurrence rates and worse cancer-specific survival.[25,26,35–40] Overall, radical cystectomy for invasive bladder cancer offers an approximate 60–70% five-year disease-free survival rate.[26] Subdivided, this percentage can increase to higher than 70% for organ-confined lymph-node-negative bladder tumours and decrease to 40–50% for those patients with non-organ-confined lymph-node-positive bladder tumours (Figures 1 and 2).[26,36] This latter group consistently demonstrates higher rates for recurrence and worse survival compared to those with organ-confined disease.[25,26,35–40]

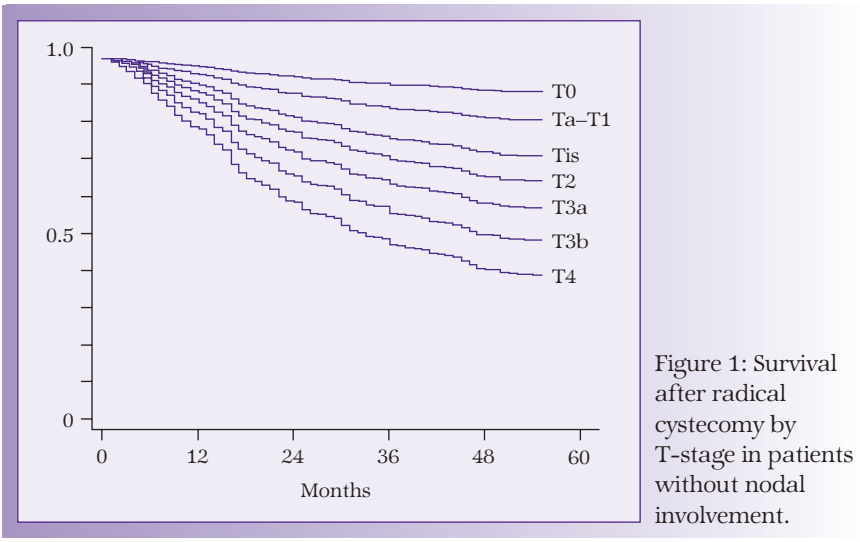

Figure 1: Survival after radical cystecomy by T-stage in patients without nodal involvement.

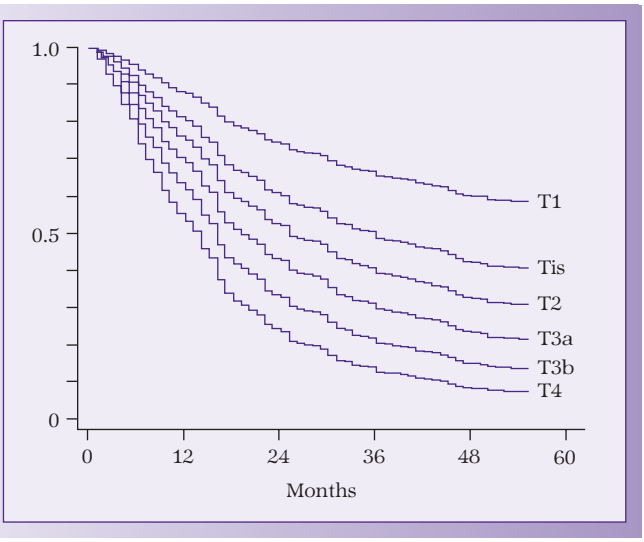

Figure 2: Survival after radical cystecomy in patients with nodal involvement.

Conclusions

Surgery remains a critical element in the management of bladder cancer.

Partial cystectomy, also known as segmental resection of the bladder, remains an incompletely evaluated surgical option in the treatment of bladder cancer of various subtypes.

Radical cystectomy, including lymphadenectomy, is the primary modality for the management of clinically localized invasive bladder cancer (stages T2/3). Radical cystectomy alone cures the majority of patients with invasive disease confined to the bladder, and a significant minority with locally advanced or node-positive disease, and only a few patients who survive five years after cystectomy will die of bladder cancer. Improvements in surgical technique, urinary reconstruction, and multimodal therapy continue to improve the prognosis and quality of life of patients with transitional cell cancer of the bladder.

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Chapter 9

Transurethral resection in patients with muscle-infiltrating bladder cancer

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Introduction

Radical cystectomy is the gold standard therapy for patients with invasive bladder cancer. However, in patients with locally advanced disease, survival is not completely satisfactory, promoting the development of combination therapies, and associating chemotherapy to cystectomy.[1,2] In patients with low local stages, radical cystectomy can be an overtreatment, according to the literature, where the absence of residual tumour (p0) on cystectomy specimens is around 12%.[3–6] This absence of residual tumour does not necessarily mean that patients are cured with cystectomy, however, as the five-year survival rate was 67% in Pagano's series.[4] This decrease in survival is essentially related to the development of distant metastasis due to the presence of micrometastasis at the time of cystectomy. Consequently, a p0 after cystectomy only means that the tumour was completely removed by transurethral resection (TUR) during the clinical assessment and patients were probably overtreated because cystectomy does not have any, or at least only minimal, impact on micrometastases.

Retrospective studies

In patients with invasive bladder cancer, the therapeutic value of TUR is controversial because of the limited possibilities of a complete tumour exeresis by this procedure and the unreliability of clinical staging.[4] Nevertheless, in uni- and multivariate analysis, a complete TUR, or the absence of clinical residual mass after TUR, is a good prognostic factor for patients included in bladder preservation programmes with radio-chemotherapy, as well as for patients treated with cystectomy after pre-operative radiotherapy or with radical radiotherapy.[7–11,12,13] This prognostic value of a clinically complete TUR suggests a potential therapy effect in patients with invasive bladder cancer.

In a retrospective study from western Sweden, Holmäng *et al*. reported that cystectomy was superior to TUR and to radiotherapy in patients with clinical stages T2–3 bladder carcinoma when tumour-related mortality is evaluated, showing rates of 56.6%, 75% and 81.8% respectively.[14] In this study, patients unfit for cystectomy were treated with TUR or radiotherapy, and, in some cases, these procedures were applied as palliative therapies, representing an important bias when these approaches are assessed in terms of therapy efficacy.

In another retrospective comparative study, carried out by Henry *et al*. on 114 patients with invasive bladder cancer, TUR achieved a better five-year overall survival rate than cystectomy or radiotherapy or pre-operative radiotherapy plus cystectomy (Table 1).[15] However, the combination therapy was slightly superior for patients with B2 stage.

Table 1: Therapies in patinets with invasive bladder tumours: retrospective studies[15].

		Five-years. Cause specific survival	*Five-years. Survival*	
Therapies	*No patients*	*General*	*B1 stage*	*B2 stage*
Transurethral resection	43	66%	63%	38%
Radiotherapy	16	31%	53%	11%
Cystectomy	15	40%	33%	25%
Pre-operative radiotherapy plus cystectomy	40	57%	48%	54%

Table 2: Invasive bladder tumours treated withTUR as initial montherapy: retrospective study.

		Five-years survival rate		
Authors	*No patients*	*General*	*B1 stage*	*B2 stage*
Flocks[18]	126	47%	56%	43%
Milner[20]	190	53%	57%	23%
Barnes[16]	114	40%		
O'Flynn[19]	123	52%	59%	20%
Barnes[17]	75	31%		
Henry[15]	43	52%	63%	38%

A literature review on retrospective studies of patients with invasive bladder cancer initially treated with TUR is displayed in Table 2. Although some patients were rescued with cystectomy after invasive recurrence, the five-year survival rate ranged from 31% to 53%, and this was particularly remarkable in patients with clinical stage B1.

In summary, as retrospective studies with no objective inclusion criteria, overall survival in these series is very variable, and sometimes not completely satisfactory. However, these results demonstrate that in a group of patients with invasive bladder cancer, it is possible to control the tumour with TUR as an initial monotherapy. Nevertheless, the problem is how to clinically identify patients in whom TUR is able to locally control the tumour, achieving a survival rate similar to patients with p0 after cystectomy, which should be the aim of TUR as a curative procedure. In this sense it is important to analyse the prospective studies.

Prospective studies

Two prospective studies have been published in the literature dealing with TUR as a therapeutic approach in patients with invasive bladder cancer. In the first study, Herr included patients in whom an initial complete TUR was performed, and a second endoscopical evaluation was carried out two to three weeks after initial TUR.[21] In this evaluation, patients had a negative urinary cytology and bimanual examination and no tumour in TUR-biopsies on scar tissues. Forty-five patients with invasive bladder

cancer were entered in this study, including 37 with clinical stage T2, seven with stage T3a and one with stage T4a. Among these patients, 21 (46.8%) developed superficial recurrence, 11 (24.4%) developed local progression, and two (4.4%) developed distant metastases with no bladder tumour. Eleven patients required cystectomy and seven (63.6%) of them were alive and free of tumour. The survival and bladder preservation rates in this series were 82% and 67% respectively. With a follow-up from three to seven years and a median of 51.1 months, these were excellent results and proved that, with a very strict inclusion criteria, radical TUR is able to control invasive bladder tumours, but it is necessary to know if these results are maintained with a minimum follow-up of five years.

The second prospective study was carried out by Solsona *et al*.[22] In this study, patients were assessed with bimanual examination, urinary cytology, and random biopsies on normal-looking bladder mucosa and prostate urethra, and they underwent an endoscopically complete and fractionated TUR. With this technique, three different samples are sent to the pathologist: first, the exofitic part of the tumour is removed; second, the endofitic part is removed until the tumour is completely resected and the muscular layer of the tumour bed is apparently clean; and third, several biopsies (more than five) are taken from the muscular layer of tumour bed and could-cup biopsies of perivesical fat – if this structure is reached, which is usual. According to this technique, the therapy scheme for patients with muscle-infiltrating bladder was as follows: 1) patients with residual mass after TUR in bimanual examination and those with positive biopsies of perivesical fat were excluded from this study and they underwent an immediate cystectomy; 2) those with positive biopsies on muscular layer were offered three courses of cisplatin-based chemotherapy in order to preserve the bladder or cystectomy; and 3) patients with negative biopsies on muscular layer of tumour bed were included in an observation programme with a very strict follow-up. In this follow-up, a second TUR on scar tissues was mandatory at the three-month evaluation.

With this inclusion criteria, 133 patients were included in the latter group. The median follow-up of this series was 83 months, all patients were followed for more than five years, and 59 (44.3%) for more than 10 years. The recurrence and progression rates are summarized in Table 3.

Only 26 (19.5%) patients died of tumour and the cause-specific survival rate was 80.5%. The bladder preservation rate was 75.2% and the overall survival rate with bladder preserved was 41%, as 48 (36%) patients died

Table 3: Recurrence and progression rates in 133 patients with invasive bladder cancer treated with radical TUR alone[22].

	No
No recurrence	61 (45.8)%
Superficial recurrence	35 (26.2)%
Progression	37 (27.7)%
Local invasion	27 (22.2)%
T>2, M1	3 (2.2)%
T0, M1	7 (5.3)%
Median follow-up (months)	83 (11–183)%

free from tumour, due to the long follow-up of this series. When analysing progression in patients with a minimum follow-up of 10 years, it was found that this essentially occurred during the first three years, an increase of 7% was observed up to the fifth year, and only one patient developed progression after five years (Table 4). Consequently, patients are at risk of developing progression during over a long time, but essentially during the first five years. After this period, the progression rate was 1.5% for patients at risk for progresssion.

As a result of these prospective studies, we can conclude that a group of patients with invasive bladder cancer can be treated with TUR alone, and the therapeutic effect lasts for more than five years of follow-up. More importantly, these patients can be clinically identified by performing a

Table 4: Recurrence and progression in 59 patients with invasive bladder cancer treated with radical TUR alone followed for more than 10 years[22,23,24].

	59 patients followed for more than 10 years		
	Follow-up > 3 yrs	*Follow-up > 5 yrs*	*Follow-up > 10 yrs*
No recurrence	30 (50.3%)	25 (42.4%)	21 (35.6%)
Superficial recurrence	14 (23.7%)	15 (25.4%)	18 (30.5%)
Progression	15 (25.5%)	19 (32.2%)	20 (33.3%)
Local invasive	10 (17%)	14 (23.7%)	15 (25.4%)
T>2, M1	2 (3.4%)	2 (3.4%)	2 (3.4%)
T0, M1	3 (5.1%)	3 (5.1%)	3 (5.1%)

second TUR with negative biopsies for tumour two to three weeks after an initially complete TUR, or with negative biopsies on the muscular layer of the tumour bed and on perivesical fat after a complete TUR.

Concerns

Regardless of the excellent results achieved by radical TUR in these prospective series, several concerns have been raised.

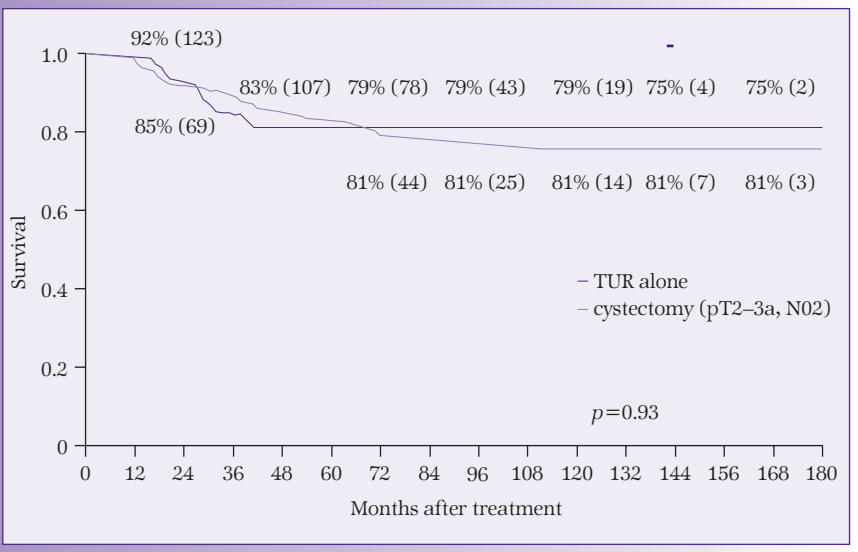
What cause-specific survival could have been achieved if patients had been treated with early cystectomy?

Obviously, an early cystectomy could have avoided most of local progression. However, regarding the pathological pattern of progression in our series, eight (88.8%) of nine patients with muscle-infiltrating bladder recurrence treated with cystectomy were alive and free of tumour. Only three (16.6%) of 18 patients treated with radiotherapy or palliative procedure were alive and free of tumour. These procedures were applied because patients refused or were unfit for cystectomy, therefore these patients would probably not have been treated with an early cystectomy. Seven patients who developed distant metastases with no bladder tumour would not have been rescued with cystectomy. Only three (2.2%) of patients who developed local progression with synchronous distant metastases could have received therapeutic benefit if an early cystectomy had been performed. However, this potential benefit would have been eliminated by the 5% mortality rate of cystectomy at that time. Moreover, in a comparative study assuming some bias, but with a very practical and clinical orientation, no significant difference was observed between the present series and patients treated with cystectomy and with pathological exam P2–P3a, N0-2, in terms of cause-specific survival (Figure 1).

What results could have been achieved with neo-adjuvant therapy to radical TUR?

One of the most important targets of neo-adjuvant chemotherapy, radiotherapy or combination therapy is to eliminate residual tumour after TUR. Considering residual tumour, when local invasive recurrence took place at the three-month evaluation, in Solsona's series the residual tumour rate was 6.7%. In radio-chemotherapy programmes, the five-year survival with bladder preserved rate is around 40%, and no survival improvement has been demonstrated in these programmes with regard to cystect-

Figure 1: Comparison between patients with invasive bladder cancer treated with radical TUR and those treated with cystectomy (pT2a-b, N0-2).



omy.[25–28] As a result of these figures, in Solsona's series the potential benefit, in terms of bladder preservation, would have been 2.6%, but almost all patients would have suffered unnecessarily the toxicity and side-effects of these aggressive treatments.

Could the inclusion criteria be improved?

There was great concern regarding the inclusion criteria of both prospective series as progression rates were 27% and 33.3%. Solsona *et al.* carried out uni- and multivariate analysis including clinical-pathological variables, taking as endpoints the true progression and understaging (residual tumour) (Table 5).[22]

In terms of true progression, the presence of bladder Tis was the only significant variable in multivariate analysis. However, this variable was clinically irrelevant as the biological behaviour of these patients was similar to patients with superficial bladder tumours associated to bladder Tis when they were evaluated with long-term follow-up. Consequently, both groups should be treated with the same conservative attitude. With regard to understaging, no variable was statistically significant, but a relation between size and morphology was noted. Stratifying variables, patients

Table 5: Multivariate analysis on predictive factors for progression in patients with invasive bladder cancer treated with TUR alones.

Variables	*True progression*	*Understanding*
Size (<3 / =/> 3 cm)	0.813	0.862
Age	0.791	0.652
Grade (G2/G3)	0.445	0.117
Morphology (papillary/sesil)	0.517	0.135
Number (unique/multiple)	0.968	0.532
Primary/recurrent tumour	0.694	0.25
Sex (male/female)	0.686	0.072
Bladder Tis (no/yes)	0.013	0.346
No recurrence/Ta-1 recurrence	0.104	

with tumour size of more than 3cm, and with solid morphology, had a close relation to understaging, reaching the limit of statistical significance. Therefore we should be very cautious when including patients for radical TUR alone with solid tumours of more than 3cm.

P53 overexpression was tested in a pilot study on 60 patients from Solsona's series. Among these patients, 10 (55.5%) out of 18 with p53 overexpression and 16 (38%) out of 42 with negative p53 developed progression. This difference was not statistically significant, and consequently p53 was not an important predictive factor for progression in patients who fulfil these inclusion criteria.

In summary, the inclusion criteria seem to be reliable, and to improve the survival of patients with invasive bladder cancer included in these prospective studies seems to be difficult with alternative or combination therapies.

Justification of the results in the prospective studies

It would seem that the excellent results achieved in the prospective studies were very surprising, with five-year survival and bladder preservation rates around 80% and 70% respectively. In trying to determine why this was, a comparative study between patients with negative biopsies of tumour bed (133 patients) treated with TUR alone, and those with positive biopsies treated with three courses of cisplatin-based chemotherapy (34

patients) or cystectomy (31 patients) was carried out by Solsona. The best cause-specific survival was achieved in patients treated with radical TUR alone, compared to those treated with more radical therapies, systemic chemotherapy or cystectomy (Figure 2).

The interpretation of these contradictory results was that both groups fulfilled the same inclusion criteria, only biopsies on the muscular layer of the tumour bed was the discriminating variable, and thus is probably an importan prognostic factor. To confirm this hypothesis, uni- and multivariate analysis was carried out (Table 6).

In univariate analysis, morphology, biopsies on tumour bed and therapy applied were the statistically significant factors. However, in multivariate analysis, biopsies on tumour bed were the only independent prognostic variable, corroborating our clinical suspicion. Therefore this factor defines two groups of patients, one of poor prognosis (patients with positive biopsies) and the other of good prognosis (patients with negative biopsies of tumour bed), regardless of therapy applied.

Thus in prospective studies, the key to good results achieved by radical TUR alone should be based on the inclusion criteria, particularly biopsies

Figure 2: Comparison between patients with negative biopsies (radical TUR) and those with positive biopsies (cystectomy or chemotherapy).

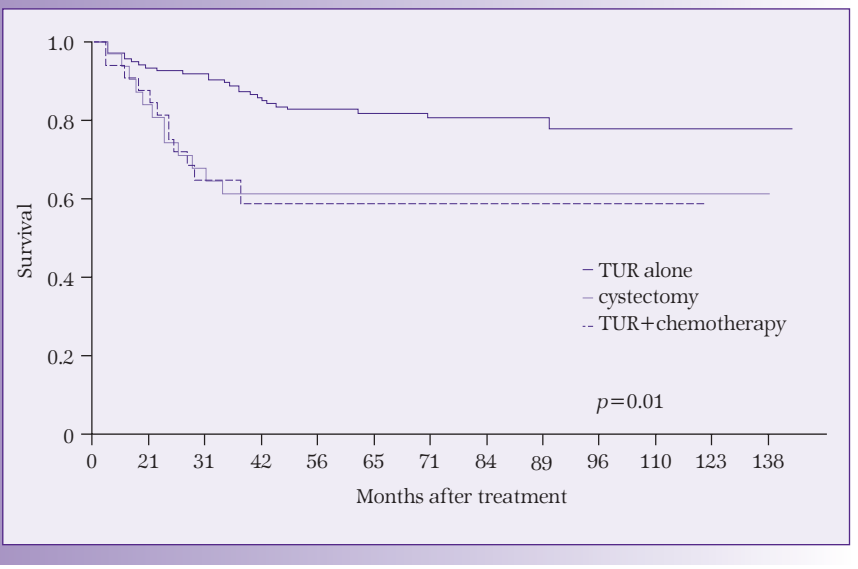


Table 6: Uni- and multivariate analysis on predictive factors for cause-specific survival in patients with invasive bladder cancer and positive or negative biopsies on tumour bed after radical TUR.

a) Univariate analysis

Variables	*p-value*
Recurrent (yes/no)	0.6903
Biopsies tumour bed (+/-)	0.0004
Age	0.9716
Grade (2/3)	0.097
Morphology (papillary/solid)	0.0452
No tumours	0.4284
Sex (male/female)	0.1381
Size	0.7421
Tis (yes/no)	0.3955
Therapy: TUR alone versus	
• TUR+chemotherapy	0.0007
• Cystectomy	0.0015

b) Multivariate analysis (cox's regression model)

Variables	*p-value*	*Expotential co-efficient*
Biopsies on tumour bed	0.0007	2.6423

on the tumour bed, which select a group of patients of good prognosis, and also confirm the radicality of the tumour exeresis accomplished by this procedure.

Comment

The importance of these prospective studies is that they have been able to clinically identify a group of patients with invasive bladder tumours of good prognosis, whose survival is approximately equivalent to patients with p0 in cystectomy specimens (Table 7). This select group of patients represents 21% and 19% of invasive bladder tumours in the MSKCC and in the IVO, during the observation period. Therefore, only a small and

Table 7: Five-years' cause-specific survival in patients with p0 after cystectomy and radical TUR (prospective studies).

Author	*No. Patients*	*Five-years cause-specific survival No*
Cystectomy:		
Mathur[29]	3	2 (67%)
Brendler[3]	13	12 (92.3%)
Pagano[4]	25	17 (67%)
Thrasher[31]	66	50 (75%)
Stein[30]	39	36 (92%)
Total	146	117 (80.1%)
Radical TUR:		
Herr[21]	45	37 (82%)
Solsona[22]	133	107 (80.9%)
Total	178	144 (80.9%)

carefully selected group of patients with invasive bladder cancer are suitable for TUR as a curative procedure.

In general, the philosophy of these inclusion criteria is to select patients with tumour limited to the muscularis propria in whom radical tumour resection can be performed, and not to perform an extended TUR, even in perivesical fat is involved (Figure 3).

In these cases, a more radical procedure, such as cystectomy or radio-chemotherapy, is mandatory. From a clinical point of view, patients with pathological T2 tumours are theoretically the most suitable patients for

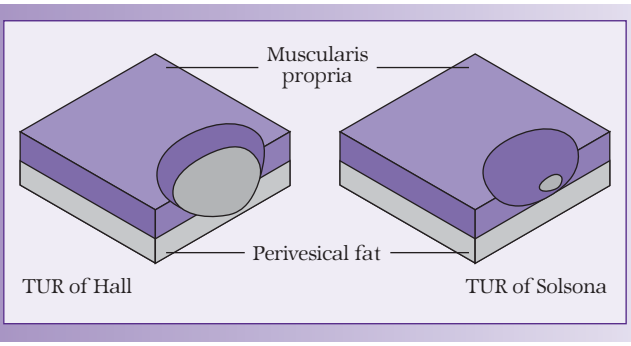


Figure 3: Radical TUR in invasive bladder cancer.

radical TUR as they have a good prognosis and it is feasible to perform a complete tumour exeresis. However, the unreliability of clinical staging makes it impossible to decide which patients are suitable for radical TUR, and it is necessary to resort to these inclusion criteria in order to select patients with tumour limited to the muscularis propria. Therefore many of the patients included in these programmes will have pathological stage T2 and some T3a. The inclusion criteria of Herr's series do not exclude patients with clinical or pathological perivesical fat, but in analysing patients' characteristics, it was found that no patients with clinical T3b were included in the series, probably because it was not possible to perform a radical TUR with pathological confirmation in the second TUR in these patients.[21]

The reliability of biopsies of tumour bed is confirmed in uni- and multivariate analysis, but this criteria is a bit subjective as it depends on the number of biopsies peformed and the places where they were taken. Regardless of the statistical reliability of these biopsies, we have observed that five or more biopsies dealing with the tumour bed size are enough to reduce the understaging to 2.3%.[22] Therefore this is the minimal number of biopsies recommended to be performed on the tumour bed, if this approach is attempted.

Patients with invasive bladder cancer treated with TUR alone are at risk of new superficial and invasive recurrences, so a very strict follow-up is necessary. Endoscopic evaluation every three months during the first three years is recommended because most invasive recurrences occur during this period, and a follow-up every six months is also recommended up to the fifth year. Thereafter, a less strict follow-up can be employed, but follow-up is still necessary as patients with bladder Tis associated can develop late recurrences. At the first endoscopic evaluation, a new TUR on scar tissues is strongly recommended in order to ensure a low understaging rate. Urinary cytology is also an important diagnostic tool.

Partial cystectomy is an alternative to radical TUR in patients who fulfil the inclusion criteria. However, it is a double open surgical procedure, and represents an overtreatment for these patients, since TUR defines the inclusion criteria and selects suitable patients for this procedure. On the other hand, partial cystectomy could reduce understaging and increase the number of patients with bladder preservation, including patients with positive biopsies of tumour bed. The inclusion criteria try to exclude these patients, however, because they have a worse prognosis than patients with

negative biopsies and they should be treated with more radical approaches such as cystectomy and radio-chemotherapy.

The role of pelvic lymphadenectomy in this group of patients is controversial because this is a group with good prognosis and the incidence of micrometastases in lymph nodes should be very low. This incidence could be included in the 7% of patients who showed distant metastases with no bladder invasive recurrence or synchronously with them. Taking into account the low incidence of occult-positive lymph nodes, and that the five-year survival rate is 14–40% in cases of N1 in patients treated with cystectomy and lymphadenectomy, the potential survival benefit should be minimal, adding unnecessary morbidity in most patients.

Conclusion

In conclusion, a small and carefully selected group of patients with invasive bladder cancer, identified by a second TUR with no tumour in chips or with negative biopsies on muscular layer and perivesical fat of tumour bed, can be treated with TUR as an initial monotherapy. This approach achieves similar cause-specific survival to patients with p0 on cystectomy specimen. An extended follow-up should be carried out and should be close during the first three years, performing a TUR on scar tissues at least during the first evaluation.

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Chapter 10

Nodal involvement

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Introduction

Radical cystectomy and bilateral pelvic lymph-node dissection (PLND) has been established as standard treatment for muscle-invasive bladder cancer.[1,2] As regards lymph-node involvement, it has clearly been shown that the presence of nodal metastasis is an indication for at least limited systemic tumour spread, and does translate into decreased survival compared to node-negative patients, despite radical surgery. However, recent data indicate that patients with minimal nodal disease and otherwise organ-confined primary bladder tumours do benefit from radical cystectomy and PLND, and that even a proportion of patients with grossly node-positive bladder cancer can be cured by surgery and thorough lymph-node dissection.[3–7]

Historical aspects of nodal involvement for invasive bladder cancer

Regional lymph-node dissection has been integrated in the management of breast, cervical, gastric and colon cancer for decades. Jewett and Strong have published an important study of autopsy cases stratified into various tumour stages.[8] This study gave the rationale basis for radical cystectomy and PLND, as well as the knowledge for local extension of transitional cell carcinoma of the bladder during the course of clinical tumour development. Brunschwig *et al.* described the technique of radical cystectomy with resection of pelvic lymphatic tissue for carcinoma of the bladder for the management of advanced bladder cancer by exenterative

pelvic surgery.[9] Whitmore and Marshall were among the first to clinically analyze the relative impact of radical cystectomy and PLND on survival.[10] Among a small subgroup of patients with limited nodal involvement, longterm survival was noted in less than 20%. Subsequent studies reported contradicting results regarding the prognostic impact of PLND in patients with proven nodal metastasis. In the early 1980s, Skinner *et al.* were the first to report data that gave a clear rationale for a meticulous pelvic lymph-node dissection for management of invasive bladder cancer.[11] However, the true impact of PLND on outcome and survival depended on the stage of the primary bladder tumour, and the number, size and location of involved lymph nodes was still a matter of debate until recently, when studies addressing these questions were reported.[3–7,12–14]

Distribution and incidence of regional lymph node metastases

Lymphatic drainage of the urinary bladder is accomplished through a network of lymphatic vessels and nodal plexus which can be divided into distinct transmitting and collecting units. Regional lymph nodes can be divided into perivesical nodes, hypogastric nodes along the internal iliac artery, obturator nodes, external iliac nodes and presacral nodes. These regional lymphatics drain into the common iliac, inguinal, para-aortal and paracaval nodes, which are usually secondary landing zones for bladder cancer metastasis. According to Smith and Whitmore, nodes in the obturator (74%) and external iliac region (65%) are of most importance because of their frequency of involvement by bladder cancer metastasis.[15] Nodes in the common iliac region (19%), the hypogastric region (17%) and perivesical nodes (16%) are less frequently involved. In a recently reported study by Mills *et al.*, 44.5% of node-positive patients had nodal involvement confined to a single region, whereas 55.5% had positive nodes in at least two regions.[14] In 7.2% of patients, nodes were positive only on the contralateral side to a lateralized bladder tumour, and in another 12% the ipsilateral as well as contralateral regions were involved. This emphasizes the importance of a thorough lymph-node dissection of the whole primary landing zone for lymph-node metastasis in the pelvis, including the region along the internal iliac vessels.

The overall incidence of nodal metastasis in patients undergoing radical cystectomy and PLND is reported to be between 13% and 28% in large

series.[16] The majority of these patients present with nodes that appear macroscopically to be normal at surgery. The incidence of nodal involvement correlates directly with the stage of the primary in the bladder, ranging from less than 5% in superficial to more than 40% in deeply infiltrating, high-grade tumours. Skinner reported nodal metastasis in 6% of p1, 30% of p2, 31% of p3a and 65% of p3b tumours.[11] Smith and Whitmore described positive lymph nodes in 2% of p1, 8% of p2 and 47% of p3 tumours.[15] In the largest reported series of 193 node-positive cystectomy patients, 77.2% of node-positive patients presented with extension of the primary tumour beyond the bladder wall (p3b to p4b) whereas only 22.8% presented with organ-confined tumours (p0 to p3a).[6] Mills *et al.* reported in their study a frequency of nodal involvement in 5–12% for organ-confined and 28–38% for non-organ-confined primary tumours.[14]

To minimize the sampling error during PLND, which influences the incidence of positive nodes, it is important to understand that neither the size of individual lymph nodes nor the location of enlarged lymph nodes within the boundaries of PLND correlates positively with the true incidence of metastasis. Therefore, selection of lymphatic tissue should not be made by the surgeon, rather the entire specimen should be sent for assessment of histology. Another factor that influences the incidence of nodal metastasis is the number of nodes in the specimens examined by the pathologist. This number does significantly impact on the local control and survival of stages pNO and pN+ disease.[13] The quality of surgical resection during PLND and radical cystectomy is critical to identify patients who have positive nodes. Herr *et al*. provide evidence that at least nine lymph nodes are necessary to allow adequate assessment of the lymph node status and to determine patient prognosis as regards the node status.[13] The more extensive the lymph node dissection, the more likely it is that an increased number of lymph nodes, including more microscopic positive lymph nodes, may be excised and examined by the pathologist. However, further prospective studies are necessary to determine the number of nodes in order to ensure a high-quality operation. On the other hand, the routine practice of lymph-node examination by the pathologist, with or without visual enhancement techniques, can vary in thoroughness. The method of step sectioning lymph nodes can account for a higher than 30% false rate of pathologic interpretation error over random pathologic evaluation when studying pelvic nodes for tumour involvement.[17]

Summary

1 Regional lymphatic drainage of the urinary bladder takes place through perivesical nodes, hypogastric nodes along the internal iliac artery, obturator nodes, external iliac nodes and presacral nodes.

2 The overall incidence of nodal metastasis in patients undergoing radical cystectomy and PLND is reported to be between 13% and 28%.

3 Positive nodes may be present on the ipsilateral and contralateral side to a lateralized bladder tumour.

4 The incidence of nodal metastasis is influenced by the number of nodes in the specimens examined by the pathologist.

Technical considerations and extent of pelvic lymph-node dissection along with radical cystectomy

Pelvic lymph-node dissection should be performed as a standard procedure. All connective and lymphatic tissue must be removed from the common iliac bifurcation along the external and internal iliac vessels to the inguinal ligament and from the psoas muscle fascia. The lateral limit is the genitofemoral nerve. All crossing tissue elements may be divided by use of electrocautery or by bipolar scissors. The caudal and cephaled side of the lymphatics should be ligated or clipped to avoid post-operative lymphoceles. However, haemoclips tend to become disloged from lymphatic vessels during the surgical procedure, therefore, ligations are preferable. The obturator fossa is cleared from all lymphatic tissue around the obturator nerve and vessels. If adequate, the obturator vessels are dissected and removed, together with the lymphatic tissue. Careful dissection along the ventral aspect of the internal iliac vein and from the obturator muscle is recommended. The presacral region and the internal iliac artery are freed from lymphatic tissue after dissection of the umbilical artery that crosses the ureter.

A pelvic lymph-node dissection as described above clearly eases radical cystectomy, since the vascular pedicle of the bladder is anatomically exposed. Based on pelvic anatomy on the one hand and clinical data on the other, some surgical centres promote a more extended PLND that includes dissection of all lymphatic tissue along the aortic bifurcation.[12,14] There is strong evidence that microscopic nodal involvement may be present in any location within the small pelvis, independent from the location of the

bladder tumour, and that even nodes above the common iliac bifurcation may be a primary landing zone for metastatic disease.

Guidelines for colorectal cancer indicate that at least 12 to 14 lymph nodes should be found and examined by the pathologist.[18,19] Similar guidelines have not yet been established for bladder cancer. Poulson *et al.* reported a survival advantage in patients with stage pN0 and organ-confined bladder tumours after more extensive lymph-node dissection.[12] Extended PLND yielded a median of 25 lymph nodes, whereas limited or conventional PLND yielded only a median of 14 nodes. Of the patients with extended dissection, 12.5% had positive nodes compared to only 8.9% with limited dissection. It is also important to point out that the number of lymph nodes may vary among institutions and surgeons, depending on patient selection, the extent of PLND, how lymph nodes are submitted for pathologic evaluation and how many lymph nodes are examined. However, there is still no data from prospective studies that prove the benefits of an extended pelvic lymph-node dissection over standard PLND.

When grossly positive nodes are found at surgery, a number of considerations influence the decision to proceed with radical cystectomy. The most important question is whether the nodes and the bladder can be resected completely without leaving gross tumour behind, and whether they can be resected safely, with low morbidity?[7] The patient's age does not seem to be a major factor, as studies prove that even octogenarians tolerate radical cystectomy and extended pelvic lymph-node dissection as well as younger patients.[20]

Complications from standard pelvic lymph-node dissection along with radical cystectomy are rarely reported. In most series, the intra- and post-operative risk of complications is not related to PLND.[3,4,21–24] Since PLND is usually performed with radical cystectomy via an intraperitoneal approach, post-operative pelvic lymphoceles are not a major problem. It appears that after this procedure, extravasated lymph is resorbed easily from the peritoneal surface, thus minimizing the risk of lymphocele formation. A rate of 3.5% lymphoceles following PLND along with radical cystectomy and orthotopic ileal neobladder has been reported.[25] With regard to extended pelvic lymph-node dissection, when a nerve-sparing procedure is planned, careful attention must be made to the preservation of the autonomic plexus and nerve fibres that run along the common and internal iliac arteries and descend into the pelvis. Damage to the autonomic innervation of the *corpora cavernosa* at the level of the autonomic plexus,

or to sympathetic fibres that contribute to the urethral smooth muscle innervation, may be a complication in concert with an extended PLND.[26]

Summary

1 Pelvic lymph-node dissection should be performed as a standard procedure. A thorough pelvic lymph-node dissection clearly eases radical cystectomy since the vascular pedicle of the bladder is anatomically exposed.

2 The number of dissected lymph nodes varies among institutions and surgeons, depending on patient selection, the extent of PLND, how lymph nodes are submitted for pathologic evaluation, and how many lymph nodes are examined.

3 Major complications from a standard pelvic lymph-node dissection along with radical cystectomy are rarely reported.

Impact of regional lymph node involvement on survival following PLND and radical cystectomy

Regional lymph node status has consistently been found to be one of the strongest predictors of survival. Cystectomy candidates found to have positive pelvic lymph nodes at time of PLND are generally regarded as having a poor prognosis, but considerable variation exists among the reported survival rates (Table 1).

While historical series report rather dismal outcomes, more contemporary analyses have demonstrated that radical surgery in combination with PLND may in fact provide favourable longterm survival in a substantial number of cases, and that patients most likely to benefit from radical surgery are those with favourable stage and/or with limited or microscopic lymph node involvement.[3–6,15] In a detailed analysis of node-positive cystectomy candidates 1-, 3-, 5- and 10-year survival rates were reported to be 67%, 33%, 25% and 21% respectively.[6] Survival appears to be especially a function of the extent of the primary tumour (Figure 1) with an actuarial five-year survival of 51% for bladder confined (pT0–pT3a), and 17% for tumours extending outside the bladder wall (pT3b–pT4b) ($p < 0.001$).

Survival also seems to be inversely related to the extent and bulk of the tumour in the regional pelvic nodes. Among patients with involvement of a single lymph node (pN1), 33% survived five years, whereas only 22% with

Table 1: Incidence and survival of patients with nodal metastases following radical cystectomy and pelvic lymph-node dissection

Authors	*Period*	*No. of patients*	*pN+*	*Strata*	*Survival >5 years*
Whitmore and Marshall (1962)[10]	1940–55	230	55 (24%)	Overall	4%
Dretler *et al.* (1973)[32]	1955–67	302	54 (13%)	Overall	17%
Reid *et al.* (1976)[33]	1966–74	135	24 (18%)	Overall	26%
Bredael *et al.* (1980)[34]	1964–73	174	26	Overall	4%
Smith and Whitmore (1981)[15]	1966–77	662	134 (20%)	pN1 pN2 pN3 pN4	17% 5% 5% 0%
Skinner (1981)[11]	1971–79	153	36 (24%)	Overall	35%
Zincke *et al.* (1985)[35]	1960–80	–	57	Overall	10%
Wishnow *et al.* (1987)[36]	1983–85	130	18 (14%)	–	–
Grossmann *et al.* (1988)[37] (followed only 40 months)	–	–	10 11	pN1 pN2,3	40% 9%
Roehrborn *et al.* (1991)[38]	1971–86	280	42 (15%)	pN1 pN2,3	23% 18%
Lerner *et al.* (1993)[3]	1971–89	591	132 (22%)	<pT3b pT3b	50% 18%
Vieweg *et al.* (1994)[4]	1980–90	686	193 (28%)	<pT3b pT3b pN1 pN2	51% 17% 33% 22%
Bassi *et al.* (1999)[30]	1982–94	369	78 (21%)	Overall	15%
Mills *et al.* (2001)[14]	1984–97	452	83 (18%)	Overall	29%
Herr *et al.* (2001)[7]	1980–90	686	82 (12%)	pN2/N3–pT2 pN2/N3–pT3	50% 19%

pN2 (2–5 lymph nodes involved) disease survived five years ($p<0.0006$).[6] Similarly, Lerner and Skinner reported about actuarial 2-, 3-, 5- and 10-year survival rates of 61%, 46%, 35% and 24% respectively, when 1–5 lymph nodes were found to be positive for cancer.[3] However, when six or more nodes were involved, prognosis was unfavourable, with 44%, 23%, 17% and

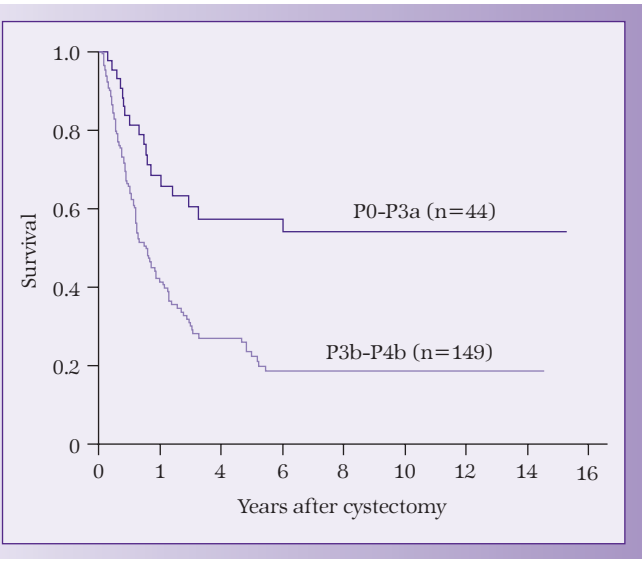

Figure 1: Disease specific survival for node-positive patients with organ-confined (p0–p3a) and non-organ confined (>p3a) disease. Differences between groups were statistically significant (p=0.000).[6]

17% (p = 0.012). Thus, pT-category of the primary tumour in addition to nodal tumour burden (pN-category) are the most important stratification variables in determining who may or may not benefit from radical surgery, and may influence the surgeon's decision as to whether to proceed with cystectomy when lymph node involvement becomes evident.

Herr *et al.* have reported a detailed analysis of the outcome of patients with grossly node-positive bladder cancer.[7] Among patients with grossly positive nodes, 24% survived for 10 years after radical cystectomy and complete pelvic lymph-node dissection. The authors conclude from their data that the prevailing opinion of the limited value of radical surgery in such circumstances needs to be modified, and that a minority of patients with extended node-positive disease can be cured by a visibly, complete pelvic node dissection.

Many other clinical and pathological factors that may predict risk of relapse and survival in node-positive patients have been analyzed, although no further factors have been consistently found to be significant survival predictors in node-positive disease. However, more factors need to be considered carefully on the subject of survival improvement. First, Herr *et al.* have demonstrated that the net result of examining an adequate number of lymph nodes is the improved survival of patients with both stages pN0 and pN+, since the increased number of nodes identified

during surgery reflects a more complete radical cystectomy and lymphadenectomy.[13] In this context, the role of an extended pelvic lymph-node dissection, as suggested by Poulsen *et al.*, may also play an important role as the number of resected nodes correlates clearly with the limited or extended boundaries of PLND.[12] Second, Mills *et al*. have presented evidence that lymph-node capsule perforation by the tumour is a sign for an ominous prognosis.[14] They found a significant decrease in survival when capsule perforation was present at the pathology examination of resected nodes. This factor achieved independent significance in a multivariate analysis. However, these factors still emerge from single institution observations and deserve further confirmation by future studies.

During the last two decades, PLND along with radical cystectomy has proven to benefit a small but significant number of patients with node-positive bladder cancer, and should be performed especially in cases where the tumour is still confined to the bladder wall. However, non-organ-confined tumours with positive nodes generally indicate a poor prognosis. In these cases, radical surgery alone is unlikely to be curative and it is hypothesized that adjuvant treatment options appear to be necessary to improve survival chances. However, this needs again to be tested in properly designed clinical trials. So far, only few controlled preliminary studies for these therapies have demonstrated a significant survival benefit in patients with low tumour burden in an adjuvant setting.[27,28] Up to now, no prospective randomized study has convincingly demonstrated that systemic chemotherapy impacts on longterm survival of these patients.[29]

Summary

1 The regional lymph node status is one of the strongest predictors of survival.
2 A meticulous pelvic node dissection can add a survival advantage when limited nodal involvement is present in patients with organ-confined bladder tumours.
3 A minority of patients with extended node-positive disease may be cured by a visibly, complete pelvic node dissection.
4 The number of resected lymph nodes may impact on the survival of patients with both, stages pN0 and pN+.
5 There is evidence that lymph node capsule perforation by the tumour is a poor prognostic factor.

Conclusions

Pathologic stage and nodal status are the main factors determining outcome in patients with node-positive bladder cancer.[6,16,30,31] PLND appears to be a safe procedure, provides the most accurate staging, and, along with radical cystectomy, benefits a substantial number of patients with node-positive bladder cancer. In particular in cases where the tumour is still confined to the bladder wall, a meticulous pelvic node dissection can add a survival advantage when limited nodal involvement is present. In such cases, overall disease specific survival rates of more than 50% can be expected following complete resection of limited nodal disease (N1 and N2).[5] Moreover, an overall cure rate of about 25% can be expected even in the presence of grossly positive nodes.[7] Since PLND renders every fourth of such patients tumour free, it doesn't seem further justified to routinely abandon planned cystectomy in patients with evident lymph node involvement, or in the face of lymph node metastasis at frozen section. However, a proven extravesical tumour extension (pT3), together with grossly node-positive bladder cancer, does generally indicate a poor prognosis.

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Chapter 11

Pre-operative and definitive radiation therapy

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Introduction

The majority of bladder cancer patients present with superficial disease and are managed with conservative measures. Approximately 20–25% present with muscle-invasive bladder cancer that is potentially life threatening and requires radical treatment. Definitive radiation therapy (RT) has been used for muscle-invasive bladder cancer since the early 1900s and there is evidence that patients can achieve durable local control and maintain a functional bladder without a compromise in the overall survival.[1] However, the standard North American approach to the management of muscle-invasive bladder cancer is radical cystectomy.[2] In the past few decades, radical radiation therapy has been used infrequently and mostly when patients either refused or were not suitable for radical cystectomy. Therefore there is a limited amount of information on the precise role that radiation therapy plays in the management of bladder cancer.

Radiation therapy has been used in the management of bladder cancer in several distinct situations. The most common therapy is radical RT to eradicate muscle-invasive cancer while preserving normal bladder function. Radical RT may also be used to secure local control following chemotherapy that has been given as definitive treatment for

locally advanced bladder cancer. In both situations, salvage cystectomy is used in the event of an incomplete response to RT, local recurrence, or development of a new invasive bladder tumour. Pre-operative RT may be considered in locally advanced bladder cancer to prevent local failure. Post-operative RT is rarely used because of toxicity associated with pelvic RT with fixed loops of small bowel present in the RT volume after cystectomy. Palliative RT is useful in selected cases of locally advanced and metastatic bladder cancer.

Pre-operative radiation therapy

The goal of pre-operative RT is to prevent pelvic recurrence following radical cystectomy. Therefore, only patients who are at high risk of local recurrence in the pelvis are likely to benefit. Patients with bladder cancer without extravesical extension (T2) are at a low risk of pelvic recurrence (<10%), while those with T3 disease are at higher risk of pelvic recurrence (>30%), but they are also at risk of distant failure. In T3 tumours, distant failure will diminish the impact of pre-operative RT on the overall survival. Since pelvic recurrence has a considerable adverse effect on quality of life, improvement in local control is a worthwhile goal of treatment. The Southwest Oncology Group (SWOG) conducted a phase III randomized trial of pre-operative RT followed by cystectomy versus cystectomy alone and found no difference in survival.[3] In this trial, a low-dose pre-operative RT (20 Gy in five fractions over one week) was used, most patients had T2 tumours and therefore were at a low risk of pelvic failure. A positive study of pre-operative RT was recently reported by El-Wahidi *et al*.[4] In this trial, patients with schistosomal bladder cancer were randomized to receive pre-operative RT with 44 Gy followed by cystectomy, or cystectomy alone. A significantly higher pelvic failure rate was observed in the surgery alone arm (29%) than in the pre-operative RT arm. This study has been published in abstract form only and no details are available on local control or survival. Huncharek *et al.* published a meta-analysis of five randomized trials of pre-operative RT and cystectomy versus cystectomy alone (not including the recent El-Wahidi study) and were unable to demonstrate survival advantage for pre-operative RT (odds ratio of 0.71, 95% confidence interval 0.48–1.06), and the impact on local control was not addressed.[5] There is little modern data dealing with the toxicity of pre-operative RT and cystectomy, but the previously conducted randomized

trials suggest that this treatment can be delivered safely. Data from several authors indicate that the use of pre-operative RT does not preclude continent urinary diversion.[6,7] The current approach to the management of patients with T3 disease consists of radical cystectomy and pelvic lymph-node dissection followed by adjuvant chemotherapy. The role of pre-operative RT in this setting is ill defined. However, it would be reasonable to recommend pre-operative RT to patients with clinical T3 tumours who are not candidates for adjuvant chemotherapy, with the primary aim of reducing pelvic recurrence.

It was recognized in the 1950s and 1960s that radical cystectomy alone or radical radiotherapy alone cured fewer than 50% of patients with muscle-invasive bladder cancer. It was hypothesized, therefore, that combining the two modalities would improve the outcome. To test this hypothesis, a number of trials comparing radical definitive radiation therapy with pre-operative radiation therapy and cystectomy were conducted. The main two include the trial by the Institute of Radiology in the UK and the DAVECA Danish Study Group.[8,9] Both trials were negative and established that pre-operative RT followed by cystectomy did not result in a significantly better survival than RT alone with the option for later salvage cystectomy. In ensuing years, it was recognized that RT alone did not provide adequate local control in bladder cancer.

Definitive radiation therapy

Definitive radiation therapy in bladder cancer is used to cure cancer and conserve normal bladder function. This treatment modality is not very popular in the United States. Indeed, the very popular textbook of cancer edited by De Vita *et al.* stated that '. . . in some countries, external beam radiotherapy is considered standard, but not in the United States'.[2] With this attitude being prevalent, few clinical trials of definitive radiation therapy are conducted.

To discuss the definitive RT in bladder cancer patients, one should address the issues of patient selection, assessment of disease extent, exact treatment plan, RT prescription technique, delivery, and assessment of outcome and follow-up care.

To address the issue of patient selection, two major factors have to be considered. The first is the adequacy of bladder function. Patients who are incontinent, or who have very irritative bladder symptoms, are not

good candidates for bladder conservation. The bladder function has to be adequate to be worthwhile preserving. The second issue is the technical ability to deliver an adequate dose of radiation to the tumour. The factors to consider as contra-indications to radiation treatment include the presence of active inflammatory bowel disease, prior pelvic surgery, prior pelvic infections, and the technical ability to control the disease is the size of radiation field that is required, presence of tumour of diverticulum, etc. The other factors relevant to patient selection are related to the potential for achieving lasting local control and therefore bladder conservation. To define this, we should examine the local control rates and survival data in patients with muscle-invasive bladder cancer treated with radiation therapy. One should remember that the information on the use of RT was gathered in the 1970s and 1980s, when the disease extent was defined clinically. Neither CT scans nor MRIs were available, and RT was planned using simulation with cystogram, and modern planning and treatment techniques including CT plans and conformal radiation therapy were not used.

The largest published series of definitive radiation therapy in bladder cancer is from Edinburgh where Duncan and Quilty reported results in 699 patients with muscle-invasive bladder cancer.[10] The five-year survival for patients with T2 cancers was 40%. Patients with T3 and T4 bladder cancers had five-year survival of 25.9% and 11.6% respectively. Similar results are available from the MD Anderson Hospital and the London Hospital.[11,12] At the Princess Margaret Hospital, 121 patients with muscle-invasive bladder cancer were treated with external beam radiation therapy between 1981 and 1985.[13] The five-year cause-specific survival was 59% of patients with T2 disease and 52% with T3a disease. A much lower survival (30% at five years) was observed in patients with T3b disease. When local control of cancer was examined in the Princess Margaret Hospital series, the local relapse-free was 45% for patients with T2 and T3a disease, but only 28% for patients with T3b cancer. In examining the factors predictive of durable local control in the Princess Margaret Hospital series, the presence of co-existent carcinoma *in situ* was found to be associated with a lower longterm local control. The patients with no demonstrable carcinoma *in situ* achieved local control in 55% of patients and in those with co-existent carcinoma *in situ*, local control was less than 30% at five years. Therefore, the presence of co-existent carcinoma *in situ* is considered a relative contra-indication to definitive radiation

of bladder cancer. However, recent evidence from Pisters *et al.* suggests that patients who have residual, or recurrent, carcinoma *in situ* following radical radiation can be treated with intravesical BCG, and response rates are similar to those obtained in patients with primary CIS.14

The low local control rates observed in retrospective series of definitive radiation therapy in bladder cancer have led to research efforts to try to improve the results of radiation therapy in bladder cancer. One of the most common strategies was the use of concurrent chemotherapy and radiation therapy in bladder cancer. Numerous chemotherapeutic agents were combined with radiation therapy. They included 5-FU, 5-FU plus mitomycin-C, and cisplatin. The most common strategy was that of cisplatin, where a number of phase II trials have been conducted.[15] The complete response rates in these trials varied between 66% and 93%. A phase II study of concurrent cisplatin and RT conducted in Vancouver by Coppin *et al*. showed an excellent progression-free survival in patients with T3–T4b cancer, and formed the basis for a prospective randomized trial conducted by the National Cancer Institute of Canada in the late 1980s.[16] In this trial, 99 patients were randomized to RT, either high-dose, pre-operative RT or definitive RT, with or without concurrent cisplatin. No difference in the overall survival was observed between the RT alone and RT with concurrent cisplatin arms. However, a statistically significant reduction in pelvic failure rate was observed in patients who received concurrent RT and cisplatin. The actuarial rate of pelvic recurrence at five years was 60% for patients treated with RT alone and 31% for patients who received combined RT and cisplatin. Distant recurrence rate at five years was 43.7% for the RT alone group and 45% for RT and cisplatin. In the early 1990s, the Medical Research Council in the UK and the EORTC GU Group conducted a large multinational study to test the use of CMV neo-adjuvant chemotherapy to improve survival in bladder cancer. The study accrued 975 patients, and with a median follow-up of three years, a 5% survival advantage was demonstrated for the chemotherapy treated group. The study was powered to detect a 10% survival advantage and, therefore, there was no statistically significant improvement for the chemotherapy treated group. It is important to note, however, that the trials that used RT with concurrent cisplatin demonstrated an approximately 40–50% bladder conservation rate. The use of radical external beam RT has not been shown to compromise the overall survival in bladder cancer patients. Therefore, the use of definitive RT with or without concurrent cisplatin should be

a recognized treatment option that is offered to patients who wish to preserve normal bladder functions rather than undergo cystectomy.

Conclusions

In summary, the current literature suggests that with appropriate selection of patients for bladder conservation, a complete response can be achieved in approximately 60% of patients with favourable disease. Approximately 30% of those patients will develop further recurrence, either with carcinoma *in situ* or new superficial tumour, or indeed, local recurrence of invasive disease. As in any other series of patients with muscle-invasive bladder cancer, distant metastasis can be expected to develop in approximately 50% of patients, and the overall five-year survival is at best 50%. Longterm bladder conservation can be expected in 40% of patients. The optimal factors for selecting patients for bladder conservation include the presence of T2a and T2b tumours (1997 UICC TNM), bladder cancer without diffuse CIS, and pre-radiation therapy optimal TURBT. A careful assessment of disease extent, preferably with MRI, CT planning and delineation of target volume, the use of conformal techniques, and the use of radiation with concurrent cisplatin, constitute the optimal treatment approach. An aggressive follow-up and early salvage cystectomy for patients who have residual or recurrent invasive disease will further improve the outcomes.

The goals of bladder conservation are often confused with the goals of minimizing treatment toxicity. A large number of patients who are elderly, have very massive disease and are unsuitable candidates for curative surgery, are referred for curative RT. The results of treatment for these patients are very poor. Often they are treated with high-dose per-fraction prescriptions and, instead of assessing the results of treatment in this group of patients in terms of symptom release and palliation, survival is being measured. Clearly, to assess the role of definitive RT in the bladder conservation approaches, reports of patients who are referred for RT by choice rather than by default should be considered.

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Chapter 12

Neo-adjuvant and adjuvant chemotherapy – true and false

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Introduction

Radical cystectomy is the gold standard of treatment for patients with muscle-invading tumours in most countries. Radiation therapy (RT) is used as primary therapy in only a few countries. Improvements in surgical techniques, peri-operative care, and early diagnosis have led to an increase in survival. This is owing to stage migration of 10–20% per stage. In addition, the frequency of deeply invasive tumours has decreased. The presence of a palpable mass is less, and the incidence of N+ disease has diminished.[1]

Predictors for relapse after cystectomy include depth of invasion, involvement of adjacent viscera, and presence or absence of nodal metastases. Recurrence is related to stage and nodal status. High-grade, high-stage (pT3–4) tumours are frequently (40–60%) found to have lymph node involvement (pN+) at the time of radical cystectomy. Current selected studies indicate a 15–20% five-year survival after cystectomy in patients with nodal metastases, and a 35–40% five-year survival for N1 (1 microscopic node ipsilateral to tumour).[2] With direct invasion into adjacent viscera, cure is obtained in less than 10% of patients. The strongest predictor

of risk for later urethral disease is TCC involvement of the prostate.[3] Other known prognostic factors include histology, grade, presence or absence of ureteral obstruction, and the extent of surgical resection.[4,5]

Neo-adjuvant chemotherapy

Following cystectomy for muscle-invasive bladder carcinoma, up to 50% of patients may develop metastases. This most often occurs within two years.[4] Most patients relapse in distant sites, only one-third of patients relapse in the pelvis alone. Response rates of 40–70% with cisplatin-containing combination chemotherapy regimens have led to their use for locally invasive disease in combination with cystectomy or RT, either as neo-adjuvant or adjuvant therapy.

'Neo-adjuvant' chemotherapy is given before cystectomy, or in some instances before RT. This approach has been useful in the treatment of several solid tumours. Patients with operable stages T2–T4a may be candidates for neo-adjuvant chemotherapy. It was devised to eliminate micrometastases present at diagnosis. It has also been used to determine response to chemotherapy, and in some cases to preserve the bladder. The bladder tumour serves as an *in-vivo* marker to evaluate response to chemotherapy. This may permit continuation of treatment to maximal response, or discontinuation of ineffective therapy. The toxicity associated with neo-adjuvant therapy has been much lower than that reported in patients with metastatic disease. These patients generally have operable disease and a better performance status. The major disadvantage is that definitive local therapy is delayed.

Non-randomized studies have established the feasibility and safety of giving neo-adjuvant chemotherapy, with overall response rates of 60–70%. CR rates in the 30% range have been frequently reported.[6] These trials have demonstrated that neo-adjuvant chemotherapy can produce tumour 'downstaging'. It has been shown that patients may become operable after neo-adjuvant chemotherapy.[7] Since these trials are not randomized, they don't necessarily implicate a survival advantage. The endpoints for clinical trials in localized disease are slightly more complicated to interpret than the endpoints in trials for metastatic disease. In the treatment of early disease, some patients will not benefit from chemotherapy, and it is clear that only those destined to develop metastatic disease will benefit, and that the earlier

patients are treated, the higher the proportion that will receive unnecessary chemotherapy.

There are a number of randomized trials of neo-adjuvant chemotherapy (Table 1). Many trials have been prematurely closed and most have not demonstrated a survival difference.[8] The problem is that in order to detect a 10% improvement in survival, for example from 50% five-year survival to 60%, one must include 1,000 patients in a randomized trial.[9]

The Nordic Cystectomy I trial has suggested a trend towards an improvement in survival for patients treated with two cycles of neo-adjuvant adriamycin and cisplatin and 4,000 rads for five days, followed by cystectomy versus RT and cystectomy alone.[13] A 20% difference in cancer-specific survival and a 15% (p=0.03) improvement in overall survival at five years in patients with T3a–T4 lesions was observed. No difference was observed for patients with T1 and T2 disease.

A subsequent Nordic Cystectomy II trial eliminated the adriamycin and randomized patients to neo-adjuvant methotrexate and cisplatin without

Table 1. Randomized trials of neo-adjuvant chemotherapy[6]

Study group	*Neo-adjuvant arm*	*Standard arm*	*Patients*	*Results*
EORTC/MRC[10,11]	CMV/RT or cyst	RT or cyst	976	5.5% diff
USA Intergroup[12]	MVAC/cyst	cyst	298	Diff
Nordic Cyst I[13]	ADM/DDP/RT/cyst	RT/cyst	311	15% chemo benefit in T3–T4a
Italy (GUONE)[14]	MVAC/cyst	cyst	206	No diff
Italy (GISTV)	MVEC/cyst	cyst	171	No diff
Aust/UK[15]	DDP/RT	RT	255	No diff
Canada/NCI[16]	DDP/RT or pre-op RT+cyst	RT or pre-op RT+cyst	99	No diff
Spain (CUETO)[17]	DDP/cyst	cyst	121	No diff
Italy (Genoa)[18]	DDP/5FU/RT/ cyst	cyst	104	No diff
MGH/RTOG[19]	CMV/DDP/RT	DDP/RT	123	No diff
Nordic 2[20]	MTX/DDP/cyst	cyst	317	No diff
Abol-Enein[21]	CarboMV/cyst	cyst	194	chemo benefit

RT followed by cystectomy versus cystectomy alone. In 317 patients with muscle-invasive disease, no survival difference was detected.[20]

The MRC and EORTC have completed the largest randomized neo-adjuvant chemotherapy trial of CMV followed by cystectomy or RT versus immediate cystectomy or RT.[10] To detect a 10% difference in survival, 976 patients were enrolled in this trial; 491 were assigned to chemotherapy and 485 to no chemotherapy. This study revealed an 8% difference in the time to progression in treated patients. A 5.5% difference in absolute three-year survival was seen (HR=0.85, 95% CI 0.71–1.02). The median survival for the chemotherapy group was 44 months and 37.5 months for the no-chemotherapy group, a difference of 6.5 months. This was not statistically meaningful, as 3,500 patients should have been included in this trial for this to be a significant difference. Of note, many patients in the no-chemotherapy group received chemotherapy at relapse, and 37% received salvage therapy. The pT0 rate was 33% with CMV and 12% without CMV. Chemotherapy demonstrated activity in the primary tumour and may have delayed loco-regional and metastatic progression. In an update presented at ASCO 2001 with a follow-up of 7.4 years, results became significant with a constant 5.5% (HR=0.85, 95% CI 0.72–1.00, p=0.048) difference in favour of CMV.[11] This, however, did not reach the 10% difference that had been targeted.

In a study from Mansoura, Egypt, published in abstract form, two cycles of carboplatin, methotrexate and vinblastine were given to 94 patients and 100 patients underwent immediate cystectomy. Five-year tumour-free survival was 59.1% versus 41.6% for the untreated patients (p=0.044). These results are difficult to interpret in that these patients may have had different characteristics than patients with TCC usually treated in Europe.[21]

An Italian co-operative group randomized patients to four cycles of neo-adjuvant M-VAC followed by cystectomy versus cystectomy alone.[14] The study was closed after only 206 patients were randomized. The sample size was calculated to detect an improvement in three-year overall survival of 15%, from 45% to 60%. Survival, however, at three years was 62% for the M-VAC and 68% for the cystectomy alone arm. Response to M-VAC was the only independent prognostic factor. Of note, one third of patients received a lower dose intensity of the planned chemotherapy.

A similar study was recently presented by the Southwest Oncology Group for the United States Intergroup.[12] Patients received three cycles

of M-VAC followed by cystectomy versus cystectomy alone. Patients who received M-VAC appeared to have a significant benefit in survival: 57.2% versus 42.1% at five years (1 sided p value=0.044). However, there are many questions surrounding this study in terms of its long accrual period and the statistical methodology used in its interpretation.[22]

For single-agent cisplatin therapy, it seems clear that no improvement in survival has been found. A study by the Spanish CUETO Group evaluated neo-adjuvant cisplatin single-agent chemotherapy in 121 patients prior to cystectomy. No survival difference was seen. Of course, it is difficult to determine the meaning of these results, as single-agent therapy is no longer considered adequate standard therapy by most oncologists. In addition, the sample size was rather limited.[17]

When the results of 255 patients in a meta-analysis from Australia and the UK were combined, and single-agent cisplatin was given prior to RT, again, no significant survival difference was detected.[15] Similarly, in a study from the Canadian National Cancer Institute, patients were treated with neo-adjuvant cisplatin and RT or pre-operative RT and cystectomy.[16] This randomized trial demonstrated significantly better local control (recurrence rate 40% versus 59%) by concomitant cisplatin and pre-operative RT. However, the initial advantage in overall survival seen at three years was not confirmed at six-and-a-half years.

In another radiation trial, the Mass General Hospital and the RTOG evaluated the combination of two cycles of CMV, cisplatin and RT versus cisplatin and RT alone. This trial was designed to detect a 20% difference in tumour-free survival, and a 15% difference in disease-free survival. However, the study was prematurely closed due to toxicity. Of 123 patients, no difference in five-year actuarial survival was observed; 48% and 49%. Five-year survival with a functioning bladder was 38% in the CMV arm and 36% in the RT and cisplatin arm. Two cycles of MCV neo-adjuvant chemotherapy were not shown to increase the rate of CR over standard induction therapy nor to increase freedom for metastatic disease. There was no impact on five-year overall survival.[19]

Randomized trials appear to demonstrate a small difference in favour of neo-adjuvant chemotherapy. Response to chemotherapy may be the most important predictor of survival. Data were collected from 147 patients with muscle-infiltrating tumours treated in eight centres with neo-adjuvant chemotherapy and radical or partial cystectomy. Five-year survival was 75% in patients who had downstaging of the primary tumour

to pT0 or superficial disease, versus only 20% in patients who had residual muscle-infiltrating disease (>pT2).[23]

These data are similar to our data in Rome, where 87 patients with muscle-invasive transitional cell carcinoma of the bladder were evaluated.[24] After three cycles of neo-adjuvant M-VAC, 40 patients were T0, 19 had Ta-1 disease, eight had CIS, 12 had T2-3 disease, and eight refused restaging. Forty-two patients had TURB alone (including three who refused surgery), 13 underwent partial cystectomy, and 32 had radical cystectomy. In those undergoing radical or partial cystectomy, the p0 rate was 12/45 (27%). Overall five-year survival was 58/87 (67%) and 32/87 (37%) with bladder preservation. Five-year survival was 71% for those who were T2–3 post-M-VAC. Five-year survivals were 69%, 69% and 53% for TURB alone, partial cystectomy, and radical cystectomy groups respectively. Response to chemotherapy is clearly an extremely important prognostic factor. Newer prognostic factors to select patients, such as p53, is discussed below.

The most significant prognostic factor for survival appears to be attainment of p0 status.[25] Response to chemotherapy is a prognostic factor of extreme importance, and should be considered when making clinical decisions. In addition, patients with invasive bladder tumours who achieve T0 status after neo-adjuvant M-VAC may preserve their bladders with bladder-sparing surgery.[26,27]

Neo-adjuvant chemotherapy and bladder preservation

Since orthotopic bladder substitution has become available, many urologists prefer early definitive therapy with this ideal form of continent urinary diversion. However, if in selected cases there is the possibility of bladder preservation, this chance should not be dismissed. This approach has been used in the treatment of other solid tumours, such as breast cancer, anal cancer, laryngeal carcinoma and osteosarcoma. Bladder preservation to the patient means less surgery, no need for a urinary diversion and a normal sexual life. These factors are clearly important in determining quality of life. Table 2 describes trials combining chemotherapy and RT.

Bladder preservation is possible with an integrated approach using chemotherapy and RT.[28,29] Table 2 outlines some of the most important studies of combined chemotherapy and RT to achieve bladder preservation.

Table 2: Non-randomized trials of combined chemotherapy and radiotherapy

Series	*Year*	*n*	*Chemo*	*Five-year survival*	*Five-year survival with intact bladder*
Radiation Therapy Oncology Group-1[30]	1993	42	DDP	52%	42%
University of Erlangen[31]	1994	139	DDP or Carbo	52%	41%
Genoa[18]	1995	76	DDP/5FU	42%	
Radiation Therapy Oncology Group-2[29]	1996	91	MCV	62%*	44%
Massachusetts General[28]	1997	106	MCV	52%	43%
University of Paris[32]	1997	120	DDP/5FU	63%	

* Four-year survival data

The combination of neo-adjuvant chemotherapy and RT is capable of producing five-year survival rates between 42% and 63%, with organ preservation in approximately 40% of patients. In the trial from Massachusetts General Hospital, patients were treated with two cycles of CMV chemotherapy followed by cisplatin and RT.[19]

Patients who responded received further chemotherapy and RT. Cystectomy was performed on non-responders. Five-year survival was 52%; 43% retained an intact functioning bladder. Prognostic factors for local curability are small tumour size, absence of hydronephrosis, papillary histology, a visible complete TURB and a complete response to induction chemotherapy. These very interesting results need to be confirmed by randomized trials.

Bladder preservation has recently been reported on by several groups in the literature.[26–28,33] It has proved to be a feasible alternative, but has also been scrutinized since the advent of neo-bladders. Bladder preservation remains a controversial topic, as radical cystectomy must still be regarded as the gold standard of treatment for muscle-invasive bladder cancer. Bladder preservation in patients on the basis of response to neo-adjuvant

chemotherapy is a feasible approach which must be confirmed in prospective randomized trials.

Attempts at bladder preservation should also evaluate the use and toxicity of these combined modalities. The true success of bladder-preserving treatment by chemotherapy and RT will require validation in prospective randomized trials.

Adjuvant chemotherapy

Adjuvant chemotherapy is given after cystectomy to patients at high risk for relapse. This approach of giving chemotherapy after local treatment has led to increases in survival in patients with several solid tumours.

The principal advantage is that the cystectomy specimen is available for pathologic evaluation. Prognostic factors for relapse and/or metastases can be determined. Patients can then be selected to receive chemotherapy that may benefit most. Since the cystectomy is performed immediately, there is no delay in definitive treatment. It also avoids patient refusal, which may occur when a complete response has been achieved with neo-adjuvant chemotherapy.[6] Orthotopic bladder substitutions and the decreased morbidity of cystectomy are reasons to perform cystectomy and adjuvant chemotherapy.

The major disadvantage to adjuvant chemotherapy is the delay in giving systemic therapy for occult metastases while treatment for the primary tumour is emphasized. Response cannot be assessed *in vivo*. Endpoint is time to recurrence. An additional disadvantage is that it is very difficult to administer chemotherapy following cystectomy.

In one of the first adjuvant trials, Logothetis divided patients into three groups. Low-risk controls, high-risk controls who had one high-risk pathological finding (refused, not offered or had medical contra-indications to adjuvant chemotherapy) and high-risk patients treated with adjuvant chemotherapy.[34,35] There was clearly a benefit for the 71 patients at high risk who received adjuvant CISCA chemotherapy. Although this study is provocative, it is not a randomized trial. These patients were selected for treatment based upon their compliance and general medical conditions. This does not substitute for a controlled, randomized trial. It may suggest a benefit for adjuvant chemotherapy in highly selected patients.

There have been very few randomized trials evaluating adjuvant chemotherapy (Table 3). The trials have been difficult to interpret due to

Table 3: Trials of adjuvant chemotherapy following cystectomy[28]

Investigator	*Year*	*Chemo*	*Chemo*	*No chemo*	*Random-ized*	*Results*
Einstein[38]	1984	DDP	41	39	Yes	Yes pre-op RT. No benefit. Single agent DDP, few patients finished therapy
Logothetis[34,35]	1988	CISCA	62	71	No	Benefit but not randomized
Skinner[36]	1991	CAP	47	44	Yes	Benefit, but too few patients received therapy
Stockle[37]	1992	M-VAC/ M-VEC	23	26	Yes	Benefit, small patient numbers, premature closure, no treatment at relapse
Studer[39]	1994	DDP	40	37	Yes	No benefit, single-agent therapy probably inadequate
Bono[40]	1995	CM	48	35	Yes	No benefit for N0M0
Freiha[41]	1996	CMV	25	25	Yes	Benefit in relapse-free survival

problems such as small sample size and early closure. These trials suggest that there may be a benefit for adjuvant chemotherapy, but have not had enough statistical power to prove this.[36,37]

Two studies in the literature have received considerable attention. The most quoted is the Skinner study.[36] This was the first randomized prospective trial that showed a significant increase in time to progression and survival in patients who were randomized to receive chemotherapy. The dominant prognostic factor was extent of regional lymph node involvement at the time of cystectomy. The authors report their results in a planned four-month course of adjuvant chemotherapy versus observation. This trial demonstrates some of the difficulties in this kind of trial. Of 498 patients who underwent cystectomy, only 229 were pT3–4

or N+. Of 160 eligible patients, only 91 were randomized. Eleven then refused chemotherapy. Only 20/44 (45%) patients received four cycles of chemotherapy as planned.

This has been interpreted as a positive study. Median survival time for patients in the chemotherapy group was 4.3 years compared to 2.4 years in the observation group. In addition, important prognostic factors included age, gender and lymph node status. (Men above 65 years did well.) The number of involved lymph nodes was the single most important variable. This study has been highly criticized by medical oncologists for its retrospective use of subgroup analyses and its statistical methodology. Use of the Wilcoxin test may have provided artificial results in the context of the survival curves, which crossed over with follow-up. While chemotherapy appeared to prolong the median time to recurrence by 14 months, there was no residual advantage at two years.

The Mainz group published the other adjuvant study that has received a lot of attention.[37] Patients were randomized to either cystectomy or cystectomy followed by M-VAC or M-VEC. It treated small numbers of patients with poor risk factors. Sixty percent had positive nodes and most were stage T4.

The study was closed prematurely after an interim analysis revealed a benefit for those randomized to the chemotherapy arm, with 27% progression in the treated versus 82% progression in the control, untreated arm. This study was first published in 1992 and updated in 1995. Survival was markedly different between the two arms, as the authors did not treat the patients who relapsed in the observation arm. In an intent to treat analysis five-year progression-free survival 59% after the recommendation to receive chemotherapy versus 13% after a recommendation of cystectomy alone.[42]

Randomized adjuvant chemotherapy trials currently in the literature are not definitive, due to inadequate numbers, premature closure, deviations from protocol entry, patient selection, subset analysis, and failure to treat at relapse.

Decisions concerning individual patients must be made after careful examination of the histologic specimen and knowledge of the known relapse rates per pathologic stage. Studies have not clearly proven any advantage for adjuvant therapy based upon muscle infiltration alone (pT2). For patients with extravesical extension (pT3), additional therapy may be useful. For patients with nodal metastases (pN+) and direct

extension into the adjacent viscera (pT4), there is a suggestion of improved survival with adjuvant chemotherapy.[6] Randomized trials addressing this important issue are clearly needed.

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Chapter 13

Oncological rationale for function-sparing surgery

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Introduction

Recent quality of life studies demonstrated a definite advantage of orthotopic neobladders over other forms of continent or incontinent urinary diversion. Satisfactory functional results of an orthotopic bladder replacement require preservation of an adequate segment of the urethra, which in turn should not compromise the oncological outcome of cystectomy.

We studied the risk of synchronous or secondary urethral tumours after a longterm follow-up in both male and female patients with bladder cancer. The charts of 910 men and 356 women treated for various stages of bladder cancer between 1973 and 1992 were reviewed. Overall, only seven of 356 female patients (2%) and 37 of 910 male patients (4.4%) had urethral tumour involvement at initial presentation.

In women statistical comparison of various defined tumour localizations in the bladder revealed that the bladder neck ($p<0.000$) and the trigone ($p<0.035$) were significantly more often the region of primary tumour occurrence in the urethral tumour group. No urethral tumour involvement was seen among 104 candidates for curative radical cystectomy (cT2–3b, N-0, M-0).

Risk factors for urethral tumour occurrence in men are tumours at the bladder neck and recurrent multifocal tumours, but not CIS of the bladder not involving the bladder neck.

Function-sparing surgery in selected patients with bladder cancer does not compromise the oncological outcome of the operation. Quality of life, on the other hand, is improved with orthotopic bladder substitution, which may persuade patients to undergo surgery 'on time', i.e. at a time when the tumour stage is still highly favourable for cure.

Orthotopic neobladder

Orthotopic neobladders are the most natural way to reconstruct the urinary bladder. An increasing number of reports dealing with medium-term experiences with ureteral intestinal urethrostomy give us more details about how to select and follow patients, and how to reduce peri- and post-operative morbidity.[1] A recent report looked at the 25-year experience of a single centre in the management of more than 1,300 patients with invasive bladder cancer by radical cystectomy; tumour progression and survival in these patients were superior to those where a multi-modality organ-sparing treatment for advanced bladder neoplasms was attempted.[2,3] Even in patients 70 years and older, or those with previous or planned adjuvant chemo- and/or radiation therapy, an aggressive, curative, radical surgical approach with an orthotopic or continent cutaneous form of diversion is a viable treatment option leading to a 65% five-year survival rate, and a 92% continence rate in the elderly patient group.[4,5]

Continence rates of neobladders have increased in recent years and range between 80% and 90% for both male and female patients followed for more than six months. In some series there is even a higher continence rate seen with orthotopic neobladders than with cutaneous continent diversions.[6] In certain patients, however, diurnal or nocturnal incontinence will persist, despite extensive conservative management. Turner *et al.*, when looking at the factors influencing continence, found that autonomic nerve preservation, apart from enhancing potency, significantly improved post-operative continence.[7] Whether this is due to the meticulous dissection of the prostatic apex, or whether the preserved autonomic nerves increase the tonus of the smooth musculature, is unclear, but the results favour nerve-preservation for patients were this can be safely done from an oncological standpoint. Another factor influencing post-operative continence may be better patient selection using more refined imaging techniques such as transurethral ultrasound.[8]

Oncological rationale of urethral preservation in male patients

The reported incidence of secondary urethral tumours in male patients with bladder cancer is diverging. This is in part due to the fact that this problem has been examined under various aspects. Gowing *et al*., for example, autopsied patients dying *with* bladder cancer and found in six of 33 autopsies (18%) carcinoma *in situ*.[9] Stöckle *et al*., on the other hand, looked at urethral tumour recurremces after radical cystoprostatectomy.[10] They found urethral recurrences in 23 of 251 patients (9.2%) and suggested therefore a generous decision to perform primary prophylactic urethrectomy. Cordonnier and Spjut presented a series of 174 patients with cystectomy due to bladder cancer, out of which seven patients (4.02%) developed urethral cancer after two to 33 months.[11] No local staging was given, but three patients had the urethral recurrence within four months, and they concluded that urethrectomy should regularly accompany cystectomy. Ashworth's series in 1,307 patients with bladder tumours is the only report available, so far, where concomitant urethral tumours are related to the total number of cases treated for bladder cancer at the same institution.[12] Fifty of 914 male patients (5.4%) with benign papillomatous lesions or cancer had urethral tumours which were preferably treated by fulguration.

In our own series, the urethral tumour involvement was examined in 910 patients treated for bladder cancer at a single institution over a period of 25 years.[13] The overall incidence in 2,052 primary and recurrent bladder tumour events was 6.1%.

Seventeen of 89 patients had one to six urethral tumour recurrences which were all treated with transurethral resection and fulguration. The majority of urethral tumours were treated with a single conservative treatment session, and did not recur thereafter. It shows us that bladder cancer patients with secondary tumours in the urethra do not necessarily have to undergo urethrectomy. It may be speculated that the same is valid for patients with an orthotopic neobladder and a recurrent superficial tumour in the remnant urethra.

This retrospective study can be regarded as one of the largest series dealing with secondary urethral tumour occurrences in bladder tumours. It is one of the few studies that deals with the incidence of urethral tumours in the overall population of patients treated for bladder cancer. The majority of these patients (96.8%) were treated conservatively, i.e.

without major surgery or radiation. This allows us to assess the incidence of urethral tumours of patients with primary and recurrent bladder tumours of all stages.

Several authors either suggested or strongly recommended urethrectomy in conjunction with radical cystectomy for bladder cancer.[10,14,15] In recent years, orthotopic reconstruction of the lower urinary tract has gained popularity both with patients and doctors, which precludes a simultaneous prophylactic urethrectomy at the time of cystectomy, We therefore tried to assess risk factors such as localization, stage, multifocality, recurrence, etc. and clinical outcome of urethral tumour occurrence in bladder cancer patients.

A 6.1% overall incidence of urethral tumours is similar to several other studies dealing with this subject (Table 1). For a pre-operative assessment

Table 1. Review of the literature with documented cases of urethral tumour involvement in male patients with bladder cancer

Reference	*Study period*	*Numberof bladder tumour events*	*Number of urethral tumour events (%)*	*Number of bladder neck tumours*	*Cis in the bladder*
Ashworth[12]	1946–54	1,307	54 (4.1)	?	?
Levinson *et al.*[25]	1969–76	324	12 (3.7)	65	22
Hardeman *et al.*[17]	1975–87	102	14 (13.7)	37	20
Schellhammer *et al.*[14]	1961–73	461	32 (7.2)	?	5
Beahrs *et al.*[33]	1965–74	349	28 (8)	?	?
Stöckle *et al.*[10]	1967–87	251	23 (9.2)	?	21
Tongaonkar *et al.*[34]	1981–90	177	15 (8.5)	35	?
Cordonnier *et al.*[11]	1953–60	174	7 (4)	?	2
Raz *et al.*[35]	1955–76	174	10 (5.4)	3	?
Zabbo *et al.*[36]	1960–79	119	7 (5.9)	?	27
Hickey *et al.*[37]	1976–85	75	7 (10)	?	16
Faysal[38]	1963–77	59	8 (13.5)	1	6
Gowing[9]	?	33	6 (18)	?	6
Erckert *et al.*[13]	1969–94	2,052	126 (6.1)	104	116
Total		5,657	349 (6.2)		

of the risk of local recurrence in an increasing number of patients where the urethra is left indwelling after radical cystectomy, however, any additional data correlating risk to clinical or histological data would be helpful. A significant difference is evident in our study between those patients where a solitary TCC occurred in the bladder for the first time (2.6%) and those with recurrent multifocal cancer (10.1%). This may be a factor in the decision-making process, whether an orthotopic neobladder is prudent or whether a synchronous urethrectomy should be performed.

We tried to sort out those patients which according to their clinical staging would nowadays be good candidates for radical surgery with the option of an orthotopic neobladder. These patients with a clinically staged T2–3 N-0, M-0 TCC had a lower rate (4.2%) of urethral tumour occurrence than the average 6.1% of the whole study group. If all node-positive patients (N0–2) were included in this group, the urethral tumour rate was still 4.3%. A tendency towards solitary tumours, a more aggressive initial therapy, and a decreased life expectancy resulting in shorter follow-up times may account for the lower urethral tumour rate in this group. Due to a changing treatment pattern of bladder cancer in an increasing number of patients resulting in radical surgery at an earlier stage, these data may be helpful when consenting a patient to a subsequent orthortopic neobladder.[16]

Another aspect is the occurrence of CIS or papillary tumours in the remaining urethra after an orthotopic neobladder. Contrary to other authors, we did not see an increased risk of urethral tumours in our patients with CIS of the bladder.[17–19] This may in part be due to the fact that dysplasia or CIS of the urethra may have been missed in conservatively treated patients. One might argue, however, that clinically important dysplasia or CIS left untreated or treated conservatively and followed long-term should eventually have resulted in overt and clinically important urethral cancer.

To evaluate the risks associated with urethral preservation and orthotopic bladder replacement in bladder cancer, the outcome of radical cystectomy was studied in 70 men with bladder cancer with a mean follow-up of 35 months.[20] The overall urethral recurrence rate was 3%. None of the patients with prostatic transitional cell cancer died secondary to a urethral recurrence. The results suggest that orthotopic neobladder reconstruction is not contra-indicated in bladder cancer patients with prostatic involvement, provided the margins are negative.

In conclusion we have found urethral tumours in 6.1% of 2,052 primary or recurrent tumour events of 910 male bladder cancer patients of all stages treated at a single institution over a period of 25 years. Risk factors for urethral tumour occurrence are tumours at the bladder neck and recurrent multifocal tumours. CIS of the bladder not involving the bladder neck, and muscle-invasive tumours with or without lymph node involvement are not significantly correlated with urethral cancer. Those patients at risk for urethral tumours should be worked up more carefully (multiple urethral biopsies and/or urethral brushings, frozen section of the membranous urethra) before an orthotopic urinary diversion to the urethra is considered. The majority of patients with urethral tumours in our study group had a single conservative treatment session, and did not recur thereafter. A conservative approach for superficial urethral tumour recurrences in patients with an orthotopic neobladder to the urethra may therefore be feasible.

Oncological rationale of urethral preservation in female patients

In the European Union, bladder cancer in women is only the 14th leading cause of cancer, whereas it is the fifth leading cause of cancer in males. Numbers in many studies dealing with concomitant urethral tumours or urethral recurrence in patients with bladder cancer have been too small to draw any conclusions or to show at least a trend for female patients. There has recently been focused interest, however, in data concerning the risk of secondary urethral tumours in female bladder cancer patients undergoing surgery.[21] If an adequate segment of the caudal urethra can be spared at cystectomy with a minimal risk of tumour recurrence, it may be used for continent orthotopic reconstruction of the lower urinary tract, as for males.[22] Risk factors for urethral involvement in female bladder cancer patients were not known up to then.

Until recently, few data existed about urethral involvement in women with bladder cancer. In the older literature concentrating in urethral tumour involvement of male patients with bladder cancer female cases are only rarely discussed.[8,12] Nevertheless, routine urethrectomy in all female patients with bladder cancer was the norm.[9]

In an endoscopy study, urethral tumours were seen in 1.4% of 293 female patients presenting with bladder cancer, in contrast to 4.1% of 1,307 male patients.[12] This has been the only study so far that used a large,

more-or-less unselected female bladder cancer population for the study of urethral bladder tumour involvement. The result is similar to the data found in Innsbruck, with a rate of 2% of urethral tumour involvement in 356 female patients with biopsy proven bladder cancer of all grades and stages and a mean follow-up of 5.5 years.

One of the reasons for the apparent lower incidence of secondary urethral tumours in females in comparison to males may be the fact that transitional cell mucosa in females covers a much smaller urethral segment, the rest being normal or metaplastic squamous cell mucosa. The majority of bladder tumours (in this study population 93%) are transitional cell carcinoma. The area at risk in the female urethra is therefore small, and probably even diminishes with increasing age because the demarcation line between squamous and transitional cell mucosa moves craniad in the menopause.[23] In the sixth and seventh decades, when most of the bladder tumours occured in these patients, metaplastic squamous cell mucosa may cover the whole urethra, bladder neck and a portion of the trigone.

De Paepe *et al*., studying urethral involvement in 22 cystectomized female patients, however, found carcinoma *in situ* or overt papillary tumour in the urethra in eight patients (36%) concluding that the urethra should be removed in all female patients undergoing radical cystectomy for bladder cancer.[24] In this study, unfortunately, there are no details regarding localization of either primary tumour(s) in the bladder or secondary tumour(s) in the urethra. We know that at least one of the patients in the series had direct extension of bladder neck tumour into the urethral wall. The overall number of eight patients with urethral involvement seen over a period of 15 years does not seem to be too different from the seven patients seen in the previous study over a period of 20 years.

The fact that tumour involvement of the bladder neck and prostatic urethra is a possible predictor for synchronous or recurrent urethral tumours in male patients has been shown by several authors.[17,25] There is also a recent report describing the close coincidence between tumour involvement of the bladder neck and urethra in females.[26] Neither in this patient group nor in our study population was there urethral bladder cancer involvement without simultaneous tumour involvement at the bladder neck. Apart from a highly significant correlation between bladder neck and urethral tumour involvement ($p=0.000$), and a marginally significant correlation between trigone and urethral tumour involvement ($p<0.035$), none of the other bladder regions coincided significantly with secondary urethral tumours in

our study. Note that all patients, regardless of the histology, had tumour at the bladder neck, whereas some of the patients with multifocal tumours had additional tumour sites at the trigone, lateral and posterior walls, and vault. We did not find any patient in the group with recurrent bladder tumours, whether progressing or not, who had overt urethral tumour at any of the recurrences over the years.

Considering only patients with invasive localized disease (T2–3b, N-0, M-0) who would have been good candidates for radical surgical treatment, just one of 104 patients (62 primary and 42 recurrent patients as outlined above), or roughly 1%, had secondary urethral cancer. Among all 96 invasive (T2–4) TCC patients were three patients with urethral tumour involvement, resulting in an involvement rate of 3.1% for this subgroup. One of the reasons for the relatively small differences in the rate of urethral cancer between the overall study population and these subgroups (2% versus 1% and 3.1% respectively) might be the fact that the urethral tumour group is small and heterogeneous.

The only consistent risk factor for urethral tumours in this study group was tumour localized at the bladder neck at initial presentation (7/7 patients). Five of the seven patients had grade 3 tumours, but neither stage, multicentricity, number of tumours, presence of CIS, nor duration of the disease seemed to play a predominant role.

From these data one may conclude that female patients without tumour either at the bladder neck or at frozen section of the proximal urethra at the time of cystectomy can probably be spared a portion of the urethra to enable lower urinary reconstruction to the urethra without running a greater risk of developing recurrent urethral tumours than their selected male counterparts. We would therefore recommend several biopsies of the bladder neck in all patients where a subtotal urethrectomy is considered. Any woman with a finding of atypia or overt tumour at the bladder neck is at risk for developing recurrent urethral tumour after cystectomy and should probably undergo simultaneous total urethrectomy. Patients in whom curative radical cystectomy is indicated and who are good candidates for an orthotopic reconstruction of the lower urinary tract may be spared a segment of the urethra for that purpose, provided that multiple pre-operative biopsies of the bladder neck and the frozen section of the urethra at the time of surgery are free of atypia or tumour.

Based on the results of this study, as well as anatomical data of the continence mechanism of the female urethra, we started a clinical protocol

offering a ureteroileal urethrostomy to carefully selected female patients undergoing radical cystectomy for localized bladder cancer, if their bladder neck was free of tumour as shown by preoperative multiple biopsies and bimanual palpation.[22] The technique and preliminary data have been reported.[21,27,28] We do not promote, however, to leave the urethra – or a portion of it – in unless it is used for reconstructive purposes, because it can easily be removed en bloc with the bladder specimen and it is difficult to follow when left in as a blind-ending sac.

Reviewing the literature, 35 cases of documented urethral tumour involvement (including CIS) in female patients with bladder cancer, was found and added seven cases of our own study population (Table 2). The overall incidence according to this table would be 4.3% (34 out of 794 patients). With the exception of the Clark reference, all authors used a highly selected group of cystectomized patients. The actual number of

Table 2: Review of the literature with documented cases of urethral tumour involvement or carcinoma *in situ* in female patients with bladder cancer

Author	*Study period*	*Number of patients*	*Number of BN tumours*	*Number of urethral tumours*	*Cis*
Riches *et al.*[39]	ng	19*	3	3	–
Ashworth[12]	ng	293	ng	4	–
Clark	1964–79	ng	ng	2	–
Richie *et al.*[19]	1969–71	21*	ng	–	1
Coutts *et al.*[15]	1974–83	18*	ng	2	1
De Paepe *et al.*[24]	1974–88	22*	ng	5	3
Stein *et al.*[26]	1982–92	65*	16	7	–
Stenzl *et al.*[40]	1973–92	356	49	6	–
Total		794		29	5

ng=no data were given
BN=bladder neck
* heterogeneously selected bladder cancer study populations

women seen and treated for bladder cancer at any of these institutions should have been higher. In order to obtain an overall urethral involvement rate for female bladder cancer patients it is therefore misleading to use percentages only out of the total number of cystectomized patients that have been worked up in these studies.

In summary, 356 female patients with different stages of bladder tumour for up to 33 years have been followed. The incidence of urethral tumour involvement was 2% for the whole study group, 3.1% for a subgroup of invasive (T2–4) TCC, and 1% for localized (T2–3b, N-0, M-0) invasive cancer amenable to radical cystectomy. The only consistent risk factor found in this study for secondary urethral cancer was simultaneous primary tumour involvement of the bladder neck. Concomitant urethral tumours were neither seen in patients with a bladder neck free of tumour nor in patients with tumour recurrences. There was no correlation between urethral cancer and any other prognostic factor. It may be concluded that a large segment of the urethra can safely be left in for selected cysectomized female patients undergoing orthotopic urinary reconstruction to the remnant urethra, provided neither pre-operative biopsies of the bladder neck nor intra-operative frozen section of the urethra at the level of dissection show any tumour or atypia.

Bladder substitution and quality of life

An increasing number of radical cystectomies in recent years have led to a growing desire for appliance-free urinary diversions to improve quality of life and body image. The results show that 96% and 79% respectively of patients with orthotopic neobladders resume their daily living activities and occupational status, and that 85% are totally continent day and night, while the remainder seem to manage a partial incontinence well with pads.[6,29] Continence, as reported by these authors, was by far better for the neobladder group than for the cutaneous continent diversions (85% versus 61%). Patients with continent cutaneous diversions when compared to wet stomas seem to respond almost equally positively, showing signs of enhanced vitality.[30] Quality of life assessment using the Sickness Impact Profile revealed an advantage for an orthotopic reservoir over a heterotopic diversion.[6]

Apparently we should rethink old doctrines claiming that orthotopic neobladders are indicated in male patients only. Clinical series comprising

female patients with orthotopic neobladders, in the majority due to bladder neoplasms, revealed results comparable to those obtained in male neobladder series. A complete daytime and night-time continence of 88% and 79–82% respectively was reported in the two largest series, with a total of 64 patients followed up to 70 months (median 30 months in one series).[31,32] In this combined series, six of 64 patients (10%) required some form of intermittent catheterization – in the majority once in the morning or evening – to completely empty their neobladder. When counselling female patients for cystectomy, an orthotopic neobladder must therefore be offered as an option of urinary diversion.

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Chapter 14

Combination therapy and function-sparing surgery for muscle-invasive bladder cancer

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Introduction

The American Cancer Society has estimated that there will be 53,200 new cases of bladder cancer diagnosed in the United States this year.[1] Of these, approximately 70% will be of the superficial subtype that can frequently be managed with transurethral resection (TUR), intravesical therapy in selected cases, and careful surveillance for recurrence or progression. The remaining 30% of patients, however, are diagnosed with a far more virulent phenotype of bladder cancer that is invasive into the muscular wall of the bladder, demonstrates significantly increased metastatic potential, and is responsible in large part for the considerable morbidity and mortality associated with the disease. Over 12,200 people are estimated to die from bladder cancer this year, and the overwhelming majority of these patients represent those who present with an invasive phenotype that progresses to metastatic disease.[1]

The goals of treatment for patients with muscle-invasive bladder cancer are to control the primary tumour, eradicate systemic and loco-regional

disease, and improve patient survival, while at the same time minimize the effects of therapy on patient quality of life. Traditionally, patients with muscle-invasive bladder cancer without evidence of systemic disease have been offered treatment with radical cystectomy and urinary diversion as a gold standard for local control of the primary tumour. Alternatively, some investigators have championed the use of partial cystectomy, radical TUR, external beam radiotherapy, and systemic cytotoxic chemotherapy as effective means of achieving local control in highly selected patients. With regard to regional and systemic disease, cytotoxic chemotherapy is the mainstay of treatment. Disease-free survival has been primarily determined by pathologic stage at the time of surgery, but has been influenced in recent years by the use of neo-adjuvant and adjuvant therapies employed with the intent of clinically downstaging the primary tumour and eliminating microscopic subclinical systemic disease.[2] These regimens have been highly effective in eradicating local and metastatic tumour, and altering the natural history of the disease in selected patients. Furthermore, these encouraging results, particularly with respect to the response of the primary tumour to therapies other than radical surgical extirpation, have served as an impetus for the development of multimodal approaches to the treatment of muscle-invasive bladder cancer with an eye towards maintaining the native bladder in situ. These 'bladder-sparing' or 'function-sparing' protocols have shown initial promise as potentially effective therapies that allow the patient to maintain a functional bladder, eliminate any microscopic systemic residual disease, and avoid the major morbidity and quality of life issues that surround radical cystectomy and urinary diversion.[3] In this review, different approaches to multimodal treatment of bladder cancer with an attempt at bladder sparing will be examined, looking at morbidity, disease specific and overall survival, and the ability to maintain a functioning bladder.

The Evolving Concept Of Bladder Conservation For Muscle-invasive Bladder Cancer

There have been many studies employing combinatorial or multimodal therapy reported in the literature for muscle-invasive bladder cancer, although not all of them were designed with bladder function sparing as

a goal of therapy. Different approaches that have been studied include radical cystectomy with adjuvant or neo-adjuvant radiation therapy, radical cystectomy with adjuvant or neo-adjuvant cytotoxic chemotherapy, radical TUR with chemotherapy or radiation therapy, or both, and partial cystectomy with neo-adjuvant or adjuvant chemotherapy. What all of these clinical investigations have in common is the recognition that the application of unimodal therapy in the treatment of muscle-invasive bladder cancer has not resulted in significant improvements in patient outcome, particularly in patients with advanced stage disease at high risk for systemic relapse. Herr reported on the efficacy of unimodal and multimodal therapy for patients with muscle-invasive bladder cancer in a recent review.[2] He noted that patient survival was not dictated by the type of procedure performed but rather by the stage of the primary tumour. In his review of the literature, Herr found similar survival rates for patients with T2 tumours who underwent radical TUR (57–70% five-year survival) when compared to patients who underwent radical cystectomy (50–88% five-year survival), but both techniques proved to be insufficient therapy in patients with more advanced stage disease. In T3b patients, the five-year survival rate for patients undergoing TUR was 2–7% and for those undergoing radical cystectomy, the five-year survival was 6–40%. In the end, these statistics serve to demonstrate that adequate local control can be achieved through a variety of means in carefully selected patients, but with more advanced stage disease, survival rates are diminished in the face of systemic metastases that are not impacted upon by the application of a local therapy. Only with multimodal approaches, such as the addition of adjuvant or neo-adjuvant chemotherapy and/or radiation therapy, were significant improvements made in the survival of patients with advanced stage disease (≥T3).

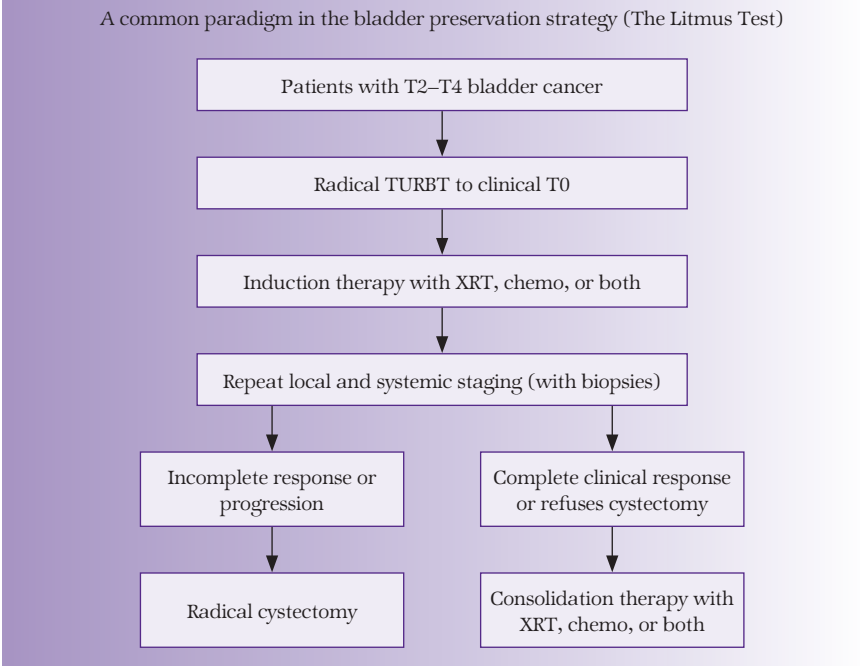
The Argument Against Function-Sparing Surgery For Muscle-invasive Bladder Cancer

If local control can be achieved in selected patients without performing radical cystectomy, why hasn't function-sparing surgery become more commonplace in the armamentarium of the urologic oncologist treating bladder cancer patients? There is significant concern that TUR alone

is inadequate as a modality that can accurately evaluate the bladder for residual cancer. Radical cystectomy specimens have frequently demonstrated submucosal spread of tumour, so called 'linitus plastica', that would not be appreciated by TUR resection. Furthermore, studies in bladder cancer have confirmed the presence of a field effect in this disease, where the remaining urothelium possesses a significant malignant potential that could result in recurrence and disease progression with treatment approaches more conservative than radical cystectomy.[4] Another argument against function-sparing surgery for muscle-invasive disease is the lack of adequate local and regional staging, and the potential loss of a window of opportunity for curative surgery in a patient with nodal disease. Lerner et al. have demonstrated an enhanced survival of patients with nodal metastases who undergo radical cystectomy and extended pelvic lymph-node dissection, which would obviously be missed in patients undergoing less invasive procedures aimed at organ preservation.[5] Finally, patients who fail attempts at organ preservation therapies involving radiation, aggressive TUR, partial cystectomy, and/or systemic chemotherapy are invariably subjected to a salvage cystectomy, provided they have not developed systemic metastases, which is significantly more morbid than a primary radical cystectomy. With the advent and widespread use of orthotopic urinary diversion, many surgeons feel that radical cystectomy with a functional bladder replacement is a reasonable and satisfactory alternative to organ-sparing surgery, while at the same time minimizing the risk of local recurrence in the pelvis due to the retained bladder.[4]

The main concern at the heart of the debate surrounding organ preservation is the question of whether the urologic oncologist can accurately assess and remove the primary tumour burden, either with surgery alone or in combination with radiation and/or chemotherapy, leaving a functional bladder intact. In a recent review, Herr examined the literature of published cystectomy series to identify the rate of p0 specimens at cystectomy after patients underwent TUR and subsequent radical cystectomy for muscle-invasive disease.[2] He noted an overall p0 rate of 12.2%, thus indicating that TUR alone, in selected patients, could remove all residual tumour in the bladder and obviate the need for consolidation with radical cystectomy. When multimodal therapies are applied, the results are even better with regard to eliminating the primary tumour from the bladder. Housett et al. reported on a series of patients who underwent a chemo-radiation protocol that combined radiation therapy with 5-

Figure 1: Paradigm for bladder preservation protocols.



flourouracil and cisplatin.[6] They noted a 70% clinical complete response rate and a 100% pathologic complete response rate in the first 18 patients who underwent cystectomy after the chemo-radiation. Similarly, Scher et al. noted a 48% clinical response rate and a 50% pathologic complete response rate in patients who underwent an aggressive TUR followed by two to five courses of MVAC chemotherapy.[7] These successes, along with those of others, have served as an impetus to design a paradigm that includes bladder preservation as a reasonable outcome of treatment, even in patients with advanced stage local disease. This paradigm is depicted in Figure 1.

Defining Success In Bladder Conservation Protocols

One of the major impediments to interpreting the literature on bladder conservation protocols is trying to define measurements of success. Clinical series in the literature report survival rates, recurrence rates, and bladder

conservation rates. Yet it remains for the reader to assess what constitutes a successful strategy based on the interpretation of the data. For example, a series might report a recurrence rate of 50%, which at first glance might seem like a poor result, but if the recurrences are easily managed with TUR or intravesical therapy, and the bladder remains in situ, this recurrence rate would be deemed acceptable. Investigators may report a high rate of bladder conservation, but if patients progress to metastatic disease and die with their bladder in situ, they should not be considered as a success in the bladder conservation category. Conversely, authors may report a significant survival rate associated with a bladder conservation approach, but the number of patients who actually survive with a functional intact bladder may be a small percentage of the number enrolled in the trial, due to the incorporation of salvage cystectomy for disease progression. Would these patients be considered failures, because they required a salvage procedure, or a success, in that the oncologist has given them more time with a functional bladder prior to undergoing cystectomy, without allowing the disease to spread systemically? Ultimately, it is patient survival and disease-free survival, with the bladder left in situ, that should serve as the standard for comparison to alternative strategies for treatment of muscle-invasive bladder cancer. Only then can the data regarding bladder preservation strategies be interpreted relative to more radical approaches.

Function-Sparing Approaches With Chemotherapy and Conservative Surgery

Herr et al. further championed the potential for bladder preservation in highly selected patients in a study that examined the role of neo-adjuvant M-VAC chemotherapy after aggressive TUR, and subsequent surgical consolidation via partial cystectomy in a select group of patients that had lesions amenable to this approach.[8] In this series, 26 of 111 patients were considered to be candidates for partial cystectomy after TUR and M-VAC chemotherapy. The pre-treatment stage of these patients included 19 T2 and seven ≥T3 tumours. After reviewing the partial cystectomy specimens, the authors noted that 77% of patients were downstaged to ≤T1 and there was a 47% p0 rate. Overall, the five-year disease-free survival was 65%, and

Table 1: Published series on bladder preservation with chemotherapy and conservative surgery.

Author	*Number of patients*	*Chemo*	*Response (CR)*	*Surgery*	*Bladder preservation*	*Survival*
Srougi (1994)[9]	30	M-VAC	47%	TUR-19 Partial-11	20%	53% (5 year)
Angulo (1996)[10]	61	M-VAC	33%	TUR	18%	47% (5 year)
Herr (1998)[11]	43	M-VAC	54%	TUR-28 Partial-15	58%	74% (10 year)
Thomas (1998)[12]	50	CM	76%	TUR-44 Partial-6	36%	48% (5 year)

C = cisplatin M = methotrexate A = adriamycin V = vinblastine
TUR = transurethral resection Partial = partial cystectomy CR = complete response

54% of patients survived with an intact and functional bladder. These data serve as compelling evidence for the implementation of more conservative surgery (radical TUR or partial cystectomy) in combination with a multimodal approach, in an attempt to preserve a functioning bladder in spite of the presence of muscle-invasive disease. As a consequence, other investigators have reported on series employing conservative surgery with chemotherapy, the results of which are demonstrated in Table 1. Looking at all of these studies to determine the efficacy of a bladder sparing approach that incorporates surgery and chemotherapy, it becomes obvious that the Herr series stands alone with regard to results for survival and the retainment of a functional bladder.

As noted above, Dr Herr's report represents a group of highly selected patients where the M-VAC chemotherapy served as a litmus test to stratify patients for suitability for an organ-sparing approach. The other series in the table do not demonstrate this same rigorous selection bias and therefore the results are not as successful. One could predict that a patient with muscle-invasive bladder cancer being considered for bladder sparing with conservative surgery and chemotherapy would have a 50% chance of surviving five years from diagnosis and a 20–30% chance of keeping their bladder in situ.

Identification Of Adverse Prognostic Factors That Might Preclude Bladder Conservation

Clearly, not everyone is a candidate for function-sparing surgery and a thorough review of the clinical presentation of patients who failed function-sparing strategies has identified risk factors that should be considered carefully when contemplating an organ-sparing approach. Herr et al. noted that the presence of residual tumour following induction therapy portended a poorer prognosis and likely failure of bladder sparing. They also note that this risk directly correlated with the stage of the tumour found after response to chemotherapy.[8] Other factors that have correlated with poor results in bladder-sparing approaches to muscle-invasive bladder cancer include the presence of hydronephrosis at presentation, involvement of the bladder neck or prostate, advanced tumour size and stage at presentation (≥T3a), advanced tumour grade (grade III), non-papillary histology, and adverse molecular markers such as a mutated p53 gene.[13,14]

Of these, the most ominous finding appears to be the presence of residual tumour following systemic chemotherapy and radical TUR. This was demonstrated in a recent series reported on by Herr et al. The authors noted that patients who were T0 following therapy had a 75% 10-year survival and a 61% chance of maintaining a functional bladder. However, patients who did not have a complete clinical response to therapy did much worse, in spite of the performance of a salvage cystectomy, indicating that the chemotherapy and TUR procedure served as a 'litmus test' to stratify patients according the biology of their disease.[11]

Function Sparing-Approaches With Radiation and Chemo-radiation

Radiation oncologists have promoted the role of external beam radiotherapy (XRT), alone or in combination with cytotoxic chemotherapy that may act as a radiosensitizer, in the treatment of muscle-invasive bladder cancer. While the traditional role of XRT in the treatment of bladder cancer has been limited to neo-adjuvant therapy or used in patients who were not candidates for surgical therapy due to co-morbidities or locally advanced

disease, recently published series have demonstrated impressive results. Sauer et al. demonstrated the significant contribution of chemotherapy to XRT, so-called 'chemo-radiation', in a recent report of 333 patients.[15] In this series, 128 patients with muscle-invasive disease underwent XRT alone, whereas an additional 205 patients received a radiosensitizing dose of a platin derivative (cisplatin or carboplatin) in addition to the XRT. All of the patients underwent an aggressive TUR prior to the initiation of therapy. The authors noted a 57% complete response rate in the XRT alone group versus an 80% complete response rate in the patients who received the platin derivative in addition to the XRT. In this series, clinical response to treatment was the most important predictor of survival and bladder preservation, which was clearly superior in the chemo-radiation group. Overall, in this study they reported that 70% of surviving patients had a functioning bladder and the five-year cause-specific survival was 40% for the XRT group and 60% for the chemo-radiation group. Not all investigators have had success with this approach, however. Given et al. recently reported on a series of 94 patients treated with TUR, XRT, and either M-VAC or MCV chemotherapy.[16] The authors noted that 57% of patients had a local recurrence during follow-up and only 18% of patients enrolled in the study were alive with a functioning bladder at five years. The five-year overall survival rate for the patients who had their bladder spared was 40%, whereas a 65% five-year survival rate was noted in patients who were brought to salvage cystectomy at time of failure. The results of this study emphasize the need for careful patient selection and close surveillance after therapy to look for evidence of recurrence in the remaining at risk urothelium.

The radiation oncology literature is replete with a series of trials incorporating various chemo-radiation protocols with a goal of bladder sparing in patients with muscle-invasive disease. A number of these protocols are summarized in Table 2. A summary of the data would suggest five-year survival rates and bladder preservation rates in the range of 50–60%, with chemo-radiation. Future trials promise to aim at improved patient selection and increasing dose delivery to the tumour to try improve on results that are comparable to some radical cystectomy series published in the literature.

Table 2: Published series on bladder preservation with chemo-radiation.

Author	*No of patients*	*Induction*	*Response (CR)*	*Consolidation*	*Bladder preservation*	*Survival*
Farah (1991)[17]	25	MVAC	32%	XRT	28%	73% (3 year)
Kaufman (1993)[18]	53	MCV/XRT+C	53%	XRT+C	58%	48% (4 year)
Dunst (1994)[19]	245	XRT+C	79%	N/A	83%	47% (5 year) 26% (10 year)
Given (1994)[16]	94	MCV+/-A	40%	XRT	41%	57% (5 year)
Orsatti (1995)[20]	76	C+FU or C/ M+XRT	81%	N/A	53%	42% (5 year)
Danesi (1997)[21]	25	MCV	52%	XRT+C, FU	81.7%	71.4% (4 year)
Sanguineti (1997)[13]	72	M, C, FU+XRT	N/A	Cycled Therapy	40%	45% (5 year)
Zeitman (1998)[22]	18	C, FU+XRT	78%	MCV	78%	83% (3 year)
Shipley (1998)[23]	123	C, XRT+/- MCV	59%	XRT+C	38%	49% (5 year)
Serretta (1998)[24]	40	MCV	47%	XRT	55%	50% (5 year)
Cervek (1998)[25]	105	MCV	52%	XRT	69%	58% (4 year)

C = cisplatin M = methotrexate A = adriamycin V = vinblastine
FU = 5-flourouracil XRT = external beam radiotherapy CR = complete response

Conclusions

Bladder preservation, through a combination of TUR, chemotherapy, partial cystectomy, and XRT, remains a reasonable approach to therapy for muscle-invasive bladder cancer in highly selected patients. Induction with chemotherapy and an aggressive TUR serves as a litmus test to determine suitability for this approach, based on tumour response. Patient selection

remains the key to success for future clinical practice of bladder conservation strategies, and recognition of risk factors that portend a poor prognosis with bladder sparing should be further refined and heeded. While radical cystectomy should still remain the gold standard of therapy for patients with muscle-invasive bladder cancer, with pelvic cure rates of 85–90%, the survival data reported in the literature for patients undergoing bladder sparing is comparable to many radical cystectomy series. Further investigations should focus on therapies that promise improved survival rates for patients with muscle-invasive bladder cancer, while at the same time increasing the likelihood of maintaining a functional native bladder after therapy. Careful follow-up and a low threshold for salvage cystectomy may improve overall survival rates with this approach, but the data presented above clearly indicate that there are a subset of patients with muscle-invasive bladder cancer who could be cured and keep their bladder in place. Opponents argue that the orthotopic diversion obviates the need for a bladder conservation strategy, but it is unlikely that bladder replacement will offer the patient the same quality of life that bladder conservation can.

In the end, it remains the challenge to the urologic oncologist to develop strategies that recognize and target tumour virulence that results in systemic disease, which is ultimately the harbinger of patient morbidity and mortality, regardless of the local therapy applied.

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Chapter 15

Chemotherapy of metastatic transitional cell cancer

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Introduction

Bladder cancer is an extremely common cancer throughout the world. It is estimated that, per year, there are 261,000 cases of bladder cancer and 115,000 deaths from bladder cancer worldwide.[1] It is the fifth most common cancer in men and the seventh in women, with an annual incidence of approximately 18 cases per 100,000 in the United States. An estimated 54,500 new cases in 1999 led to some 12,000 deaths.[2] The male to female occurrence is three to one. It is primarily a disease of the elderly, with 80% of cases in the 50–79-year age groups, and a peak incidence in the seventh decade.

In the Western world most bladder cancers are transitional cell carcinoma (TCC). Squamous cell carcinoma (SCC) and adenocarcinomas account for 5% and 2% respectively. Adenocarcinomas may arise in the dome of the bladder from a primary site in the urachus, but most often occur in the trigone. SCC is often associated with chronic irritation or infection. SCC of the bilharzial bladder differs from the bladder cancer seen in Europe and the United States. SCC has diverse etiologies and biology from TCC and merit separate discussion.[3]

In cases involving regional spread or distant spread, five-year survival rates are 49% and 6% respectively. Seventy-five percent of all bladder cancers are superficial at presentation, limited to the mucosa, submucosa, or lamina propria. Recurrence rates after initial treatment are 50–80%,

with progression to muscle-invading tumour in 10–25% of cases. In muscle-invading bladder cancers, there is a 50% risk of distant metastases. In both instances, the challenge to physicians is to identify those tumours that are biologically aggressive and that have the potential to result in mortality.

Systemic chemotherapy is the only current modality that provides the potential for longterm survival in patients with metastatic urothelial tumours. Anti-tumour activity has been demonstrated with several single agents, with only rare improvements in survival.[4] Response rates to single agent chemotherapy are detailed in Table 1.

The development of cisplatin-based combination chemotherapy regimens for the treatment of patients with metastatic urothelial cancer was

Table 1: Response to single agents in advanced urothelial cancer

Single agent chemotherapy	*No.*	*CR + PR %*	*95% confidence limits*
Methotrexate	236	29	23–35
Cisplatin	578	30	26–34
Adriamycin	269	19	14–24
Vinblastine	42	14	3–25
Cyclophosphamide	26	8	0–10
Ifosfamide	47	21	9–33
Epirubicin	33	15	3–27
Carboplatin	174	13	8–18
Piritrexim	29	38	20–56
Trimetrexate	51	17	7–30
Mitomycin C	42	13	3–23
5-Fluorouracil	75	35	24–46
Gemcitabine	120	28	20–36
Gallium nitrate	66	17	8–26
Taxol	26	42	23–63
Lobaplatin	22	12	0–30
Topotecan	46	10	3–23

CR=complete response PR=partial response
95% confidence limit=95% confidence limits, modified from Sternberg[5]

pre-eminent in the 1980s. M-VAC (methotrexate, vinblastine, adriamycin, cisplatin), CMV (cisplatin, methotrexate, vinblastine) CM (cisplatin, methotrexate), and CISCA/CAP (cyclophosphamide, adriamycin, cisplatin) have been considered among the most active regimens.[6–8]

A combination of the most active single agents at the time created these schemas. The median duration of survival for single agents varied between four and six months. Survival with combination regimens, such as methotrexate plus vinblastine or for adriamycin and cisplatin was eight months.[9]

It has been 15 years since the M-VAC regimen was first developed at Memorial Hospital.[10] In 121 cases with bidimensionally measurable disease, the CR and PR rate was 72%. Thirty-six percent of patients attained a CR. Long-term survival was achieved in patients who attained CR. Patients who achieved a CR to chemotherapy plus surgery had twice the survival of patients who had PR alone.[6] Overall survival for the whole group was 13.1 months. Chemotherapy was shown to be more effective against nodal disease than visceral metastases.[6,11]

These data have been updated by the Memorial group, who reported results in 203 patients treated with M-VAC regimens. At a median follow-up of 47 months, 46 patients attained a CR with chemotherapy alone. The five-year survival rate was 40%. In 30 patients who had a CR with chemotherapy plus surgery, five-year survival was 33% at a median follow-up of 37 months. Post-chemotherapy resection of viable tumour resulted in long-term survival in selected patients.[12]

Of note, response to cisplatin-based therapy is usually rapid. Elderly patients over 70 years old, particularly those with compromised performance status, may be treated by reducing all doses of chemotherapy by 20–30% in order to evaluate their tolerance to therapy.

Given these high response rates with M-VAC, the Southeastern Cancer Study Group studied M-VAC versus single-agent cisplatin (DDP). In 246 evaluable patients, response was observed in 12% treated with DDP, compared with 39% treated with M-VAC. Seventeen (13%) patients achieved CR with M-VAC ($p<0.0001$). The median duration of response was 4.3 months with DDP compared to 10 months with M-VAC. Median survival for M-VAC-treated patients was 12.5 months compared with 8.2 months for patients given DDP ($p=0.0002$).[13]

The question of M-VAC superiority versus CISCA was evaluated at MD Anderson. M-VAC was found to be superior to CISCA. The median survival

was 11.2 months after M-VAC compared to 8.4 months with CISCA. The CR + PR rate was 65% with M-VAC and 46% with CISCA ($p<0.05$).[11]

Thus, two prospective randomized trials have clearly proven the superiority of M-VAC over single-agent chemotherapy. The median survival after M-VAC in these two studies was approximately one year, similar to the median survival reported at Memorial (13 months).[11,13] M-VAC is not the only cisplatin-based regimen in use. In Europe, CM, CMV and M-VEC (cisplatin + methotrexate + vinblastine + epirubicin) are also commonly used.

Unfortunately, the use of cisplatin-based combination chemotherapy results is associated with significant toxicity and produces long-term survival in only approximately 15–20% of patients. The median survival duration is only 13 months, and long-term survival is attained in approximately 15% of patients with metastases in visceral sites and 30% of those with nodal disease. In one study, only 3.2% of patients with metastatic lesions treated with M-VAC were alive and free of disease.[14] Therefore, other therapeutic options and strategies are clearly needed.[15,16]

Increasing the dose intensity of established chemotherapeutic regimens such as M-VAC by adding haematopoietic growth factors may or may not lead to an improvement in overall survival. Novel chemotherapeutic agents, such as the taxanes and gemcitabine, are among the most interesting therapeutic options available.[5]

Haematopoietic growth factors and dose intensity

Strategies to increase CR include augmenting the dose of chemotherapy with haematologic growth factor support. When M-VAC was given with G-CSF, mucositis and myelosuppression were ameliorated.[17] After initial favourable reports of responses in heavily pre-treated patients with escalated M-VAC and growth factors, several groups performed phase II trials of escalated chemotherapy.[4,18–20] In the United States, this approach was largely abandoned due to toxicity.[19,20]

The EORTC Genitourinary Group trial is the only study that addressed the issue of dose-intensity in a randomized trial compared to standard M-VAC.[21] With a two-weekly schedule plus G-CSF it was possible to deliver twice the dose of DDP and ADM in half the time, with fewer dose delays and less toxicity. This decrease in toxicity as compared to standard M-VAC was most likely attributable to the G-CSF. This trial revealed survival rates

of 14.5 months versus 14.1 months and less toxicity with high-dose M-VAC due to the addition of G-CSF. Although there was no significant difference found in median survival, there was a significant difference in favour of HD-MVAC in response rate (RR), and CR rate. Furthermore, two-year survival was 35% compared to 25% with M-VAC. This regimen may be very useful in the neo-adjuvant or adjuvant setting as it is delivered in 1/2 of the time of traditional M-VAC.

Gemcitabine

Gemcitabine is a new antimetabolite that inhibits DNA synthesis and is an analogue of cytosine arabinoside. Gemcitabine is usually given weekly for three weeks, every four weeks. Used as a single agent, response rates of 23–29% have been obtained in both pre-treated patients and in those who have not had prior therapy.[22–25,28] Single-agent studies with gemcitabine can be found in Table 2.

Gemcitabine is clearly an active new agent in the treatment of TCC of the urothelium. Its mild toxicity profile merited further studies in combination with cisplatin and other agents. For patients with mild renal failure or who have significant underlying poor medical conditions, gemcitabine may be considered a reasonable alternative to be used as monotherapy. Combination studies clearly deserve a high priority considering the response rates comparable to that of cisplatin. Table 3 details phase II trials with gemcitabine and cisplatin in advanced bladder cancer.[29–32]

In a joint Scandinavian, Italian and German study, gemcitabine and cisplatin were given weekly to patients who had had no prior chemotherapy.

Table 2: Single agent trials with gemcitabine in advanced TCC

Author	*Year*	*No.*	*Prior therapy*	*RR*	*CR*	*Gemzar mg/m²*	*Median survival (months)*
Pollera[24]	1994	15	Yes	4 (27%)	1 (7%)	875–1,370	NR
Stadler[26]	1997	39	No	11 (28%)	4 (10%)	1,200	13.5
Moore[27]	1997	37	No	9 (24%)	3 (8%)	1,200	8
Lorusso[28]	1998	31	Yes	7 (23%)	4 (13%)	1,200	5
Gebbia[25]	1999	24	Yes	7 (29%)	1 (4%)	1,000	13+

Table 3: Gemcitabine and cisplatin combination regimens in advanced TCC

Author	*Year*	*No.*	*Prior therapy*	*RR*	*CR*	*Median survival*
Von der Maase[33]	1997	44	No	16 (43%)	6(16%)	12.5
Kauffman[30]	1998	47	No/Yes	66%		–
Moore[31]	1999	31	No	16 (57%)	6 (22%)	13.2
Mancarella[32]	1999	54	No	26 (48%)	8 (15%)	9

A 40% response rate was obtained, with a median survival of 12.1 months. Significant myelosuppression, particularly thrombocytopenia, resulted, most likely due to the unusual dosage schedule of cisplatin chemotherapy.[33] However, responses were seen both in osseous and hepatic sites.

A more rational dose of gemcitabine and cisplatin (GC) was chosen for a randomized international trial in 19 countries with the majority of patients coming from Denmark, Germany and England. This study, sponsored by Eli Lilly, compared gemcitabine on days 1, 8 and 15, and cisplatin at 70 mg/m^2 every four weeks to M-VAC. Eligibility criteria include patients with T4b, N2, N3 and M1 disease. The trial was designed to detect a difference in survival from 12 months with M-VAC to 16 months with GC. This study revealed that GC was less toxic, with survival of 13.8 months, as compared to 14.8 months in patients treated with M-VAC.[34] Many investigators have come to consider this combination to be equivalent to the M-VAC regimen that has long been the only gold standard. An improved quality of life, secondary to reduced chemotherapy toxicity, is surely an important endpoint in the treatment of patients with metastatic urothelial cancer.

Taxanes

The taxoids represent a novel class of antineoplastic drugs. Paclitaxel (taxol) and docetaxel (taxotere) share a similar mechanism of action: the promotion of microtubule assembly and inhibition of microtubule disassembly. Taxol is the active ingredient of the bark. Taxotere was prepared from the needles of *taxus baccata*. A 42% response rate (27% CR) was reported in previously untreated patients when a relatively high dose of taxol (250 mcg/m^2) was administered with G-CSF.[35] Single-agent taxotere

produced a 13% RR in previously treated patients at the Memorial Hospital.[36] However, as first line therapy, the regimen produced a 31% RR.[37]

Tu *et al.* then combined taxol, methotrexate and cisplatin and reported a 40% response rate in patients who had received prior M-VAC.[38] Several phase II trials have evaluated the combination of taxol and cisplatin, and of taxol and carboplatin.[38–45] With taxol and carboplatin, investigators have reported high response rates with median survivals of 8–9 months.[43,44,46] Taxotere has also been combined with cisplatin.[47]

New combination regimens

Based upon a phase I dose-escalating trial by Rothenberg, we combined gemcitabine (2,500–3,000 mg/m^2) and taxol (150 mg/m^2) given every two weeks in Italy and Israel.[48,49]

Gemcitabine and paclitaxel combination chemotherapy has been evaluated in several studies with excellent results, even in pre-treated patients. Results are reviewed in Table 1.[50–55] In a phase II study, 40 patients who had been pre-treated with M-VAC had a 60% RR (28% CR and 33% PR) when treated with paclitaxel 150mg/m^2 and gemcitabine 2,500–3,000 mg/m^2 every two weeks on an outpatient basis.[50] Of note, the RR was 27% in patients who had failed prior chemotherapy for metastatic disease within the last year as compared to 80% for patients who received prior neo-adjuvant or adjuvant M-VAC. The median survival for all patients was 14.4 months, equal to that seen in another American study.[51]

The Spanish regimen of gemcitabine, paclitaxel and cisplatin (GCP) has led to a very high RR, around 78% (CR 28% and PR 50%).[56] The first report from the phase I trial reported survival of 24 months, probably due to patient selection. In the multi-centre phase II study, the median survival was 15.6 months, more consistent with currently available doublet regimens.[57] The combination study of gemcitabine, paclitaxel and carboplatin compared favourably with a 14.7 month median survival, and 1-year survival of 59%. The RR was 68% (CR 32% and PR 36%).[58] In a third study from MSKCC, the triplet ifosfomide, paclitaxel and cisplatin (ITP) revealed a 68% RR (CR 23% and 45% PR). Median survival was 20 months in this single centre study.[59] This regimen is used in an ongoing EORTC/SWOG Intergroup randomized trial. When gemcitabine and paclitaxel were incorporated into a multi-agent chemotherapy combination with or carboplatin at Wayne State, results were extremely interesting.[60]

Prognostic factors

At Memorial Hospital, Geller first reported prognostic factors predictive of response to chemotherapy that included alkaline phosphatase, age greater or less than 60 years and performance status.[61] Subsequently, the Intergroup Study reported similar clinical features which predicted a poor outcome: weight loss during the preceding six months, Karnofsky Performance Status (KPS) less than 80%, and the presence or absence of extranodal metastases.[13] A database of 203 patients treated at Memorial Hospital in New York has provided an excellent prognostic factor model for patients treated with M-VAC chemotherapy.[62] Two factors had independent prognostic value: KPS less than 80% and visceral (lung, liver or bone) metastasis. Median survival for patients who had 0, 1 or 2 risk factors was 33, 13.4, and 9.3 months respectively ($p=0.0001$). The median survival time of patient groups could vary from nine to 26 months simply by altering the proportion of patients from different risk categories.

More recently, a significant interest in molecular markers such as p53 Rb, and p21 to help optimize therapy and predict chemo-sensitivity has developed.[63] The p53 tumour suppressor gene has been implicated in the pathology of many solid tumours.[64] P53 gene over-expression is generally considered to be an adverse prognostic factor. In a retrospective series, adjuvant chemotherapy was associated with a threefold decreased risk of recurrence, and a 2.6-fold improvement in survival when given to patients with p53-altered tumours.[65] Results concerning p53, however, have been contrasting, in part due to differences in methodology.[66]

Retinoblastoma gene (Rb) is another tumour-suppressor gene. Altered expression is found in 30–40% of muscle-invasive cancers, and absent or heterogeneous expression has been associated with poor survival.[65]

P21, a cyclin-dependent kinase inhibitor, is responsible for some of the action of p53. In 242 patients with organ-confined disease, 156 were positive for p21, and 86 were negative. A decrease in recurrence rate ($p<0.00001$) and an increase in overall survival ($p<0.00001$) was noted for patients who were p21 positive. This was true despite alterations in p53 status.[67]

Improved understanding of the biologic predictors of outcome will hopefully lead to more effective management of bladder cancer.

The last 10 years have established the chemo-sensitivity of urothelial tumours, highlighted by the M-VAC regimen, which has been the gold

standard for more than a decade. The gold standard may be shifting, due to patient selection, early diagnosis, stage migration, and the development of newer less toxic regimens such as GC. In 1989, the median survival with M-VAC was approximately 1 year. Reports of under nine-month survival despite high response rates should be viewed with caution. The shift in more recent trials may be towards a higher median survival of 18–20 months.[68,69] Therefore, only randomized controlled phase III trials with an endpoint of improving survival can definitively change the gold standard.

Conclusions

Chemotherapy for patients with metastatic bladder cancer is changing significantly with the addition of new chemotherapeutic agents and strategies to our therapeutic armamentarium. The integration of these agents into the initial chemotherapy plan for patients with TCC is still under development. Growth factors may enable us to maximize drug delivery. Finally, patients who fail first-line chemotherapy should be considered for investigational protocols.

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Chapter 16

Invasive transitional cell cancer in the elderly

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Introduction

The subject of invasive transitional cell cancer in the elderly raises several issues. First, what does the diagnosis of invasive transitional cell cancer imply biologically? Second, what is the efficacy of various treatments and what are their risks? Third, how large is the ageing population and what is the magnitude of the problem of invasive transitional cell cancer in this population? Fourth, how do the health of the elderly, the physiology of various organ systems, and their functional reserve during ageing influence the course of disease, the choice of treatment, and the impact of both on the host?

Invasive transitional cell cancer: biological considerations

Urothelial cancer initially presents as 'superficial' disease in 70% of patients and as muscle-invasive disease in the remaining 30%.[1] In those patients who present with 'superficial' disease, 70% (50% of the total) have mucosally confined, generally low–moderate grade tumours, and only 2–4% of these will progress.[2] In contrast, 30% of the remaining patients who present initially with 'superficial' disease (20% of the total) have tumours that have infiltrated the lamina propria and 30–50% of these may progress.[2] Overall, 1–2% of mucosally confined disease, and 6–10% of lamina propria invasive

disease will thus ultimately progress to muscle invasion. An additional 6% of all lamina propria invasive tumours (20% of 30%) are already muscle-invasive at initial diagnosis, having been understaged at initial transurethral resection.[3]

These figures allow us to estimate the scope of the problem of bladder cancer in the general population. The 30% of all bladder cancers that are muscle-invasive at initial diagnosis and the 50–60,000 new diagnoses of bladder cancer in the United States annually account for 15–18,000 patients with muscle-invasive bladder cancer. The 10–15% of initially superficial tumours that develop into muscle-invasive cancer account for an additional 5–9,000 cases. Thus a total of 20–27,000 muscle-invasive cancers will require treatment every year.

Of those patients who present with muscle-invasive disease, 50% have occult metastases.[4] Superficial muscle invasion (stage T2a) may be less likely to be metastatic and a 60–80% cure rate described for a variety of treatments (transurethral resection, segmental cystectomy, total cystectomy, and even radiation therapy in combination with transurethral resection) may reflect the presumably less aggressive biological behaviour of these tumours.[5] Deeply invasive cancers (stage T2b) may more likely be metastatic and permit 'cure' rates of only 15–40% with aggressive treatments.[5] These rates are even worse for those tumours that have penetrated beyond the muscularis propria (stage T3a/b), with distant failure even more likely and survivals ranging between 5% and 15%.

Changing demographics of the elderly in the general population

Urothelial cancer is likely to affect a more elderly population. The increasing life expectancy in the general population and an increased and more prolonged exposure to urothelial carcinogens could produce a substantial increase in the number of muscle-invasive bladder cancers we will see in the elderly in the future.

The magnitude of this problem could be substantial. During the past century, women in the United States experienced an increase in survival to age 65 from 58% in 1900 to 89% in 1990.[6] Survivals to age 85 increased from 26% in 1900 to 55% in 1990. Corresponding figures for men were comparable, albeit approximately 10% lower in each category. In addition,

the risk of death at younger ages has decreased such that the proportion of a birth cohort surviving to old age has increased. Thus a growth rate of 1% will permit a doubling of the population in 70 years.[7] Both birth rates and death rates have shifted to more stable lower levels, resulting in population ageing and increased longevity.

Since 1900 the population of the United States has tripled from 76 million to 255 million, and persons above the age of 65 now comprise 13% of the population (versus 4% in 1900).[6] More than 70% of people now live to be 65 years or older (versus 25% in 1900) and more than 30% live to the age of 80. Of the 65+ population, the number of people 85 years or older has increased from 4% to 10%. Sixty percent of those older than 65 years are female. The ratio of females to males over 85 years is 2.5 : 1.

Between 1900 and 1992, females had a 25% decrease in death rates, while males had a 33% decrease.[6] Since 1900, age-adjusted death rates have decreased by 40% in males and by 60% in females. Life expectancy was 48 years for females and 46 years for males in 1900. In 1992 it was 79.5 years for females and 72.5 years for males. Persons reaching age 65 can now expect to live an additional 17 years on average (15 years for men and 19 years for women).

At the same time, there has been a 17% *increase* in age-adjusted death rates from malignancies, an increase (100–200% in males and over 400% in females) largely due to respiratory cancer death rates and clearly reflecting the timing and development of smoking habits.[7] The same may become true of bladder cancer, given its strong association with cigarette-smoking, and may well account for an increasing risk as the population ages, particularly in younger cohorts, unless smoking habits change.

Organ system function and ageing

The function of various organ systems changes as people age. In bladder cancer (as with other disorders), this is relevant not only to quality of life issues associated with ageing, but also to risk factors and side-effects associated with various treatments that may influence the choice of therapeutic approach.

Renal function deteriorates in the elderly. The normal glomerular infiltration rate of 140 ml/min/1.73m^2 is maintained until the fourth decade and then decreases by 8 ml/min/1.73m^2 per decade.[8] In addition, a normal

renal blood flow of 600 ml/min is maintained until the fourth decade and then begins to decrease by 10% per decade. Each of these determinants of renal function is further affected by hypertension and diabetes, both of which become more common and severe with ageing. By the eighth decade, glomerulosclerosis increases to involve 30% of glomeruli.

Immunologic function also declines with age and appears to correspond to the increased occurrence of infections and cancer in the elderly.[9] Involution of the thymus accelerates decreased immune function. Interactions between the immune system and the nervous and endocrine systems, each affected by neural and cellular networks and also by chemical transmitters, may all be compromised in ageing.

Although ageing *per se* is not a cause of anaemia, anaemia is common in the elderly, its prevalance increasing to as high as 40%.[9] Malignancy and marrow sclerosis are often found to account for this problem. Similarly, various gastrointestinal symptoms and conditions appear to increase with age.[10] These include dysphagia, ulcers and ischaemic bowel disease. Drug-induced liver disease is associated with increased drug sensitivity in the elderly. Each may play an important role in therapeutic options in bladder cancer.

Chronic obstructive pulmonary disease is the fourth leading cause of death in the elderly.[11] Risks are increased by co-morbid diseases, cigarette-smoking, decreased ventilatory responses to hypoxia and hypercapnia, and a decreased perception of dyspnea. Smoking is associated with a fourfold increase in post-operative pulmonary complications.[12] Risks of pulmonary complications can be significantly reduced by cessation of smoking, and this is mandatory before any major surgery. Indeed, significant reduction of such risks can be achieved with cessation of smoking as early as four to eight weeks before surgery.

The prevalance of heart failure and various arrhythmias also increase with age.[13] Most patients with coronary disease, congestive heart failure secondary to coronary disease, and acute myocardial infarction are over 65 years of age. Interestingly, more elderly women than men have myocardial infarctions (38% verus 23% respectively). The mortality from myocardial infarction is increased tenfold in the elderly.[14] Hypertension doubles the risk of cardiovascular events in the elderly. Control of hypertension decreases the risks of complications associated with cardiovascular problems. In this regard, both non-pharmacologic and drug treatments can be effective in the elderly.

Medical considerations for treatments for invasive bladder cancer in the elderly

Deterioration in physiologic function, prolonged exposure to deleterious and damaging substances, and the consequent co-morbidities associated with ageing may affect considerations of various treatment approaches for invasive bladder cancer in the elderly. Therapeutic efficacy, side-effects, potential complications, and effects on overall quality of life are all important factors in this context. In addition, various individual host factors (life expectancy, co-morbid conditions, physiologic reserve, and psychologic and environmental support) can also affect considerations in therapy.

Treatments for invasive cancer of the urinary bladder include cystectomy, extensive transurethral resection, external radiation therapy, systemic chemotherapy, and combinations of all of the above. Importantly, the need for urinary diversion with cystectomy also has implications for additional risks and side-effects of treatment that need to be considered in the context of an individual's physiologic and co-morbid status.

In considering major surgery such as cystectomy, pre-operative management of factors associated with the increased risk of specific complications may minimize such risks. At the outset the extent and severity of co-morbid conditions need to be evaluated. In addition, current and anticipated pharmacologic therapy (including anaesthetic management) need to be assessed.

The major risks associated with cystectomy are cardiac, respiratory, thromboembolic, and central neurologic (delirium). Cardiac risk is increased in patients with hypertension, and such patients may be especially vulnerable because of the fluctuations in blood pressure that may occur during surgery. The elderly are particularly susceptible in this regard because of their sensitivity to various anaesthetic agents, their use of various medications, their vulnerability to vascular changes and changes in intravascular volume, and their unpredictable responsiveness to various pain stimuli.[15] As a consequence the elderly may be particularly sensitive to perioperative myocardial infarction. If this occurs, a mortality rate of 50–80% has been reported.[16] Evaluation and correction of coronary artery disease have therefore been considered of major importance prior to elective major surgery.

In the elderly, respiratory problems are the cause of post-operative morbidity in approximately 40% of patients.[17] Therefore, cessation of smoking, use of prophylactic antibiotics, application of physiotherapy, and use of incentive spirometry may all contribute to a decrease in morbidity. The incidence of deep vein thrombosis and embolus also increases in the elderly due to their decreased leg musculature, hypercoagulability, and their accumulation of increased systemic disease risk factors.[18] Of patients undergoing general surgery, 20–30% develop deep vein thrombosis.[19] Significant pulmonary emboli have been reported to occur in 1–5% of all patients undergoing major surgery, a risk that is increased to >20% in the elderly.[20] The mortality at one year after pulmonary embolus approaches 40%.[21]

The 30–50% decrease in numbers of glomeruli that can be seen by the seventh decade may lead to compromised renal function and diminished renal reserve that can affect the outcome of major surgery. The loss of functioning nephrons with age increases the solute load per nephron, adversely affects the nephron's concentrating capacity and can thereby produce volume depletion, which can contribute to failure in other sytems.[22] Acute renal failure as a consequence of surgery and anaesthesia has been found to have a 40–80% mortality rate.[23]

Deterioration of endocrine function in the elderly is also important.[24] Diabetes mellitus predisposes to increased morbidity from cardiovascular and infectious complications. Maintenance of good control in diabetics is critical in preparing them for major surgery and anaesthesia. Hypothyroidism has a prevalence of approximately 10% in the elderly who are hospitalized. The consequence of this in the metabolism of various drugs and responsiveness to surgery needs to be taken into account in planning for a safe perioperative course.

Although the nutritional status of a person is thought to be important in considering major surgery, the role of pre-operative nutritional assessment, and even pre-operative nutritional therapy, remains unclear.[25] However, positive anabolic balance in the post-operative period, or at least avoidance of prolonged catabolic balance, is thought to be important in maximizing successful recovery following major surgery.

The prevalance of dementia has been reported to be as high as 25% in persons over the age of 80 years, while delirium has been suggested to be as high as 45%.[26] Each of these is of major importance when considering post-operative assessment and management of patients who have

undergone major surgery. This may be of particular relevance in bladder cancer when urinary diversion is required and management is considered in the context of the overall capabilities of many elderly patients.

Various classifications in the assessment of patients for major surgery have been developed. These include classification of physical status for anaesthesia, cardiac scores, based on an index of cardiac risk in patients undergoing non-cardiac surgery, and classification of probabilities for post-operative cardiac complications.[27] Each of these can be used to advantage in identifying patients who may present particular risks for major surgery. Such patients will then benefit from pre-operative rehabilitation to minimize certain risks, intra-operative and post-operative monitoring and treatment measures to intervene either in preventing risks or recognizing their appearance sufficiently early to permit reduction in the morbidity they may cause, and post-operative recovery measures to facilitate rapid return to health and normal function, and to maximize quality of life and reserve systemic function, particularly if adjunctive treatments become necessary.

The importance of these considerations is based upon the assumption that cystectomy offers the best opportunity for curing muscle-infiltrative transitional cell cancer of the bladder. This impression is supported by observations of an increased likelihood of regional and distant disease recurrence in those patients who undergo alternative treatments and whose longevity and disease-free survival may be compromised accordingly. Even though cystectomy has not been predictably successful, largely because of the occult metastases that a substantial proportion of such patients have, in those individuals fortunate enough to have disease confined to the bladder when initial diagnosis of muscle-invasive cancer is made, the outcome in terms of longevity and the absence of regional morbidities appears to be served best by this approach, in association with an appropriate form of urinary diversion.

These considerations are of particular importance in the elderly because of their compromised physiology and organ functional reserve, their accumulation of risk factors and co-morbid conditions that may accentuate potential complications following surgery (both from the cystectomy itself, the form of urinary diversion selected, and the type and duration of general anaesthetic used for the procedure), their possibly limited life expectancy, their overall health limitations from the presence of cancer itself and other treatments that may already have affected other systems in their bodies,

and considerations involving their expected degree of recovery and ability to tolerate morbidities of varying severity. Consideration of these factors makes it clear that patients need to be selected carefully for particular treatments. However, even with a selected group of patients, success rates and outcomes can be compromised, morbidities and complications can occur, and the predictability of each may be inadequate.

The literature concerning results of cystectomy in the elderly generally suggests that the surgery may be well tolerated and successful. However, the procedure is not without risk. Moreover, it generally involves highly selected patients and the good outcomes they experience may reflect the biology of their disease in the context of their own body's biological and functional reserve.

In analyzing one report of 404 patients over a median age of 70 years (selected from 1,176 total patients who underwent cystectomy), as an example, mortality rate was only 2.8% (11/404), but the complication rate was 32% (129/404).[28] These included persistent urinary leak in 20, intestinal leak in six, bowel obstruction in 13, renal failure in 11, cardiovascular complications in 19, and pulmonary emboli in seven. Given the potentially compromised reserve of these patients (see above), any or all of these complications could have contributed to mortality. It is a testament to the successful perioperative management that the mortality rate was kept as low as it was. On the other hand, this was a highly selected group of otherwise presumably healthy patients and their *median* age of over 70 (implying that many were younger than 70) may not necessarily have made them physiologically elderly.

In this study, non-diversion-related complications occurred in 24% (85/352) of patients 70–79 years old, in 29% (15/52) of patients over the age of 80, and 17% (129/762) of those <70 years. The somewhat higher rate of complications observed in the older patients could conceivably be interpreted as age-related, as the initial selection of patients may have been far more rigorous in this age group than in those <70. Certainly their rate of complications is not something that can be easily dismissed, especially in view of the possible long-term effects that these complications could have (see below).

Although overall five-year survival of patients >70 years was less than that of patients <70 years, their *disease-free* survival was comparable. This appears to be a manifestation of biologic selection. Thus, patients chosen for cystectomy in the elderly age group comprised 32% with

organ-confined disease, 41% with extravesical disease, and 27% with positive lymph nodes.[28] The latter two groups of patients had disease sufficiently extensive that it undoubtedly would have predisposed them to failure, as indicated by the disease-free five-year survival of only 35%. However, these results still compare favourably with those of radiation therapy, in which five-year survival has ranged between 15% and 20%, pelvic recurrence has ranged between 40% and 70%, and the complication rate has been significant (see below). In those patients who had organ-confined disease, therapeutic efficacy was far better.[28] Although quality of life measures were not included, this series suggested the value of cystectomy in such patients, the importance of careful selection, and the unpredicability of risk notwithstanding preventive perioperative measures.

Similar observations have been made in other cystectomy series. Wood *et al*. demonstrated a 5.3% (2/38) mortality in patients >70 years old, and a 34% morbidity (14/38).[29] The occurrence of myocardial infarction and renal failure was higher in the elderly population. Similarly, in a series of patients >80 years old (comprising 44 of 1,186 total cystectomies) from Memorial Hospital, a 4.5% (2/44) operative mortality, a 51% (23/44) morbidity, a 66% (29/44) rehopitalization rate for complications, and a 50% (22/44) disease-specific mortality (with a median survival of only 25 months) were reported.[30] The mean Karnovsky score of all patients in this series was 72 (range 50–90). Of these, 34/44 had co-morbid conditions, which included 55% with cardiac problems, 20% with hypertension, 18% with chronic obstructive pulmonary disease, and 13% with vascular disease. The 65 patients with advanced transitional cell cancer who did not undergo cystectomy succumbed rapidly to their disease. However, this may have reflected the severity of their co-morbid conditions that excluded these patients from surgery, or the degree of disease that precluded them from being candidates for 'curative' surgical treatment (15 patients had hydronephrosis and 14 had a palpable mass, both ominous risk factors suggesting that at least a third of those who underwent surgery had more advanced disease and were destined to die of their disease).

These observations prompted the suggestion that cystectomy was justified largely when life expectancy was greater than two years, since most patients with untreated invasive transitional cell cancer presumably would die within a lesser time.[30] However, since conservative or alternative strategies would often result in progressive, uncontrolled cancer associated with various local symptoms and the need for repeated bladder

instrumentation and possibly frequent hospitalization, it was felt that cystectomy could improve the quality of life by eliminating these symptoms and problems. Measures of quality of life were not reviewed, and risks and complications were substantial despite a high degree of selection of patients as candidates for surgery.

Each of these studies implied benefits in the rigorous selection of patients on the basis of co-morbid conditions and performance status. Each suggested the value of pre-operative assessment and intensive treatment to prevent or minimize the effects of potential medical problems. However, results in these series indicated that the occurrence of even one complication could lead to other complications and could increase mortality. On the other hand, each study suggested that death caused by undertreated cancer was more likely than death related to intercurrent medical diseases. The consensus, therefore, appeared to favour the position that avoidance of surgery in the elderly on the basis of age alone was unjustified. It was further felt that the elderly patient who is thought to be suitable for surgery but is not offered this possibility is not only deprived of the right to definitive curative therapy (if the biology of the disease is such that this is possible), but is also exposed to higher morbidity, mortality and a worse quality of life with other treatments.

Nonetheless, there remains an understandable tendency to assume that an increased risk of complications is likely to characterize surgery in the elderly. The consequence of such thinking is the inclination to advocate definitive radiation therapy in such patients. The standard technique has involved use of a linear accelerator applied through a number of fields with delivery of a total split fractionated dose that ranges between 50 and 70 Gy.[31] The frailty of many of these elderly patients, however, and their poor condition, together with radiation toxicity to the bladder and the bowel have often limited the intensity and dose of treatment. It has been suggested that this has interfered with the potential efficacy that might otherwise hve been achieved.

In one series, for example, Philips reported on 76 patients (mean age 78.4 years), only 53 of whom (70%) completed the full course of treatment.[32] Of these, 19 (36%) had an apparent complete response (but with a median survival of only 14 months). The median survival of the entire cohort was only 13 months. Significant toxicity was seen in 10/53 (18%). Similar findings were made by Sengelov *et al.*, who reported on 71/94 (80%) patients (median age 78 years) who completed their course of treatment and experienced a

median survial of only 18.8 months.[33] Toxicity resulted in hospitalization of 49 patients. Recurrent disease was experienced by 53% of the patients completing radiation (median time to recurrence 7.3 months). Only 7% of the entire group survived for five years, and only 29% survived for two years. Good performance status and stage of disease were the major determinants of survival.

In a series of 120 patients reported by Bell *et al*., 67 (59%) experienced local recurrence (30% with invasive disease) at a median time of 7.4 months.[34] The five-year and median survival were 50%, but the series included 18 patients (15%) with stage T1 disease. Of the 27% (33/120) who underwent salvage cystectomy, the median disease-free survival was only 12.5 months.

In view of the limited access in achieving durable survival in these series, some have suggested a possible palliative role for radiation in treating transitional cell cancer of the bladder in the elderly. McClarin *et al.* treated 65 patients (median age 78 years) who were unable to tolerate a full course of radiation because of poor performance status or co-morbid illnesses with 30–36 Gy.[35] All had muscle-invasive disease and 85% had severe symptoms. Palliation was 'successful' in 28/55 (51%) patients, but for only seven months' duration. Transient worsening of symptoms (29% urinary and 25% bowel) was seen in 28 patients. The medial survival was only nine months, with 52/55 dying of disease.

Overall, radiation therapy has not been well tolerated, has resulted in significant toxicity in at least 50% of patients, has demonstrated limited durability of response, and has had minimal salutary effect on disease-free survival. The most important factors associated with survival have appeared to be primary stage and performance index, which is similar to results with exenterative surgery. However, radiation therapy has additionally been compromised in the elderly by these patients' decreased tolerance to this treatment, their slow recovery, and their limited life expectancy.

Holmang *et al*. summarized their studies of radiation therapy in the elderly with the treatment of 74 patients between 70 and 75 years old who were considered unfit for surgery.[36] Included in this series were 17 patients with stage T0–1 disease (median survival of 32 months), 40 patients with stage T2 disease (median survival of 16 months), and 17 patients with stage T4 disease with positive nodes (medial survival of nine months). Of the 'superficial' tumours, 9/11 who became tumour free

recurred, and only 4/17 (24%) were alive at five years. Among those with muscle-invasive disease who were tumour free after radiation, 9/19 (48%) recurred and only 6/40 (15%) were alive at five years. Ninety percent of stage T4 tumour patients (5/7) recurred and none were alive at five years. On the basis of these disappointing results, Holmang *et al*. expressed their concern that 50% of treated bladder cancer patients appeared to have no response to radiation therapy and would have a poor prognosis if their bladder was retained. Thus, of those who responded initially, 25–50% recurred. They also suggested, however, that such results could probably have been biased, at least in part, because of the selection of the 'best' patients for cystectomy, the selection of patients with best performance status for 'curative' radiation, and the remaining frail and elderly patients to receive only palliative radiation. Thus, they concluded both from their own studies and from their review of other reports that the results of radiation were worse in the elderly, that survival in the elderly was not improved with salvage cystectomy, and that the elderly experienced a high rate of treatment morbidity and mortality.

Furthermore, in association with a very low rate of local 'cure' with radiation and a high rate of local recurrence, there was also a high rate of serious complications.[36] Therefore, not only was there a question as to whether radiation added any benefit to transurethral resection in the elderly, but whether radiation that was only palliative actually provided any benefit or was only harmful. Side-effects were often seen even with palliative radiation with minimal therapeutic efficacy. There appeared to be no improvement in local symptoms, and 23% of patients needed rehospitalization among the 47% who experienced acute side-effects.

To compound these problems, guidelines that have been used to evaluate the results of radiation have been criticized because of the means by which outcomes are assessed. Shipley *et al*. have suggested that the major endpoint in characterizing efficacy was cystoscopic 'response' at six months, 'which has been shown to be a good predictor of outcomes'.[37] Phillips *et al*. suggested more recently that 'cystoscopic response is more appropriate than survival in the elderly cohort'.[38] These criteria in assessing efficacy are difficult to accept, and one wonders whether these statements are acceptable in the context of actual experience with efficacy and complications.

Much has been made of the possible efficacy of chemotherapy in treating advanced transitional cell cancer of the bladder. Although various agents

have been found individually and in combination to have measurable effects, they have ultimately been found to be ineffective in enhancing survival.[39] Protocols that have tested the possibility of combining extensive transurethral resection with radiation and systemic chemotherapy, in an effort to eradicate tumour or possibly even palliate patients with advanced bladder cancer, have not only been unsuccessful in terms of their efficacy in survival and palliation, but their morbidity and mortality have been substantial.[40,41]

Although several studies of extensive transurethral resection and chemotherapy in selected elderly cases have reported 50% complete and partial responses, the durability of these responses has only been for 8–12 months on average, with an actuarial median survival of only 10–14 months.[42,43] Dose modification has often been necessary to accommodate the reduced physiological capabilities of the various organ sytems in the elderly, particularly to minimize cardiotoxicity (from adriamycin) and nephrotoxicity (from cisplatin). In one oft-quoted study, Kaufman et al. reported complete responses in 11/20 (55%) patients with muscle-invasive disease.[44] In those who were initially staged as having only superficial muscle invasion, complete response was more likely and five-year survival was 49%. In contrast, all patients with incomplete response died within three years. Moreover, overall actuarial five-year cause-specific survival was 43%. Toxicities were often significant and included leukopenia in 10%, gastrointestinal symptoms in 15%, and cystitis in 10%.

Because of the toxicity of chemotherapy, some have suggested that extensive transurethral resection alone may be appropriate in selected elderly patients. The primary consideration mandatory for success in this setting is the documentation of disease limited to the superficial muscularis propria. Those patients who are found to have no residual cancer after an aggressive repeat transurethral resection have been found to have a five-year survival of 15–45%, figures comparable to those achieved with more extensive disease, and other treatments, either alone or in combination.[45,46] However, such figures are at odds with those suggesting that superficial muscle invasion may have a much higher rate of response and survival by various treatment modalities.[47] Moreover, the need for salvage cystectomy to consolidate survival in 20–30% of these patients suggests further that many of these patients may actually have more extensive disease and points to the difficulty of assessing the extent of a bladder cancer with sufficient accuracy to permit appropriate treatment decisions.

Conclusions

We are left with an extremely difficult issue in approaching the treatment of invasive transitional cell cancer in the elderly – that treatment with the greatest chance for cure is surgery, and this probably also provides the greatest chance for palliation. However, the frailty of the elderly and the frequency of co-morbid conditions demand that some degree of selectivity be used in identifying those that are most likely to benefit and least likely to experience side-effects or complications. Careful attention to pre-operative assessment and attempts to correct, or at least maximize, the function of various organ systems prior to surgery may assist in the successful treatment of these patients through reduction of morbidity and complications. As such, the quality of life of these patients may be enhanced.

Our need to identify succcessful treatments for this disease extends to all patients. Special considerations need to be provided for the elderly, whose organ systems lack the reserve and whose overall frailty may limit their ability to tolerate the various forms of therapy currently available.

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Chapter 17

Quality of life

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Introduction

In clinical oncology, health-related quality of life (QL) is defined as a multi-dimensional concept of a cancer patient's overall wellbeing as seen through his or her eyes. QL is usually evaluated by psychometrically evaluated questionnaires completed by the patients themselves. The use of ad-hoc designed questionnaires should be avoided.

Cancer-specific instruments have been developed as the European Organization for Research and Treatment of Cancer (EORTC) QLQ C-30 or the Functional Assessment of Cancer Therapy (Fact)-G, addressing symptoms and functional disturbances generally encountered by the majority of cancer patients (reduced physical, social and emotional function, insomnia, fatigue, loss of appetite).[1,2] Often the patient is also asked to complete a treatment- and cancer-type specific module as the Fact-BL (bladder) or Fact-P (prostate) questionnaire. The EORTC GU group has almost completed the development of a module for superficial and muscle-invasive and prostate cancer. The time-consuming process of to and fro translation represents the final and important step of the development of internationally applicable questionnaires. Such QL instruments are used in prospective trials and in surveys in connection with cross-sectional studies. Results from cross-sectional surveys should preferably be compared with those from the 'normal population'.

Observations from many cross-sectional QL studies have shown that QL is more than organ-specific treatment-induced and disease-related morbidity. Reduction of physical function, emotional distress and fatigue are in general more important for a cancer patient's QL than specific dysfunctions such as erectile dysfunction or mild to moderate urinary leakage, which can be controlled by pads.

Muscle-invasive bladder cancer (MIBl)

Radical cystectomy

In most urologists' view, the principle treatment of MIBl is radical cystectomy combined with urinary diversion. Three types of urinary diversion are used, dependent on the patient's age, co-morbidity, mental status and extent of the disease.

12. Ileal conduit (IC) with an incontinent urostomia at the abdominal wall, which has to be covered by a plastic bag for urine collection.
13. Heterotopic bladder replacement (HBR). A continent reservoir is constructed from a bowel segment. The patients have to catheterize themselves at regular intervals through an abdominal stoma.
14. Orthotopic bladder replacement (OBR). A similar reservoir as in alternative 2 is anastomized with the remaining urethra, thus enabling a more 'natural' urine passage, and hopefully continence.

The typical morbidities after radical cystectomy are erectile dysfunction and disturbed sexual life on the one hand, and urinary leakage and stoma problems on the other.[3–6] Change of body image and disturbed sexuality may be followed by decreased self-esteem.

Radiotherapy

High-dose radiotherapy is another therapeutic option which in non-randomized series seems to result in similar survival rates comparable to patients with small tumours (T2).[7] An important condition for a favourable outcome of such an approach is the feasibility of qualified follow-up combined with salvage cystectomy if necessary. Typical radiotherapy related side-effects are diarrhoea due to the irradiated bowel, irritative symptoms from the bladder, dryness of the vagina and erectile dysfunction.

No large (>100 patients) prospective QL study has been reported in MIBl, but such results will be available in a few years' time. Several cross-sectional studies have been compared QL after the different types of urinary diversion and after radiotherapy. Three treatment-related dimensions have been assessed by specific modules: urinary symptoms, stoma problems, and sexuality. However, one has to consider that some of these domains may be affected already before any treatment is applied due to the disease itself, high age and/or co-morbidity.

Dependent on age and co-morbidity, 64% of the patients with MIBC recorded erectile dysfunction present before any treatment was given, and 51% recorded decreased libido.[8] Urinary symptoms were present in 26–61% of the patients with muscle-invasive bladder cancer before the start of any treatment.

Overall reduced sexual life represents the most frequently reported problem after cystectomy experienced by almost all patients, independent of the type of urinary diversion. Nerve-sparing operation techniques have been introduced in selected cases to reduce the incidence of this side-effect. Forty to fifty percent of patients with ileal conduit (IC) will experience stoma problems. Gerharz *et al*., supported by Okoda *et al*., demonstrated significant differences in patients with IC as compared to those with heterotopic bladder replacement (HBR) as to important specific dimensions and single item of global QL (Table 1).[9,10] HBR seemed to be combined with more favourable outcomes. On the other hand, no significant difference

Table 1: Comparison of QL dimensions after cystectomy combined with ileal conduct and heterotopic bladder replacement, favouring the latter alternative[9]

Stoma-related problems	0.001
Social life	0.005
Physical / emotional function	<0.04
Leisure activities	0.005
Sexuality	0.7
Global QL (single items)	<0.001
Satisfaction with life (scale)	0.12

became evident as regards satisfaction of life. A limitation of this report was the low compliance rate (<40%). Comparing patients with IC, HBR and OBR, Hart *et al.* did not find any statistical difference as to stoma-related problems, social life, physical function, sexuality or global QL.[11]

In a prospective study of 57 patients, Månsson *et al.* observed that elderly patients adapted well to IC, whereas males at any age had more problems adjusting to OBR than females.[12] These authors also emphasized the significance of the patients' pre-treatment psychological defence mechanism as an important predictor of post-cystectomy adjustment.

There is no doubt that 30–40% of tumour-free patients after radiotherapy for MIBC display urinary problems (nightly urination, different degrees of leakage) and reduced sexual life, including erectile dysfunction and decreased libido.[13] However, a cross-sectional comparison of QL in irradiated versus cystectomy patients performed among Norwegian patients and those from the UK did not reveal any statistical differences of the general QL dimensions (Figure 1).[14] The overall score for sexual function after radiotherapy was superior to that after cystectomy.

So far, all surveys have dealt with patients who were rendered tumour-free by their treatment. Much less is known about QL in patients who have developed a recurrence and who are be treated by palliative means. Future studies have to evaluate the effect of palliative transurethral resection of the intravesical bladder tumour and the impact of radio- and chemotherapy on QL.

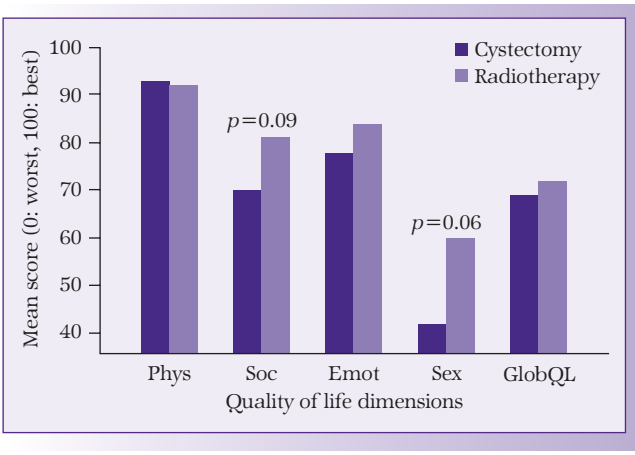

Figure 1: Quality of life in tumour-free patients treated for muscle-invasive bladder cancer (increasing mean scores are compatible with improved function.

Conclusion

Reduced sexuality and at least transient problems with urine passage have to be expected after radical cystectomy. Patients must be informed about these unavoidable side-effects. They should be encouraged to participate in the process of medical decision-making about their treatment.

Independent of the chosen therapeutic option (radiotherapy or cystectomy) tumour-free patients report a high overall satisfaction in their lives and a good QL in spite of non-neglectable, treatment-related side-effects. Patients with a continent urinary diversion seem to experience fewer specific post-cystectomy problems.

Prospective studies are needed to explore the relationship between the different therapeutic options, QL and side-effects, with the emphasis on the patients' ability to adjust to new somatic and psychosocial conditions of their lives.

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Chapter 18

Urethra involvement and bladder cancer

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The cause of the problem

Transitional cell carcinoma primarily involves the bladder, but quite frequently it also involves, either simultaneously or metachronously, the urothelium of the urethra and the upper urinary tract.[1] In fact, transitional cell carcinoma is a multifocal disease and it is well known that the urothelial lining of the pyelocaliceal system, the ureters, and the proximal urethra are at equal risk as the bladder because of a uniform sensitivity of the urothelium to neo-plastic stimuli. Therefore, seeding and implantation of exfoliated cells, as well as lymphatic spread, has been proposed to explain urethral recurrence, although definitive proof of the existence of this pathway is yet to be demonstrated.[2]

Incidence and risk factors

The main reason why urethrectomy *at the time of radical cystectomy* has been advocated is the risk of subsequent urethral recurrence, which is estimated to range from 4–19%.[3] The wide variation in the reported incidence of urethral recurrence is due to several factors. The first is the retrospective reviews of patients who were selected for surgical treatment according to different criteria. Secondly, the incidences of carcinoma *in situ* and of bladder neck or prostatic urethral involvement have not been comparable in the reported studies. Duration of follow-up has also varied widely. Some investigators have considered only clinically overt urethral recurrence, while others have also included patients with carcinoma *in situ*,

or even those with urothelial dysplasia.[3] However, in unselected patient series, the incidence of urethral recurrence after cystoprostatectomy is estimated to be about 10%.[3] It should be clear that all patients with transitional cell carcinoma of the bladder are at risk for tumour recurrence in the remnant urethra.[1]

The risk factors for metachronous urethral tumour recurrence have been identified on the basis of retrospective clinical studies.[3] Some authors have clearly demonstrated that the incidence of urethral recurrence after cystoprostatectomy is much higher (reaching 37%) in patients presenting with invasion of the bladder neck or of the prostatic urethra.[4–6] A much lower incidence of recurrence (3–7%) has been found in patients with multiple tumours, or those with multifocal carcinoma *in situ*.[4–8] This incidence is only slightly higher than that reported after cystectomy for solitary tumours (3–4%).[5,6,8] Involvement of the urothelium of the ureters has also been described as an indicator for eventual urethral involvement.[4]

Indications to urethrectomy

In absence of tumour in anterior or posterior urethra, the indication to urethrectomy are controversial. Urologists are nowadays willing to find reasons why only a minority of their patients should undergo simultaneous urethrectomy. Some urologists fear extending the time of an already long radical procedure in order to perform simultaneous urethrectomy. Also, as already mentioned, some authors are convinced that a urethral recurrence can be detected early, permitting a subsequent effective therapy. However, when the urethra remains intact without function after cystoprostatectomy, it presents a risk as a likely site for tumour recurrence, and a close surveillance of the urethra (washing urethral cytology) is recommended.

A more important factor in the last decade is the availability of procedures for successful reconstruction of the lower urinary tract. Bladder substitution procedures in male, and more recently in female, patients have become routine practice and the presence of the urethra is of pivotal importance in the overall management of the patient. A new trend towards potency-sparing cystectomy is also going against urethrectomy as it has been shown that resection of the urethra significantly impairs sexual function.[9–11] Finally, it has been reported that simultaneous urethrectomy increases morbidity, or gives rise to perineal pain and

delayed mobilization and therefore carries an increased risk of thrombo-embolic complications.[12,13]

It is, therefore, vital to identify pre-operatively those patients who are at risk of developing a recurrence in the remnant urethra. Unfortunately, there is at present no prospective study on the use of prophylactic urethrectomy.

Pre-operative and perioperative assessment of the prostatic urethra

When the urethral involvement is the determining factor in the decision to perform a prophylactic urethrectomy or to leave the urethra behind (to be used for a bladder replacement), the assessment of the prostatic urethra before surgery is of great importance. The need for accurate sampling of the prostatic urethra was first suggested by prostate mapping studies, which showed malignant changes in the prostatic urethra in 50–70% of patients.[14,15] In another extensive study, 4-mm step sections were performed in 84 cystoprostatectomy specimens.[16,17] Thirty-six patients (43%) were found to have transitional cell carcinoma of the prostate. Of this group, 94% had prostatic urethra involvement and 6% had a normal prostatic urethra, but transitional cell carcinoma was present in the periurethral structures. This high incidence of involvement suggests that increasing the intensity of the search for prostate invasion results in an increased incidence of this diagnosis.

Not all patterns of prostatic urethral involvement present an equal risk for recurrence. The tumour involvement can be limited to the urethra or to the epithelium of the periurethral ducts, or it may include the prostatic stroma. Duct and stromal invasion has been the most striking prognostic factor for subsequent urethral recurrence and survival. Therefore, pre-operative staging with transurethral and transrectal biopsy techniques has been advocated.[5,6] Although several authors have confirmed the necessity of a thorough pre-cystectomy assessment, or rigorous screening of the prostatic urethra, the technique of endoscopic assessment has not always been described in detail. Random biopsies, either cold punch or resection biopsies of the prostatic urothelium, have been proposed. It is now agreed that transurethral resection biopsy of the prostate is necessary in order to screen for prostatic involvement and that this biopsy should be routinely performed in patients with bladder cancer. In most patients

the prostatic urethra will appear normal cystoscopically. As regards the extent of prostatic resection, it has been pointed out that an insufficient or limited transurethral resection biopsy of the prostatic urethra could fail to detect prostatic involvement. Therefore, extensive biopsies are now advocated.[5,6,16,17] Such biopsies will help to correctly diagnose the prostatic involvement in 90% of patients, as was shown in a detailed examination of cystoprostatectomy specimens.[16,17] This problem was further studied by Sakamoto *et al*., and it was demonstrated that transurethral resection random biopsies of the prostate may frequently fail to detect prostatic invasion.[18] An appropriate transurethral resection sampling of the prostatic tissue at the 5 and 7 o'clock positions of the verumontanum portion proved necessary to detect any prostatic duct and acinar involvement. More recently, Lebret *et al*. have reported in a prospective study that only positive frozen section of the urethral stump at the time of the radical cystectomy is the contra-indication to urethra sparing and to continent urinary diversion to the urethra.[19] It is, therefore, important to perform frozen sections of the ureters during surgery in order to recognize carcinoma *in situ*.

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Chapter 19

Lower urinary tract reconstruction

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Introduction

During the past century a fascinating development in procedures for lower urinary tract reconstruction has taken place. Within few fields of surgery has greater ingenuity been exercised than in the methods devised for diversion of urine. Since the first report on such a procedure 150 years ago, the urine stream has been conveyed to the outside of the body with the use of an infinite number of surgical techniques.[1] The practicability of the described techniques has often not corresponded to their theoretic advantages, and only a few have been accepted for clinical use. Today the most commonly used methods are conduit diversion, continent cutaneous diversion and orthotopic bladder replacement. For these methods there are now long-term results available with regard to functional outcome, i.e. flow, storage and emptying of urine. Renal function and metabolic consequences of incorporating bowel segments into the urinary tract have been clarified and the impact on patients' quality of life studied. During the past 10 years, development has concentrated on refining these methods.

The majority of procedures for urinary diversion and bladder replacement are performed in patients with bladder cancer undergoing radical cystectomy with curative intent. Although the introduction of bladder replacement in clinical practice in some centres seems to have

stimulated 'the physicians and the patients toward earlier cystectomy',[2] the issue of indications for cystectomy is completely separated from the issue of how the urinary tract should be reconstructed. Once the indication for cystectomy is present, the timing of surgery should not be delayed. The place of surgery is also of importance. Not only does it require expertise in locally advanced bladder cancer; it also requires knowledge in reconstructive urology. Centres which handle these cases must be able to offer the patient any of the reconstructive methods available. In our opinion this means that a minimum of 25-30 cystectomies yearly is required.

With the advent of continent reconstruction the ICS has recommended that the terms 'bladder substitution' or 'bladder replacement' are used to describe 'a surgical procedure for *in situ* (or orthotopic) total substitution/replacement of the bladder'.[3] Often the term 'urinary diversion' is used when describing bladder replacement, which is not correct.

Information given to the patient

Radical cystectomy is a demanding procedure, associated with mortality and considerable morbidity and permanent changes in urinary and sexual function with consequent effects on mental and psychological wellbeing. Of fundamental importance is the honest pre-operative information given to the patient and, preferably, also to the partner, about the planned procedure and its consequences. Alternative methods that might be applicable for reconstruction should be described, including those of which the urologist has little or no experience. Withholding such information because referral of the patient may be necessary is an abomination and must not occur.

Consulting with the patient twice before surgery is the minimal requirement. It is important that the patient is made fully aware of all the facts, especially of disadvantages with specific procedures, like risk of incontinence, need of self-catheterization, etc. To have the patient meet a patient with the type of reconstruction planned will allow for an optimal understanding of how the 'new' urinary tract will work. Possible changes in sexual function should be described to the patient and to the partner. Preserved erectile potency is reported in 10–80% of cases after cystoprostatectomy.[4,5] In our experience, the vast majority of patients are impotent. We do not routinely perform nerve-sparing cystoprostatectomy

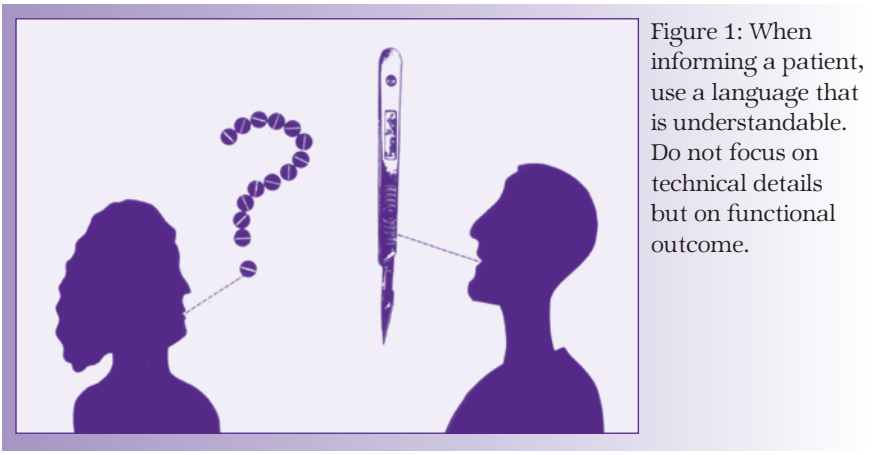

Figure 1: When informing a patient, use a language that is understandable. Do not focus on technical details but on functional outcome.

for fear of compromising surgical radicality.[6] The likelihood of preserved potency after cystourethrectomy is close to nil.

The key to successful results is a patient with realistic expectations, which can be obtained only by honest information. Unfortunately incomplete information is not uncommon and this will only serve to make the patient feel incompletely prepared from a mental and psychological standpoint.[7,8] One should remember that 'the responsibility lies with the urologist to understand and address the individual patient's need for information, remembering that the majority will appreciate more rather than less' (Figure 1).[9]

Pre-operative studies

Intravenous urography to exclude presence of pathology in the upper tracts is mandatory. If the patient has a non-functioning kidney, simultaneous nephroureterectomy may be indicated.

It is important to realize that serum creatinine provides only a crude measure of renal function. A normal serum creatinine does not rule out loss of renal function and a value of 120–150 μmol/l indicates a considerable loss in glomerular filtration rate (GFR). It is recommendable to estimate GFR when in doubt about renal function and at present this is usually done by determining the plasma clearance of ^{51}Cr-EDTA or iohexol with the single-injection technique. As these compounds are not, or at least only negligibly, absorbed through the intestinal mucosa, this technique is well

suited to follow GFR in patients after reconstructive procedures involving intestinal segments.[10,11] Renographic studies may also be of value. By combining it with a clearance study, separate GFR can be determined.

Aspects to consider when deciding the type of reconstruction

There are several aspects that have to be carefully reviewed when recommending to a patient the most optimal method for urinary tract reconstruction in conjunction with cystectomy.

- Age
- Prognosis
- Risk of urethral recurrence
- Previous pelvic irradiation
- Renal function
- Physical status
- Mental constitution.

Age

High age is a relative contra-indication to continent reconstruction, which requires an active and alert attitude with regard to body functions. The patient must be able to recognize the symptoms of a full pouch and understand the importance of regular emptying. S/he must be able to carry out intermittent self-catheterization, a requirement that might occur not only after continent cutaneous diversion. In one series of patients followed for five years after ileal neo-bladder construction, 44% were on clean intermittent self-catheterization (CISC).[12] In our own series of colonic neo-bladders, this was used by 37% of the patients.[13]

Another problem clearly related to age is incontinence after orthotopic bladder substitution. The older the patient, the poorer the result with regard to continence.[14–16] Although a permanent catheter may solve the problem in the short term, an indwelling catheter may give rise to severe complications, such as septicaemia, stone formation, retention due to mucous plug and rupture of the pouch. Such potential problems form the basis for our reluctance to perform continent reconstruction in the octogenarian and in fact many patients above the age of 70, after being thoroughly informed, settle for an ileal conduit. At the same time we realize that there may be single individuals in excellent condition at high age in whom continent

reconstruction is justified, indicating that it is the patient's biological age that is the determining factor.

Prognosis

Advanced disease is, in our opinion, another relative contra-indication to continent reconstruction. If grossly enlarged positive lymph nodes ('bulky disease') are found at exploration, we usually perform an ileal conduit. Patients are informed about this possibility before surgery. Our main reason is that we want as short and as smooth post-operative course as possible. We think that conduit diversion is associated with less risk of early and late problems than continent reconstruction, enabling the patient to commence adjuvant chemotherapy early and spend as little time as possible in hospital. Although some series during the last decade have shown five-year survival in the range of 20–30% in node-positive disease, for most patients survival is short and the majority of them will succumb within one or two years. In this situation, most patients will change priorities in life and the issue of type of reconstruction will be of secondary importance. On the other hand, it can be argued that an ileal conduit with the external collection device might be an additional burden on a patient already mentally distressed by advanced malignancy. This issue is to a large extent a philosophical question.

In patients with one or a few small positive nodes we usually proceed with the planned type of reconstruction. In patients with neo-bladders who suffer pelvic recurrence, several reports, however, have shown that complications from the pouch are rare, that neo-bladder function has been maintained and that the patients have been able to undergo adjuvant chemotherapy.[17–20]

Risk of urethral recurrence in the male

This is a major issue when contemplating orthotopic bladder substitution. The risk of urethral recurrence after cystoprostatectomy and urinary diversion is around 10%, classical risk factors being multiplicity of the bladder tumour, wide-spread carcinoma *in situ*, bladder neck tumour and prostatic involvement, the latter usually considered to be present in 10–20% of patients undergoing radical cystectomy.[21] However, it seems that prostatic involvement in TCC of the bladder is more common than has previously been thought. Two studies employing whole mount technique in studying the prostate of the cystoprostatectomy specimen showed

prostatic involvement in 43%.[22,23] We used longitudinal whole mount sectioning and found TCC in 30%.[24] With regard to prostatic involvement, ductal and particularly stromal growth have been associated with highest risk of urethral recurrence.[25,26] Common practice, therefore, has been to rule out such engagement by performing deep transurethral resection biopsies of the prostate, preferably at the 5 and 7 o'clock position at the level of the verumontanum pre-operatively.[27] In many centres, patients with positive biopsies and those with widespread carcinoma *in situ* have been recommended prophylactic urethrectomy.

In the surge of the current interest in orthotopic bladder substitution, the reliability of the pre-operative transurethral resection biopsies and the impact of prostatic involvement for urethral recurrence have been challenged by several groups.[28–31] Donat *et al*. found sensitivity and specificity of the biopsies for stromal invasion to be only 53% and 77% respectively, and many centres today have abandoned these biopsies, relying only upon frozen section of the urethral margin obtained at surgery, and accepting all patients for orthotopic reconstruction providing the frozen sections are negative.[28–31] In the study by Lebret *et al*., all 106 patients with negative margin were without recurrence, contrary to the experience by Donat *et al*.[28,29] It is thus obvious that we are today lacking optimal instruments for correct assessment of the prostatic urethra/prostate. Some patients with prostatic involvement will be at risk of developing urethral recurrence after bladder substitution, but we have difficulties in correctly identifying them pre-operatively.

Although the incidence of urethral recurrences after neo-bladder construction is lower than reported for diversion with retained urethra, one has to remember that follow-up in some series is still short. The calculated five-year recurrence rate with any prostatic involvement was 5% after ileal neo-bladder construction.[30] The true incidence may prove to be even higher. In one series, an overall incidence of urethral recurrence of 6% was reported, increasing to 12% in those followed for five years, the majorities being carcinoma *in situ*.[32,33] These figures certainly provoke reflection and it is obvious that great care has to be exercised in recommending patients for orthotopic substitution.

Risk of urethral recurrence in the female

In studies of female cystectomy specimen, the incidence of urethral tumour has been reported to be around 10%, with the main risk factors

being bladder neck tumour, but also widespread carcinoma *in situ* and vaginal wall involvement.[34–37] It was demonstrated that providing the bladder neck was free of tumour, there was no tumour in the urethra.[36] Thus, pre-operative bladder neck biopsies should be obtained. However, the occurrence of urethral tumour without bladder neck involvement has been described.[35]

Previous pelvic irradiation

In a few centres, radiotherapy is still the treatment of choice for invasive bladder cancer. Usually 60–70 Gy is delivered. Today there is a growing interest in chemo-radiotherapy following aggressive TUR ('bladder-sparing treatment modality'). In most schemes, a break with assessment of the bladder is made after 40–45 Gy and if no tumour is noted, consolidating radiotherapy up to a total dose of 65–70 Gy is given. Some patients will not be rendered free of tumour or they will have recurrence with remaining treatment option being 'salvage cystectomy'.

Several reports confirm an increased risk of early as well as late complications in irradiated patients following cystectomy and ileal conduit diversion.[38,39] The same holds true for continent cutaneous diversion, in which the risk of outlet malfunction was greater in irradiated patients with a Mainz pouch or a Kock pouch than in non-irradiated patients.[39,40]

Neo-bladders have also been constructed in full-dose irradiated patients, but the procedure was reported 'more challenging than is usual'.[41] Not surprisingly, early complications have been reported more commonly in irradiated patients with intestinal obstruction and delayed healing of the anastomosis to the urethra.[42] Late complications, such as bowel perforation and fistula formation from the neo-bladder, and poor functional results, further emphasize the risk the urologist is taking when anastomosing tissues within a previous radiation field.[41,43] If such surgery is contemplated, large experience in reconstructive urology, correct intra-operative assessment of the intestine and the ureters and a well-informed patient are necessary components. If any of the above are lacking, the result can be disastrous.

The governing rule should be to use non-irradiated tissue; the 'stay away' principle. Ureters should be divided high. If conduit diversion is the most suitable alternative for the patient, a transverse colonic conduit is usually the best choice.[44,45] Continent cutaneous diversion can also

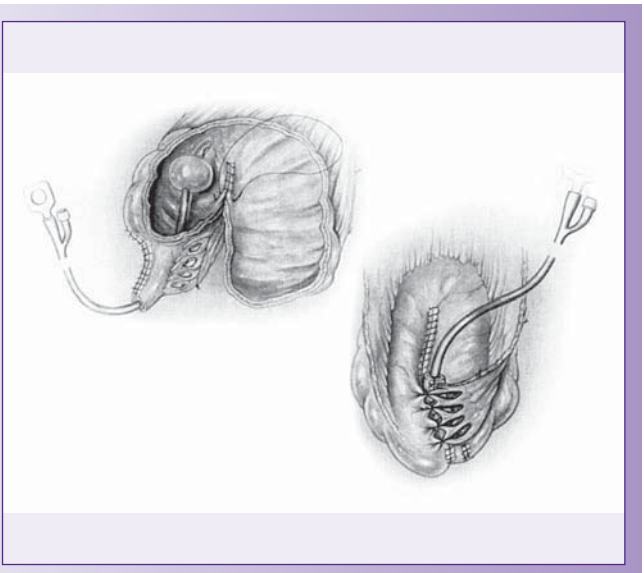

Figure 2: Construction of a Mainz III pouch from the left colonic flexure. The oral end is tapered and the rest of the colonic segment is detubularized and mesenteric windows created. Ureters are implanted with anti-refluxing technique, the pouch closed and the efferent segment embedded by serosa-to-serosa sutures placed through the mesenteric windows.

successfully be performed using the transverse colon, as in the Mainz pouch III, with low reported incidence of early and late complications (Figure 2).[39]

Renal function

The issue of renal function is of importance in the choice between continent reconstruction and conduit diversion. For a given glomerular filtration rate (GFR), the risk of hyperchloremic metabolic acidosis, with possible risk of defect bone mineralization in the long run, will be higher after continent reconstruction, due to more extensive contact between urine and intestinal mucosa. Different upper limits of serum creatinine for accepting patients for continent reconstruction are given in the literature; 250 μmol/l by Skinner's group, 200 by Hautmann's group and 150 by Studer's group.[2,46,47] However, these values all signify considerably reduced renal function with risk of acidosis. We have studied two groups of patients after continent diversion using the right colon; one group with a mean GFR of 100 ml/min and another with a mean GFR of 55 ml/min.[48] Although there was a tendency towards statistically significant

difference in acid-base balance, the values were within normal limits in both groups. Nor was there any difference in the ability to handle an acute acid load. However, in the group with reduced GFR, ionized calcium was significantly lower than in the other group, probably an expression of increased calcium release from the bone with subsequent loss in urine. It is our opinion that continent urinary reconstruction should not be performed in individuals with GFR below 40 ml/min.

Physical status

Is continent reconstruction associated with higher risk of complications than the ileal conduit? In comparisons, a common problem is that case series are not really comparable due to differences in age and, particularly, in co-morbidity. Some studies have tried to properly answer the question by stratifying the patients to levels of co-morbidity. Thus, using a 'fitness score', no significant differences were found between the two groups with regard to operative mortality or morbidity.[49] The Charlson co-morbidity index was applied in a study comparing ileal neo-bladder patients and ileal conduit patients.[50] No differences were noted in post-operative complications and hospital stay, but there were more late complications among neo-bladder patients. Although one would expect that patients with co-morbidity would do worse than those without, no differences with regard to complications, length of hospitalization and re-admission rate were found in patients undergoing radical cystectomy and bladder substitution when stratified with the Charlson co-morbidity index.[51] Although these studies do not support major differences between methods for reconstruction, nor between patients with different physical status, clinical experience nevertheless has taught most of us that there are correlations between outcome and physical status as well as surgical intricacy. The major impact on the patient is probably the cystectomy trauma, but it is of course impossible to separate the effects of the cystectomy from those of the reconstruction.[52] The risk of late complications with need of revisional procedures of the urinary tract is definitely higher after continent reconstruction than after conduit diversion.

Mental constitution

Although little studied, this subject is of importance, especially with regard to post-operative adjustment. In the clinical setting it is the delicate task of

the urologist to try to understand the personality of the patient; therefore the need of repeat communications with the patient pre-operatively.

Although orthotopic substitution is usually the first option for reconstruction, this procedure may not be ideal if the patient finds the prospect of urine leakage repugnant. A highly nervous patient may not be the ideal candidate for continent cutaneous diversion, after which difficult catheterization is a possible complication. The patient's coping ability is a complex issue, but important for post-operative rehabilitation. Instruments like questionnaires may be of importance in this context. We studied the influence of psychological defensive strategies, by which the patient was assigned to a 'risk' or a 'non-risk' group with regard to expected post-operative difficulties after cystectomy.[53] Men using primitive strategies such as projection seemed to run a long-term risk for poor psychosocial adaptation, while those with sensitivity were at risk relatively early in the rehabilitation period. However, we know little or nothing with regard to the importance of such strategies in relation to different modes of reconstruction.

Surgical procedures

Patient preparation

Together with the stomal therapist, the urologist should mark the site of the stoma prior to surgery. It should be placed in an area free of scars and skin folds. Most often the site will be slightly below a line between the umbilicus and the anterior superior iliac spine. The adhesive portion of the bandage is usually a quadrant with the side 7–8cm, which will influence position. The patient should wear the appliance for a day or two pre-operatively.

There are many suggestions of how to prepare the bowel. In Lund, the patient drinks four litres of polyethyleneglycol in the afternoon and evening before surgery. Two hours before the bowel is opened 2g of cefoxitin is given.

Non-continent urinary diversion

Although continent reconstruction has become the first option in many centres, non-continent diversion still seems to be the most commonly employed technique in conjunction with cystectomy. Thus, in Sweden, 63% of all patients undergoing radical cystectomy in 2000 received a

non-continent type of diversion (Swedish National Register of Urinary Bladder Cancer). The last decades have seen considerable improvements in the quality of the necessary appliances. Equally or more important is the fact that enterostomal therapy has developed into a specific field of its own. These factors, together with more close follow-up of the patients with early interventions should complications occur, are reasons for less dismal results today than were reported in the 1970s and 80s of non-continent diversion (Figure 3).

Cutaneous ureterostomy

The main indication for this procedure is palliation in patients with advanced bladder cancer. It is performed less often today, due to the introduction of percutaneous nephrostomy and double-J stents. Stricture of the cutaneous stoma is a well-known complication, which more or less limits its use to cases with dilated ureters. If there is a non-dilated ureter, a Z-incision of the skin and suturing of the skin flaps into the spatulated ureter may lower the risk of stenosis. In certain cases, cutaneous ureterostomy can be combined with a transuretero-ureterostomy. The procedure, however, has a poor reputation. One risk is urine pendulating from one ureter up into the other, the 'yo-yo phenomenon', due to disrupted ureteric peristalsis. The recipient ureter therefore should be mobilized only to the level where the anastomosis will be performed.[54] The end of the non-dilated donor ureter is cut obliquely and sutured without tension end-to-side to the recipient ureter, which is usually dilated. The ureter below the anastomosis may

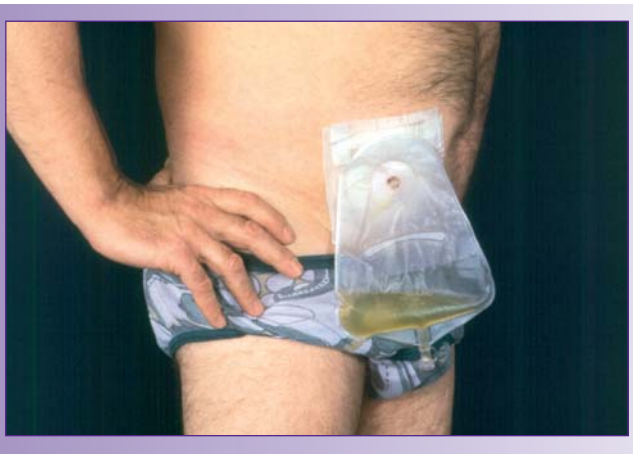

Figure 3: Urostomist with ideal position of stoma for optimal fitting of the appliance.

suffer stricture due to ischaemia. This complication was one of the few ones in a large series of transuretero-ureterostomy but without cutaneous diversion.[55] It is a valuable procedure in some cases of lower urinary tract reconstruction.

Conduit diversion

Conduits can be constructed from jejunum, ileum and colon. Of these, jejunum is seldom used because of the risk of specific electrolyte disorders; 'the jejunal conduit syndrome' (see below). Although ileum is most often used, there are two important indications for a colonic conduit. One is in children in whom an intermediate diversion is necessary, awaiting continent reconstruction at a higher age. Several reports during the 1980s testify to the poor outcome of ileal conduit diversion in children. Anti-reflux ureteric implantation is necessary in this group of patients and this may be more easily accomplished with the colon. Excellent long-term results have been published using the colon, most often the sigmoid colon.[56]

Another indication for the use of this procedure is patients who have received high-dose pelvic irradiation (see above).

In constructing the conduit, it is important to create a spout at least 2cm in length. The more obscene it may look, the better. This will decrease the risk of parastomal complications. The appliance will fit much better and there will be less risk of urine leakage. The spout should protrude into the appliance bag. Peristomal dermatitis with risk of hyperkeratosis and fungal infection is almost always caused by urine between skin and appliance and is often a consequence of retracted stoma or ill-fitting appliance. Stomal and peristomal complications reached 50% in some old series and even recently published series present figures around 30% (Figures 4 and 5).[57,58]

Perastomal hernia is seen in 5–15% and may occur also after continent cutaneous diversion (Figure 6). They are large rather than small and although the majority of patients are asymptomatic, some need surgery. A high recurrence of cases requiring re-operation is seen.[57] For first-time parastomal hernia repairs, stoma relocation may be superior to fascial repair.[59] We have seen infections with erosion and fistulas using synthetic mesh, which is usually employed in recurrent hernia repair. Newer techniques with the incision placed lateral and far away from the stoma, with closure of the fascial defect and using mesh material as onlay, have been reported as yielding good results.[60,61]

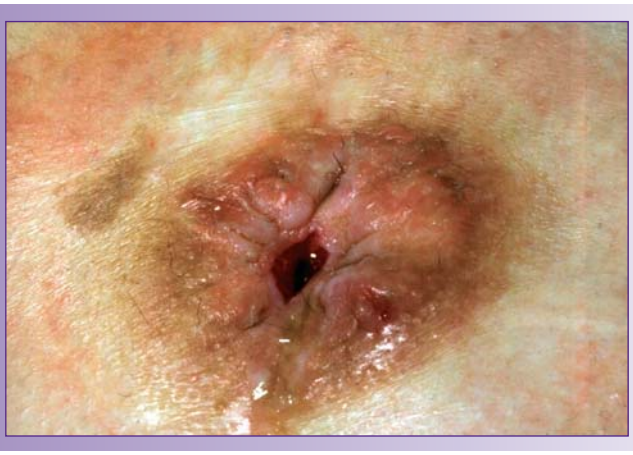

Figure 4: Peristomal hyperkeratosis due to retracted stoma.

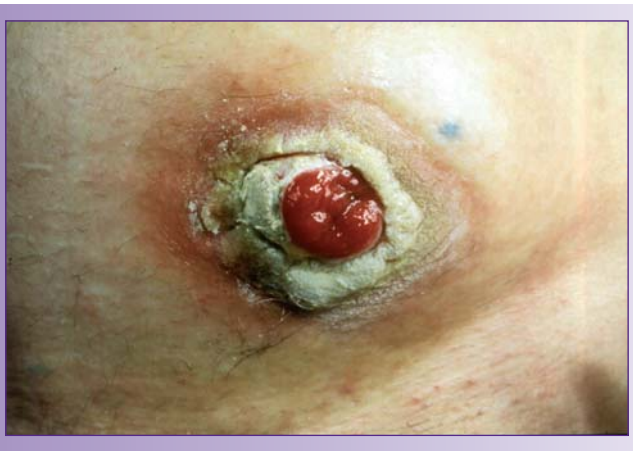

Figure 5: Severe peristomal candida infection because of poorly fitting appliance.

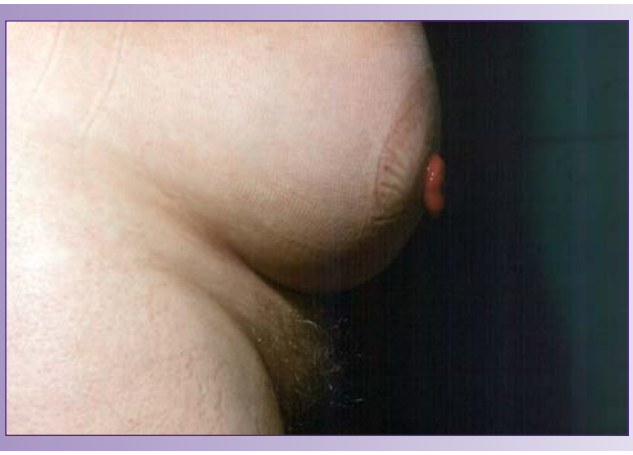

Figure 6: Parastomal hernia in an ileal conduit patient.

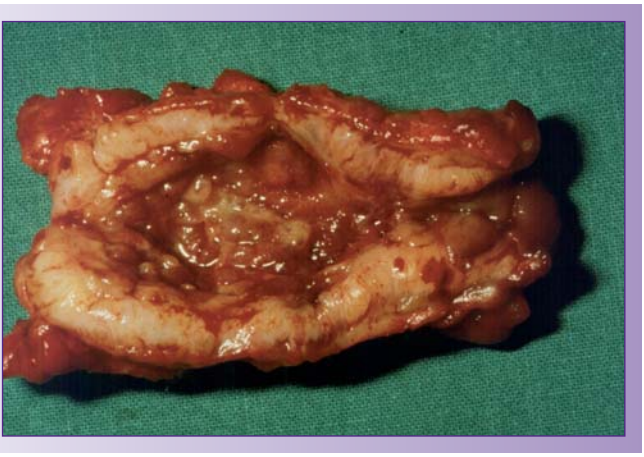

Figure 7: Ileal conduit 11 years after construction. Shrunken, thick-walled conduit with ulcerated and inflammed mucosa.

Conduit stenosis is a condition affecting ileal conduits. It has never been described in colonic conduits, indicating fundamental but unknown differences between ileum and colon in resistance to urine exposure. The whole, or part of the conduit, is transformed into a thick-walled tube without peristaltic activity (Figure 7). The pathogenesis of this disorder, which manifests late after diversion, is obscure. The clinical picture is colicky flank pain and/or fever and is produced by upper tract obstruction. Treatment is by removal of the conduit or partial resection with or without ureteric re-implantation.[62]

A recent report underlines the need for close indefinite follow-up of patients with conduit diversion.[66] Complications related to ileal conduit developed in 2 of 3 patients and almost 40% needed surgical re-intervention. The authors raise the provocative question of whether the ileal conduit really is a "gold standard".

Continent reconstruction

Whether for continent diversion or orthotopic substitution, three parts are essential in the construction; the pouch, the inlet and the outlet. The issue of how to fashion the first two in an optimal way are common to both types of reconstructive procedure.

The pouch

Large capacity and storage under low pressure in the pouch are essential requirements of continent reconstruction. This is achieved through

detubularization and the dynamic behaviour of such pouches has been explained in general and in biomechanical terms (Figure 8).[63,64] No proper prospective study has been performed to elucidate if any bowel segment is superior to others in terms of urodynamic behaviour. One study indicates superiority of ileum over colon, but functional differences may only be minor, if any.[66,67] A prospective multi-centre study comparing ileum and colon has now started in Scandinavia.

Pharmacological attempts to reduce intra-reservoir pressure using anti-cholinergics and alfa- and beta-adrenoceptor agonists have had little clinical success. Potential interesting agents in this context are opiod-receptor agonists, calcium antagonists, potassium-channel openers and nitric oxide donors.

For colonic segments, surgical measure as multiple taeniamyotomies has been suggested for reducing intra-luminal pressure.[68]

Late complication is stone formation, the incidence of which appears to increase with longer follow-up (Figure 9). Use of staples exposed to urine in the pouch or in the outlet should be abandoned, as they will serve as nidus for stone formation (Figure 10). Mucus and residual urine may contribute. Eight out of 64 patients operated with right colonic neo-bladder in the years 1987–99 and followed for a mean of 71 months formed one or more stones, although staples were not used.[13] Of these, seven could be removed endoscopically. Regular irrigation has been suggested to lower the risk of stone formation, but its true value remains unclear.[69]

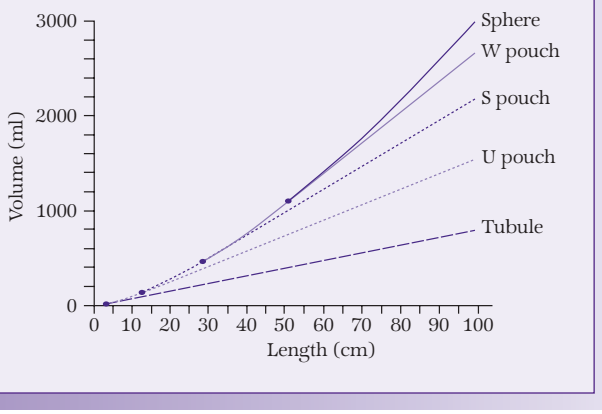

Figure 8: Volumes of different types of ileal reservoirs, each calculated as a function of the length of bowel used for construction.

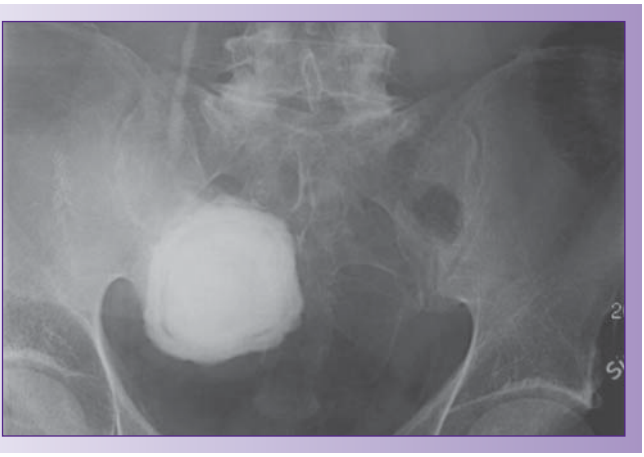

Figure 9: Giant stone in a continent right colonic reservoir with ileal nipple valve outlet.

A more serious, potentially lethal complication, is rupture/perforation of the pouch. The incidence seems to be 1–2%, but may increase the longer the follow-up. In a survey among 1,700 patients operated upon in the Scandinavia, 20 episodes occurred in 18 patients.[70] Aetiology can be trauma from catheterization, but several cases were spontaneous, often occurring with a full pouch. Noticeable findings were long delay to treatment and that investigational procedures, such as enterocystoscopy, enterocystography and CT were seldom employed. This complication should always be suspected when a patient with a continent reservoir for urine is admitted with abdominal pain. The risk is much higher after continent cutaneous

Figure 10: Reservoir stone formed on staple.

diversion than after bladder substitution, when the urethral sphincter will yield to too high pressure.

How should the ureters be implanted – with or without reflux protection?

This is a never-ending issue of discussion, partly due to the fact that prospective studies that have tried to measure GFR accurately are rare. Such measurement is necessary if one would like to answer the question. Many reports have revealed a high incidence (13–41%) of renal deterioration associated with refluxing ileal conduit, as evaluated using serum creatinine and urography.[56,71,72] Dilatation of the upper tract is a common finding, but it does not necessarily signify obstruction or renal deterioration.[57]

In a prospective, randomized study on the fate of separate GFR after ileal conduit urinary diversion, no difference was noted between units with or without anti-refluxing ureteroileal anastomosis, but severe renal scarring was more common on the side with refluxing anastomosis.[73,74]

There is presently a trend towards using refluxing techniques when implanting ureters into orthotopic neo-bladders.[75–78] The proponents give several rationales:

1 Anti-refluxing anastomosis is associated with higher incidence of stenosis than refluxing anastomosis.
2 Intraluminal pressure is low.
3 Urine is sterile.

The common denominators in these reports are that follow-up is short and that renal function is evaluated by serum creatinine and urography only.

The critical factors with regard to renal function in the presence of reflux are pressure and infection, making refluxing anastomosis not recommended for patients with continent cutaneous diversion as intermittent very high pressure can be achieved and urine is always heavily colonized. The decrease in renal function that has been noted after ileal conduits with refluxing ureters have been converted into continent pouches with abdominal stoma testifies to the danger.[79]

However, intraluminal pressure can be substantial in orthotopic bladder substitutes and the expression 'low pressure reservoir' is clearly unsuitable, as evidenced by the report of pressure up to 150cm H_2O, the mean being 77cm H_2O, during voiding in patients with ileal neo-bladders.[80] Obstruction of the urethrointestinal anastomosis is one risk factor for high

pressure. It is also important to remember, contrary to general belief, that urine in orthotopic bladder substitutes is often not sterile.[81,82] Bacteriuria is a common phenomenon, although the heavy colonization after continent cutaneous diversion is usually not seen. However, CISC, common in some series, will increase the microbial burden, with consequent risk for the upper tracts in case of reflux and high pressure.[12] Therefore there are reasons for the statement 'conventional wisdom suggests that unless an anti-reflux technique is used during construction of a urinary reservoir, deleterious effects on renal function might be expected'.[83]

The question cannot be solved without a prospective study employing accurate measures of renal function. We suggest that this should be done by implanting one ureter with and the other without anti-refluxing technique in a randomized fashion, studying separate GFR pre-operatively and at follow-up. This is also the only way to find out if anti-refluxing anastomosis are associated with higher risk of stricture than refluxing anastomosis.

At present the most commonly used methods for anti-reflux ureteric implantation into ileal pouches are the Le Duc technique, the afferent ileal loop, as in the Studer pouch, and the serous-lined extramural tunnel (Abol-Enein technique) (Figure 11).[47,84,85] The afferent nipple valve, as used in the Kock pouch, will probably disappear, some instead using a variation, although rather complicated, of the Abol-Enein principle, as in the T-pouch.[86] For colonic pouches, the submucous tunnel and the Le Duc technique are used.[87]

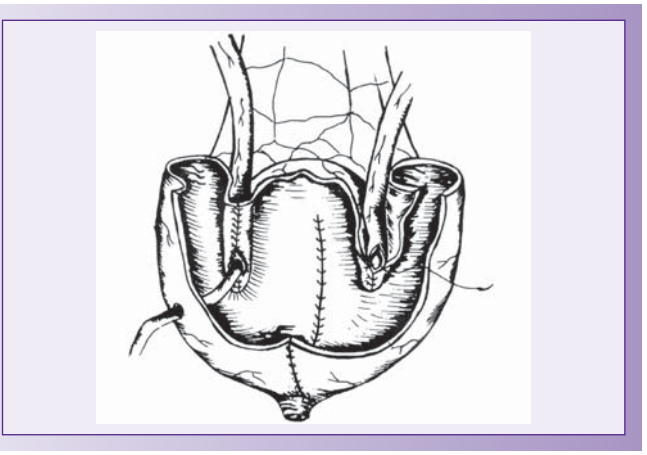

Figure 11: Spatulated ureters in serous-lined intestinal troughs, which are transformed into tunnels by closing the intestinal mucosa over the implanted ureters; the Abol-Enein technique.

Continent cutaneous diversion

In Lund, as in most other centres, continent cutaneous diversion is the second choice after orthotopic bladder substitution, and offered if urethrectomy has to be performed in conjunction with cystectomy. The success or failure of continent cutaneous diversion stands or falls with the outlet. However compliant the reservoir, the outlet must have an effective leakage-prevention mechanism that also permits easy catheterization. Furthermore, it must be easy to construct. The advice by Albert Einstein that 'everything should be made as simple as possible, but not simpler' is certainly applicable in this context. Numerous methods have been designed, reported once but not reappeared in the literature, most often probably due to high complexity. The most commonly used methods among urologists have been the Kock pouch, the Indiana pouch, or variation thereof, and pouches employing the appendix as outlet. The stoma is usually placed in the right lower quadrant or in the umbilicus, which may have aesthetic advantage (Figure 12).

The Kock pouch

This was the first method for continent cutaneous diversion that was accepted by the urological community after description by Kock (Figure 13) and then refined by Skinner's group.[88,89]

The method uses a long ileal segment that is detubularized, and reflux protection and outlet is by intussuscepted ileal nipple valves. Skinner's modifications were stapling of the valves, creation of a mesenteric window, and using synthetic mesh around the nipple base for stabilization of the intussusception and for fixation of the nipple base to the abdominal wall. Continence is achieved by the combination of intraluminal pressure equilibrium and intraluminal flap valve.[63]

Urological departments worldwide adopted the technique, but it was soon obvious that the technique was complicated and time-consuming, requiring meticulous attention to detail. The learning curve was also long. Fatty mesentery can cause difficulties in fashioning the nipple valve and fixation of the nipple base to the abdominal wall may present problems. Erosion by the mesh, pin-hole fistula, stenosis or even sloughing of the valves, as well as prolapse and sliding of the valve may occur, with consequent urine leakage and/or difficulties in catheterization (Figures 14, 15 and 16).

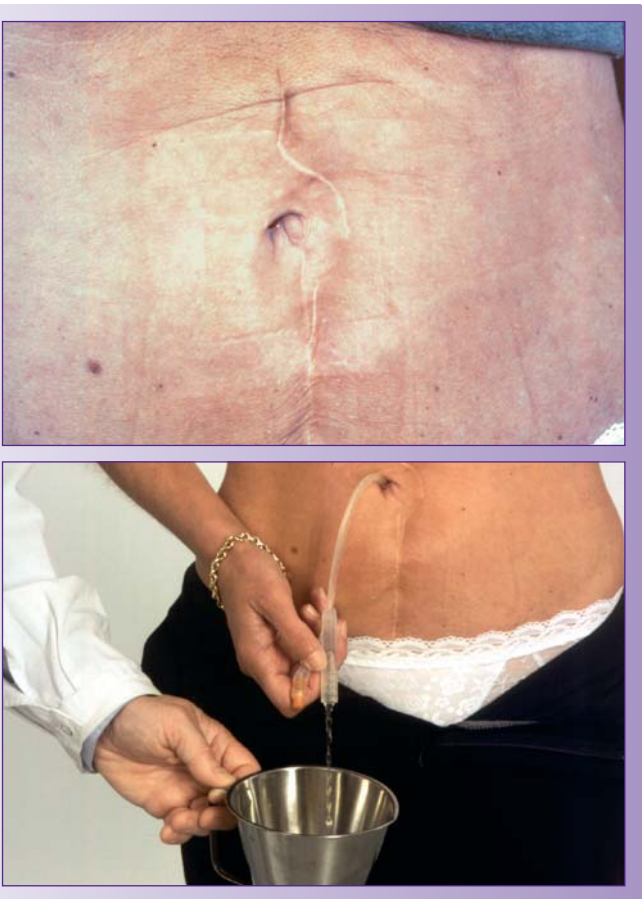

Figure 12: Concealed appendiceal stoma of continent reservoir.

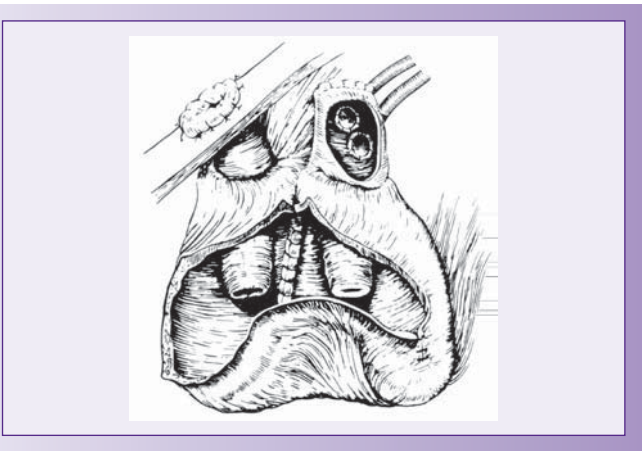

Figure 13: Continent ileal reservoir for urine; the Kock pouch.

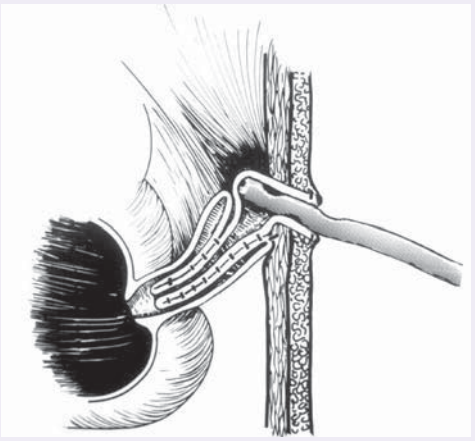

Figure 14: Difficult catheterization through detachment of ileal nipple base from the abdominal wall.

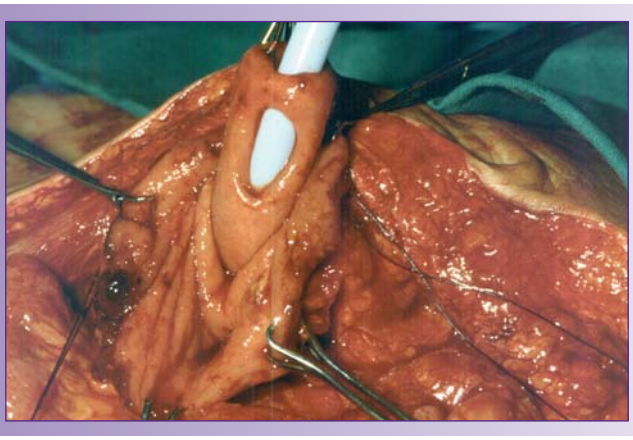

Figure 15: Fistula through ileal nipple valve.

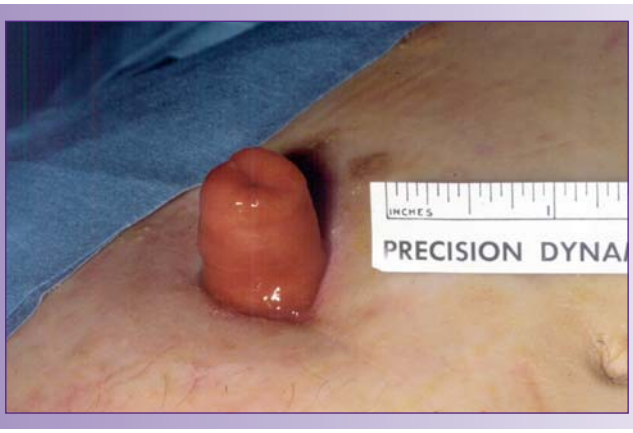

Figure 16: Prolapse of ileal nipple valve.

Outlet revision rate up to 50% has been reported.[90] Also, with the wide experience of this technique in Skinner's department, the outlet failure rate after introducing several modifications was still as high as 15% in their last operated 239 patients.[8] To this problem should be added the one of stone formation on exposed staples.[92] In the most recent long-term follow-up of Kock reservoir patients from Gothenburg it is noted that all the first-operated 25 patients were re-operated. Of the patients operated on since 1984, 31% had outlet revision; this figure dropping to 21% in those operated on since 1993.[93] Ninety percent of all surviving patients received a well-functioning reservoir. Despite this, it seems that the ileal nipple valve in most centres has been abandoned due to the high technical complexity and the high revision rate. Time will tell if the flap valve known as the T-mechanism, which has replaced the nipple valve in a few centres, represents improvements in this regard.[86]

The Indiana pouch

Described by Rowland *et al*. from Indiana in 1987, this type of diversion uses the detubularized right colon or the ascending colon patched with an ileal segment, outlet being a 10cm-long plicated or stapled ileal segment (Figure 17).[94]

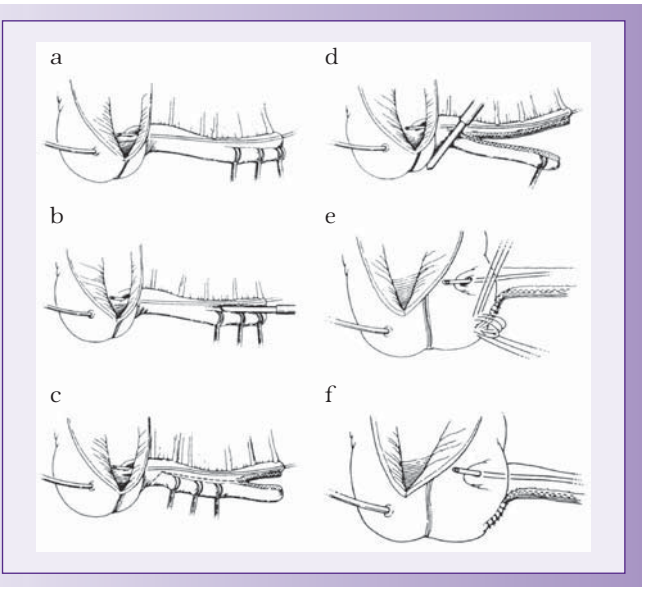

Figure 17: The classical Indiana pouch.

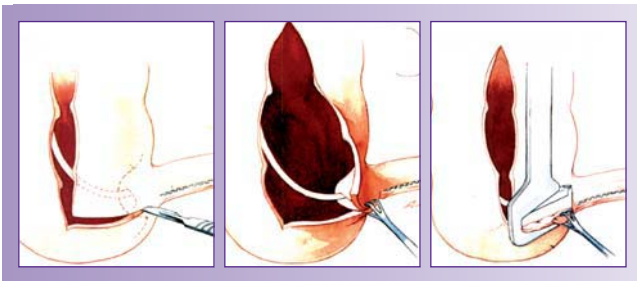

Figure 18: The Lundiana pouch.

In the last report from the group, only one of 81 patients needed outlet revision due to urine leakage.[95] The advantage with the technique is that it is simple, the disadvantage that the outlet lacks an intra-luminal closure mechanism. Instead, continence is achieved by extra-luminal 'sphincteric' compression, which might be less reliable, although proper studies to elucidate that have not been commissioned. Many modifications of the technique has been described. One is by incorporating the ileocaecal valve that is diminished in diameter and fixed to the caecal wall as a small flap valve; the Lundiana outlet (Figure 18). In a comparative study, this outlet proved equally effective as the intussuscepted ileal nipple valve. However, the urodynamic characteristics were not as optimal as those of the nipple valve.[96]

We have now analysed our series of Lundiana pouches operated from 1992 to 1999 and followed to December 2001.[13] Of 97 patients, six underwent revision of outlet due to leakage (two revisions in one, three revisions in two). Six patients needed revision of the stoma due to stenosis (two revisions in two, three revisions in one) and one had dilatation due to stenosis. Inability to catheterize a full reservoir necessitated percutaneous puncture in two patients. Augmentation for an inadequate pouch capacity was done in two patients. Four patients never achieved continence and in two of these the pouch was continuously drained due to rapidly recurring cancer. Studies comparing the Kock pouch with the Indiana pouch have reported less need of surgical revision in the latter.[90,97,98]

Appendicial outlet

The use of the appendix as a catheterizable continent outlet for vesicostomy was described by Mitrofanoff and later by Riedmiller *et al*. for continent cutaneous diversion.[99,100] Several techniques for the use of the appendix as continent outlet have been described, but the most popular seems to be

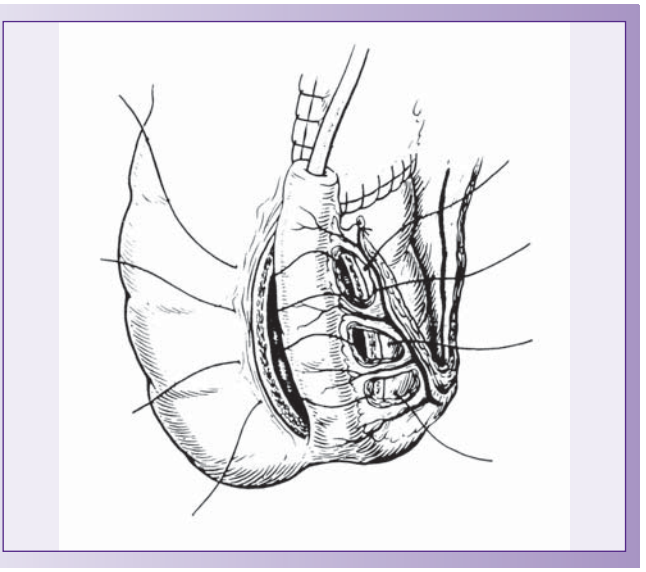

Figure 19: The appendix is positioned in a seromuscular trough and this layer is then closed over the appendix with interrupted sutures through the windows in the mesoappendix.

the embedded appendix as it is used in the Mainz pouch I, and excellent results have been reported (Figure 19).[101] Apart from three out of 118 patients who suffered ischaemic necrosis of the appendix and needed re-operation because of complete incontinence, no other patients underwent revision due to incompetence of the outlet. The main problem is the tendency towards stomal stenosis, causing difficult catheterization and in the above-mentioned series revision for that reason was necessary in 19 patients.

The advantages of using the appendix are that it is 'ready-made' and that a smaller amount of bowel is needed for the diversion. Disadvantages are that it is sometimes missing or too tiny to use. Familiarity with some other method for continent diversion is therefore necessary.

Other types of outlets

There are some other outlets that it is important to know about as they can be used as 'salvage' methods. One is the 'Monti technique', or the transverse retubularized ileum.[102,103] Two to three centimetres of ileum are isolated, opened close to the mesenteric attachment and then closed transversely, creating a small-bore tube that can be handled like an appendix. So far experience of this is limited. It is simple, but there is probably the same risk as with the appendix as regards stenosis.

Other possible outlets are the tunnelled bowel flap tubes, one being a seromuscular tube and the other, seemingly more useful, a full thickness bowel flap tube.[104]

Continent anal urinary diversion

There is in the literature a large number of reports on complications of ureterosigmoidostomy, and this type of diversion was therefore abandoned in most centres due to the problems of ascending infections, loss of renal function, metabolic acidosis and the possibility of secondary malignancy. However, there are also series showing that the clinical results can be favourable, with high continence rate, if the operation is performed in childhood.[105,106] The concept of detubularization with creation of recto-sigmoid pouches may have lead to a revival of interest in anal diversion and different techniques have been described.[107,108] Although excellent functional results have been published, it seems that acceptance by Western urologists has been low, presumably due mainly to instinctive mental reservations and the contemporary enthusiasm for orthotopic reconstruction.[107–109]

Orthotopic bladder substitution

Although first performed 50 years ago, the impetus to widespread use and acceptance of this type of reconstruction came with the report by Lilien and Camey in 1984 on the Camey bladder.[110] Today it is first option in most centres for reconstruction in conjunction with radical cystectomy, and also in female patients. The majority of bladder substitutes are constructed from detubularized ileal segments, most commonly those described by Studer (Figure 20), Hautmann (Figure 21), Abol-Enein, and Pagano (Figure 22).[47,85,111,112] Goldwasser and Reddy have described the use of right colonic segment and sigmoid segment for this purpose (Figure 23).[113,114] Yet another possibility is to construct an ileocaecal pouch.[115]

The main problem after neo-bladder construction is voiding dysfunction, i.e. urine leakage and retention. Due to considerable variance between the multitude of series now published, it is impossible to claim superiority of one type of neo-bladder over another. Not only may patient age and follow-up vary, but the technique of performing the cystectomy and the type, length and detubularization of the intestinal segment may

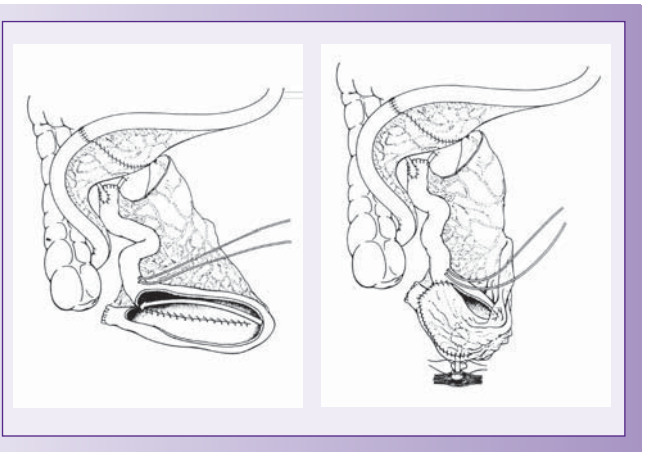

Figure 20: The detubularized ileal neo-bladder with an afferent tubular segment; the Studer pouch.

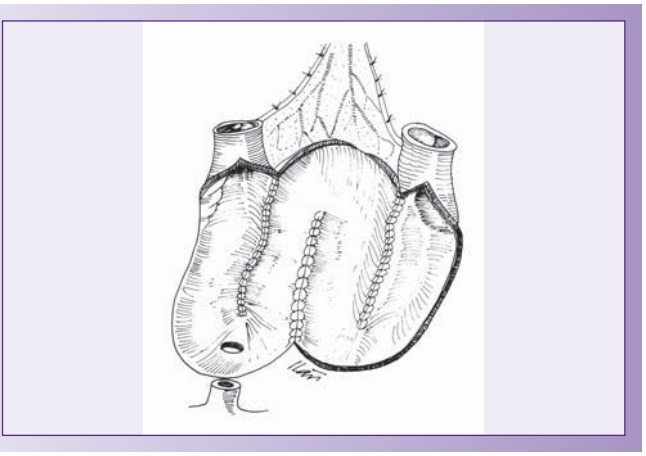

Figure 21: The ileal W neo-bladder; the Hautmann pouch.

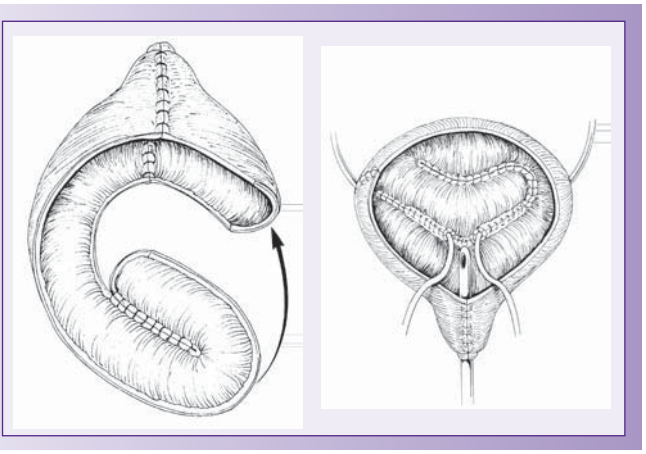

Figure 22: The Padova ileal neo-bladder; the VIP pouch. The ureters are implanted using the Abol-Enein technique.

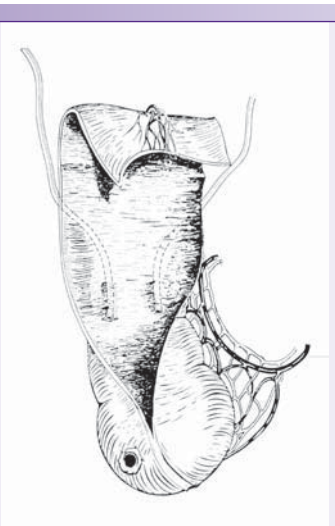

Figure 23: The detubularized right colonic segment for orthotopic neo-bladder; the Goldwasser pouch.

be different. Semantics also differ. Thus, continence has been described as 'continence', 'good continence', 'satisfactory continence' and 'social continence', with definitions that vary widely. As has been pointed out, neo-bladder function has rarely been assessed using validated outcome instruments and/or voiding diaries.[116] Good clinical research within this field is clearly needed.

In a recent review paper, daytime incontinence in published series varied between 0% and 67%, with a mean of 13%, and the corresponding figures for night-time incontinence were 7%, 70% and 29%.[115] Between 4% and 44% of neo-bladder patients need intermittent self-catheterization.[12,116]

Introduction of bladder substitution in females was late, due to fear of compromising continence and radicality at cystectomy. It has since been established that female continence after cystectomy is through the rhabdosphincter in the distal half of the urethra, innervated by the pudendal nerve which, due to its course, is not likely to be damaged during surgery.[117,118] There is an ongoing debate regarding the importance of preserving the autonomic nerves during cystectomy. Proponents for this measure argue that sacrificing the nerves increases the risk of urine retention as nerves sprout from adjacent adrenergic neurons into the denervated urethra.[118–120] Other authors claim these nerves to be insignificant with regard to emptying.[121,122] This latter view is supported by

a recent experimental study showing that autonomic denervation resulted in a moderately reduced pressure in proximal urethra, no fibrosis and caused no residual urine.[123] The functional results obtained in men and women seem equivalent.

Our results from use of the Goldwasser technique for orthotopic substitution are not encouraging. In 64 patients with mean follow-up of 71 months, stenosis of the urethrocolonic anastomosis occurred in three patients. AUS was required in three patients, two needed augmentation of the neo-bladder and conversion to ileal conduit was necessary for one patient. Twenty-six patients used CISC. The continence situation is not as good as for patients with a Lundiana pouch.

Follow-up

Renal function

Studies by us and by the Gothenburg group have shown that GFR is well preserved at long-term follow-up after continent reconstruction and compares favourably with renal function after conduit diversion.[73,93] The same was found in a recent follow-up of patients after different types of continent urinary reconstruction.[124] Five years after surgery mean GFR had fallen from 98 to 90 ml/min.

Recommendation

Upper urinary tract morphology and function are studied with IVP and serum creatinine or, if in doubt about renal function, with method giving the glomerular filtration rate (GFR). Most centres in Scandinavia are using ^{51}Cr-EDTA or iohexol for this purpose. These methods do not overestimate GFR in patients with intestine incorporated in the urinary tract. Sometimes a scintillation camera renography is valuable to determine the separate GFR and to evaluate obstruction.

We disagree with the recommendations in the EAU guidelines, in which follow-up is by ultrasonography and plain film.[125] Ultrasonography can never be a substitute for IVP as obstruction can be present without gross dilatation, and vice versa.[57] In addition, ultrasonography is user-dependent. In Lund we perform IVP a couple of days after removal of the ureteric catheters, after three months, after one year, after two years and then biannually indefinitely.

Metabolic aspects

In most cases, ileum or colon will be used for the reconstructive procedure. These segments seem to behave rather similarly in terms of flux of ions across the mucosa when in contact with urine. The body is presented to an increased acid load due mainly to absorption of ammonia, ammonium and hydrogen ions. Chloride ions are absorbed to maintain electroneutrality. There is also some secretion of bicarbonate. This will result in hyperchloremic metabolic acidosis. With normal renal function, excess H^+ are trapped in the renal tubules and excreted mainly as NH_4 and titrable acids and there will be no acidosis, or only a respiratory compensated slight acidosis. However, with impaired renal function, ammoniagenesis will also be impaired and metabolic acidosis will occur.[126] Therefore, continent reconstruction in patients with GFR below 40–50 ml/min should be seriously questioned. Such patients will require life-long alkali treatment, a treatment that may be difficult to tolerate.

The most important implication of chronic metabolic acidosis is bone demineralization. Bone buffers, mainly carbonate, will be released, and thereby also calcium. Increased urinary excretion of calcium and somewhat low serum calcium occur. Some clinical studies have shown a decrease in linear bone growth and an increase in morbidity following orthopaedic surgery. If there is also a negative effect on mineralization when only subtle changes in acid-base balance are present is unknown. In patients with normal renal function and long follow-up after diversion/continent reconstruction, no effect on mineralization or bone morphometric parameters have been found using absorptiometry and bone biopsy analyses.[127] Patients with rapidly growing skeleton, e.g. children and adolescents, should perhaps be given alkali, even if they have normal GFR, to ensure that they achieve an optimal peak bone mass. It is doubtful if such treatment should be given to adults with normal renal function. However, a recent report shows that our fear of severe bone disturbance after continent reconstruction in children and adolescents may have been exaggerated.[128]

Hyperkalaemia and hyperammonemia are rarely seen complications of urinary diversion.

If jejunum is used, a specific electrolyte disturbance characterized by hyperkalaemia, hyponatraemia, hypochloraemia and acidosis is seen in 20–40% of the cases, 'the jejunal conduit syndrome', usually requiring

treatment with saline solution and salt tablets.[126,129] This segment of the intestine should be avoided if possible. However, a recent report expressed satisfaction with this type of diversion, reporting a low incidence of electrolyte problems and stressing that a short conduit, 10–12cm, should be used.[130]

Vitamin B_{12} (cobalamin) is absorbed in the distal 30–50cm of ileum. Several studies have reported low vitamin B_{12} levels in 10–20% of patients after ileal conduit diversion and after continent cutaneous diversion and neo-bladder construction using ileum or an ileocolonic segment. It is considered that normal vitamin B_{12} values can be maintained for three to five years through cobalamin stored mainly in the liver. The main problem is that analysis of serum vitamin B_{12} does not adequately mirror the tissue content.

Recommendation

It seems sufficient to follow the patients with Base Excess. It is doubtful if routine determination of serum sodium, potassium and chloride is of any value with regard to the reconstructed urinary tract. We do not perform bone studies, but this is probably of value in children and adolescents. Serum vitamin B_{12} should be determined after three to five years and then biannually. If a trend towards low value is noticed, methyl malonic acid and homocysteine should be measured. However, do remember that many patients who are operated on are elderly and may have a low vitamin B_{12} already pre-operatively. Therefore, be generous with analysis.

Urothelial recurrence in the upper urinary tracts

The incidence of urothelial malignancy in the upper urinary tract after cystectomy varies between 2 and 17%, the latter high figure when cystectomy is performed due to CIS.[131] The surveillance of patients at risk is a major problem, as imaging studies generally provide inadequate information.

Recommendation

Maintain high suspicion when a patient complains about flank pain or haematuria. Urine cytology. Endourological studies if access to the upper tract is possible. Urine cytology yearly in risk patients.

Urethral recurrence

Urethral recurrence rate as high as 12% has been reported after neo-bladder construction.[33] Risk factors are prostatic involvement and widespread CIS of the bladder.

Recommendation

Urine cytology and annual/biannual urethroscopy.

Secondary malignancy

Adenocarcinoma after ureterosigmoidostomy is a well-known entity. The risk is several hundred times that of the normal population, with a latency of one or two decades. These adenocarcinomas are situated at or close to the ureterosigmoid anastomoses. Whatever the cause, it seems that the mixture of urine and faeces is important for the tumour to arise. Only single cases have been reported in isolated bowel used for conduit or continent pouch construction.

Recommendation

There is no reason presently to submit patients with conduits or continent pouches to regular check-up to control for secondary malignancy. However, patients with ureterosigmoidostomy or detubularized recto-sigmoid pouches should undergo surveillance colonoscopy yearly, starting 5–10 years after surgery.

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Chapter 20

Salvage cystectomy

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Introduction

The term 'salvage cystectomy' refers to surgical removal of the urinary bladder in patients who have previously undergone unsuccessful definitive therapy for bladder cancer. Historically, this term was most commonly used when patients underwent radical cystectomy after prior radiation therapy. Salvage cystectomy was considered a formidable surgical procedure with significantly increased morbidity and mortality, and cancer recurrence rates were also very high.[1–6] Although this bleak outlook improved a little when reports from the University of Southern California, Memorial Sloan-Kettering Cancer Center, and the University of Texas MD Anderson Cancer Center were published in 1980 and 1981, salvage cystectomy was clearly still a difficult procedure, helpful only in carefully selected patients and probably best reserved for institutions experienced in the management of this type of problem.[7–9] Multiple reports since that time have re-affirmed the technical difficulty of salvage cystectomy, with high morbidity and even mortality rates, and its benefit for limited numbers of patients.[10–17]

Today, three questions are important. First, can salvage cystectomy be performed safely after definitive radiation therapy? Second, do the results justify its continued use? And third, since irradiation alone is rarely used today as definitive therapy, particularly in the United States of America, is the problem still relevant? I believe our experience at the University of Texas MD Anderson Cancer Center, and the results reported in the literature, support an answer of yes to all three questions.

Morbidity of salvage cystectomy

Mortality rates of 15–33% and complication rates of 44–66% were reported in early reports of radical cystectomy and ileal conduit urinary diversion following definitive irradiation (Table 1).[1–5]

Furthermore, very few patients were known to survive five years. Edsmyr *et al.* reported in 1971 that after a median follow-up of 20 months after cystectomy, only nine patients were alive, three of whom had cancer; by then 26 patients had died: 19 of cancer, six in the perioperative period, and one of intercurrent disease.[5] In 1976, Nerstrom *et al*. concluded that total cystectomy after high-dose radiation therapy was justified only for relief of symptoms and not as potentially curative.[6] In their experience with 47 patients who underwent cystectomies following a radiation dose of 60

Table 1: Operative mortality and morbidity after salvage cystectomy

Series	*Ref no*	*Number of patients*	*Years of study*	*Perioperative mortality rate*	*Morbidity rate*		
					Early	*Late*	*Total*
Riches	1	12	N/A	22%			44%
Hecker	2	15	N/A	25%			50%
Higgins	3	9	1961–64	33%			66%
Whitmore	4	81	1959–66	15%			53%
Edsmyr	5	35	1957–67	17%			57%
Crawford	7	37	1971–77	8%	24%		
Smith	8	80	1971–74	5%	46%		
Swanson	9	62	1969–79	0%	32%	32%	
Freiha	10	42	1962–77	5%			40%
Boccon Gibod	11	14	1979–82	14%			29%
Konnak	12	18	1971–83	11%	28%		
Lindell	13	19	1967–83	11%	63%	47%	
Rasmussen	14	47	1976–84	13%			32%
Nurmi	15	20	1973–85	0%			70%
Nissenkorn	16	31	1976–83	0%	36%		
Abratt	17	46	1981–92	7%			35%

Gy as definitive radiation therapy, the survival rate was extremely poor, especially when recurrent malignancy had been histologically proven. In 1980, Crawford and Skinner reported on 37 patients treated with salvage cystectomy between June 1971 and July 1977.[7] Three patients died in the perioperative period, for an operative mortality rate of 8%, and nine patients (24%) had early complications. Crawford and Skinner attributed their low complication rate to the fact that 13 of the 37 cystectomies were performed as staged procedures (the urinary diversion was performed first and the cystectomy followed in a second operation) and that 15 patients had undergone a combined abdominal and perineal approach. Smith and Whitmore reported in 1981 that of 80 patients who underwent single-stage salvage cystectomy between 1971 and 1974, four patients (5%) died post-operatively and 37 patients (46%) had early complications.[8] Our own report in 1981 described 62 patients on whom we performed single-stage salvage cystectomy between 1969 and 1979.[9] No patients died post-operatively, but 20 patients (32%) did have early complications, and there were 25 late complications in 20 patients, 13 of whom required re-operation. One patient did die following the surgical repair of an intestinal fistula five months after cystectomy. Together, these latter three papers helped show that cystectomy can be performed safely after definitive radiation therapy if performed in centres of excellence where radical cystectomy is performed regularly and where there is experience in dealing with patients who have been heavily pre-treated.[7–9]

Since our report in 1981, there have been other reports that help support this conclusion. Freiha and Faysal reported on 42 single-stage salvage cystectomies performed between 1962 and 1977 after radiation therapy of 70 Gy given over seven weeks.[10] There were two operative deaths (5%), but four additional deaths occurred within 12 months of surgery among patients who had severe radiation enteritis. Three patients suffered rectal lacerations. Boccon Gibod *et al.* described their experience with 14 salvage cystectomies using a combined abdominal and perineal approach between 1979 and 1982.[11] Ten patients underwent single-stage procedures and four underwent staged cystectomies; nonetheless, there were again two operative deaths (14%). These authors stated they believed that the abdominal perineal approach offers a safer dissection and helps prevent rectal lacerations and that the staged procedure was better for debilitated patients. In 1985, Konnak and Grossman reported two deaths among 18 patients who underwent salvage cystectomy, one patient dying early and

one late.[12] In 1987, Lindell also reported an 11% operative mortality rate for 19 patients who underwent salvage cystectomy between 1967 and 1983, with an early complication rate of 63% and a late complication rate of 47%.[13] In 1988, Rasmussen *et al*. reported on 47 salvage cystectomies performed between 1976 and 1984.[14] Six of their patients died in the perioperative period, for an operative mortality rate of 13%. Two series reported zero operative mortality. Nurmi *et al*. performed 20 salvage cystectomies between 1973 and 1985, but there were complications (early or late) in 14 patients (70%), and in seven of these a re-operation was necessary.[15] Nissenkorn *et al*. performed 31 salvage cystectomies between 1976 and 1983, with an early complication rate of 36%.[16] Finally, Abratt *et al*. reported in 1993 only three operative deaths (7%) among 46 patients who underwent salvage cystectomy between 1981 and 1992.[17] Their early complication rate was also 35%.

Thus it is safe to conclude that salvage cystectomy is a relatively safe procedure for selected patients for whom definitive radiation therapy for localized bladder carcinoma was unsuccessful. Surgical experience may be important, however, and will be discussed again later in the context of technical considerations to minimize the morbidity during salvage cystectomy.

Survival after salvage cystectomy

Do the results of salvage cystectomy justify its use? As mentioned earlier, the cancer control rates as reported through the 1970s were very poor following salvage cystectomy (Table 1). It was only with the three reports in 1980 and 1981 that it became apparent that survival could be relatively good.[7–9] These three reports, however, as well as those that followed, clearly demonstrate that the survival rate is much better for patients with superficial recurrences than for those with advanced disease. Crawford and Skinner reported a five-year survival rate of 65% for patients who had no residual tumour, or who had tumour confined to the bladder wall in the pathologic specimen, whereas for patients with tumour extending into the perivesical fat or invading adjacent organs, or who had lymph-node metastases, the five-year survival rate was only 15%.[7] Smith and Whitmore found a similar five-year survival rate of 68% for patients with stage pT0 disease or tumour confined to the bladder wall, whereas for patients with tumours extending through the bladder wall or metastatic to the lymph

nodes, the survival rate was only 14%.[8] Our own experience was very similar.[9] We saw a 73% five-year survival rate for patients with no tumour or with pathologic stage 0/A or B1 (pT0–pT2), whereas the three-year survival rate for patients with pathologic stage B2/C or D1 (pT3–4, N+) disease was only 32%. Recognizing that it is important for the clinician to be able to recommend therapy to the patient on the basis of clinical stage, we reviewed our experience to ascertain whether clinical staging could be accurate enough in these pre-treated patients to help clinical planning. Although we noted extreme difficulty in determining the precise clinical stage before cystectomy (only 26/62, or 42%, were the same pathologic stage as clinical stage), we were able to separate patients with locally advanced tumours (B2, C and D1) from patients with superficial tumours (CIS, O, A and B1). These new clinical groups enabled us to predict correctly the pathologic groups in 46 of the 62 tumours (74%) before cystectomy and to validate this assessment as a way of helping to predict survival. On the basis of clinical stage, we found a 64% five-year survival rate for patients with superficial tumours compared with a 25% survival rate for those with advanced tumours.[9] Similarly, Smith and Whitmore found rates of 52% and 21% respectively for these same two categories.[8]

Since then, this same observation has been confirmed by others.[10,12–15,17] Collectively, these studies demonstrate that survival rates can be quite good, especially for patients with low-stage recurrent disease. Thus, the increased morbidity and potential mortality of the procedure are acceptably low, and the procedure is justified in carefully selected patients.

The current relevance of salvage cystectomy: broadening the definition

Although radiation therapy alone is rarely used today in the United States as definitive therapy for bladder cancer, it is still important to discuss salvage cystectomy for many reasons.

The first and foremost reason is the patient with advanced urothelial tumour who, after undergoing definitive chemotherapy, has persistent or recurrent disease within the bladder, despite the absence of distant metastatic disease. Since the difficulty of performing surgery after multiple courses of chemotherapy is in many patients very similar to the difficulty after radiation therapy, salvage cystectomy is also appropriate for these patients and these individuals now constitute a large pool of eligible

patients. Looking at our report of salvage cystectomy in 1980, we performed an average of 6.2 salvage cystectomies a year between 1969 and 1979 for patients for whom definitive irradiation had failed.[9] An unpublished review of our experience from 1979 to 1987 showed that we were still performing 6.1 salvage cystectomies per year, predominantly for treatment failure after radiation therapy. Looking at the years 1993 to 1998, however, we performed only 1.4 salvage cystectomies per year after definitive radiation therapy, including cystectomies on four patients who underwent planned combination therapy with irradiation and chemotherapy on so-called 'bladder preservation' protocols. During this same timespan, however, we also performed 7.2 salvage cystectomies a year for patients who had undergone definitive chemotherapy and had persistent or recurrent disease. In fact, if we were to expand the use of the term 'salvage cystectomy' to also include patients who had received non-definitive doses of irradiation for urothelial cancers, or definitive doses of irradiation for other cancers, or who had received systemic chemotherapy with or without irradiation, we performed a total of 97 salvage cystectomies between 1 July 1993 and 30 June 1998, which amounts to 19.4 per year (Table 2).

While it is true that the term 'salvage cystectomy' has classically meant salvage therapy after prior definitive therapy, if we consider it from the standpoint of technical difficulty (which is why this procedure has a bad reputation), then the difficulty after multiple courses of chemotherapy, or chemotherapy plus radiation therapy, or surgery plus chemotherapy or irradiation is sufficient to warrant including these patients. The procedure

Table 2: Treatments that might precede salvage cystectomy

Cancer of the bladder and/or urethra
- Definitive irradiation
- Combined irradiation and chemotherapy
- Definitive or neo-adjuvant chemotherapy
- Miscellaneous (e.g. thermal or photodynamic therapy)
- Pelvic surgery plus irradiation (e.g. partial cystectomy)

Other cancers (e.g. prostate, uterine, cervix, rectal)
- Definitive irradiation
- Combined irradiation and chemotherapy
- Definitive or neo-adjuvant chemotherapy
- Pelvic surgery (e.g. radical retropubic prostatectomy, abdominal perineal resection)

is difficult largely because tissue planes have been obliterated, small vessels in the skin, the ureter and the bowel have been compromised, and there is no reserve to the blood supply. This pathophysiologic injury secondary to radiation therapy also occurs in many patients who have had chemotherapy, particularly multiple courses of chemotherapy, and expecially in those patients whose tumour was extravesical and who experienced a significant tumour response.

It is currently very popular to give chemotherapy to patients with locally advanced (and sometimes lesser stage) bladder cancer followed by planned cystectomy. Such neo-adjuvant therapy has been shown to reduce the tumour size and sometimes clinical stage of patients with bladder cancer, but there is no agreement about how many courses need to be given or whether surgical morbidity is increased in these patients. We recently completed a prospective randomized trial that offered either immediate cystectomy followed by five courses of post-operative, adjuvant chemotherapy or two courses of neo-adjuvant chemotherapy, followed by radical cystectomy and then the remaining three courses of adjuvant chemotherapy. Two-thirds of the patients had stage T3b or T4 disease. In an interim analysis of 95 of these patients, we noted that cystectomy after two courses of chemotherapy increased such surgical variables as operative time, estimated blood loss, and number of units transfused.[18] We also noted that more patients had complications (28 compared with 19) and that the total number of complications was higher (36 compared with 20), as were the number of catastrophic complications (14 compared with eight). However, none of these differences was statistically significant. Despite the absence of statistically significant differences, however, it was the subjective impression of all surgeons who participated that cystectomy was more technically demanding in the patients who had completed two courses of chemotherapy before surgery, which was clinically important. Because of the relatively small number of patients, it is not possible to answer whether there was truly no difference in morbidity between the two approaches or whether our sample size was too small to detect a statistically significant difference.

Contemporary 'true' salvage cystectomies at the University of Texas MD Anderson Cancer Center

We recently reviewed our cystectomy experience for the period between 1 July 1993 and 30 June 1998. During this time we performed 311 radical

Table 3: Prior therapy in 311 patients who underwent cystectomy between July 1993 and June 1998 at the University of Texas MD Anderson Cancer Center

214 patients had no prior therapy
97 patients had prior therapy
60 had chemotherapy
17 received ≥60 Gy irradiation (plus chemotherapy in 15)
19 received ≤50 Gy irradiation (plus chemotherapy in 8)
1 received photodynamic therapy

cystectomies: 214 of these were performed in patients who had had no prior therapy, and 97 were performed following prior therapy (Table 3).

Forty-two patients underwent 'true' salvage cystectomy, as originally understood, meaning cystectomy following previous definitive therapy for urothelial carcinoma (Table 4). This included 35 patients who underwent previous definitive chemotherapy for T3–4 or N1–2 disease, one of whom had a T3 recurrence after previously receiving 65 Gy of radiation for a bladder cancer. Seven patients received at least 60 Gy of radiation, four of whom had received simultaneous chemotherapy as part of 'bladder preservation' protocols, one who also received thermotherapy, and one who received irradiation alone. One patient was treated with multiple courses of photodynamic therapy and had a very small contracted bladder with tumour recurrence.

It should not be surprising that at least some of the contemporary operations considered to be salvage cystectomies by the original definition would be performed on patients who have been enrolled in protocols for

Table 4: Contemporary 'true' salvage cystectomy at MD Anderson Cancer Center after definitive therapy for urothelial cancers

34 patients had received chemotherapy for T3–4 or N1–2
7 patients had received ≥60 Gy irradiation
4 received chemotherapy (planned 'bladder sparing')
1 received chemotherapy for T3 recurrence after 65 Gy
1 received thermotherapy
1 received irradiation alone
1 patient had received photodynamic therapy

bladder preservation. Shipley *et al*. reported in 1998 on 123 patients entered in a phase III trial of bladder preservation and treated with combined radiation therapy and chemotherapy.[19] The patients received 39.6 Gy of radiation plus concurrent cisplatin; some of these patients had received two cycles of methotrexate, cisplatin and vinblastine before initiating radiation therapy plus cisplatin. Patients were reassessed for response after 39.6 Gy of radiation plus two courses of concurrent cisplatin, and 25 of the 123 patients were noted at this restaging to be incomplete responders; these 25 underwent radical cystectomy. Among the responding patients who received an additional 25.2 Gy and a third dose of concurrent cisplatin, 12 patients later underwent salvage cystectomies. In our current series, four patients who underwent contemporary salvage cystectomy had previous unsuccessful bladder preservation with radiation therapy and concurrent chemotherapy.

Of our 35 patients who received doses of chemotherapy considered to be definitive, five had stage T3 tumours, two of which were small-cell carcinoma; one patient, previously described, had already undergone definitive irradiation unsuccessfully. Twenty-three patients had stage T4 tumours, in one of whom treatment failed after a bladder preservation protocol. Four patients had N1 disease and three patients had N2 disease, but these patients had an apparent complete response in the lymph nodes and underwent cystectomy as consolidative therapy for their bladder cancer. Four patients had three courses of chemotherapy, 12 had four courses, 12 had five courses, and seven had six courses. Although a strict linear relationship was not observed, it does appear that the technical difficulty of radical cystectomy increases with the number of prior courses of chemotherapy.

It is possible, of course, that the patients who had received more courses of chemotherapy may have had more advanced disease, which would account for the increased difficulty. We have observed that patients with extravesical tumour who respond well to chemotherapy tend to have more of a desmoplastic reaction outside the bladder, which makes the surgery slightly more difficult because of obliteration of tissue planes. Nonetheless, the morbidity rate is quite acceptable. We had one operative death among the 42 patients undergoing true salvage cystectomy. A 67-year-old man with grade III transitional cell carcinoma in muscularis propria in June 1996 received 60 Gy of radiation with concurrent chemotherapy with cisplatin and 5-fluorouracil (5-FU) plus two more courses of chemotherapy

following completion of the radiation therapy. In January 1997, he had recurrent muscle-invasive transitional cell carcinoma and underwent radical cystoprostatectomy with an Indiana continent cutaneous diversion. The surgeon noted that the bladder and pelvic structures were 'very stuck' in dense fibrous tissue, but he was able to successfully complete the surgery without undue operative morbidity. On the third post-operative day, the patient had a pulmonary embolus, followed ultimately by renal failure and sepsis, and he died 25 days after surgery.

Otherwise, when we consider the other most feared complications of salvage cystectomy, namely rectal injury and ureteral-ileal leak, our results in these 42 patients who underwent surgery between 1993 and 1998 were not dissimilar from results for 114 salvage cystectomies performed between 1969 and 1987 at the MD Anderson Cancer Center. Although there were no operative deaths among those 114 patients, three patients had rectal injuries that required colostomy and two patients had ureteral-ileal leaks. In the present series, there were two rectal injuries, one of which was treated with primary closure alone and one with primary closure plus colostomy, and no ureteral-ileal leaks.

Although it was relatively easy to assess survival for patients who received salvage cystectomy for tumour recurrence after previous definitive radiation therapy, it is difficult to make such an assessment for patients who have been treated with definitive chemotherapy because many, if not most patients receiving definitive chemotherapy do so for advanced disease and have known or suspected metastatic disease. Thus, this is a very heterogeneous group, and survival ultimately depends more on the response to chemotherapy than on the surgery. Two patients in our series help illustrate this. One patient was a 53-year-old man diagnosed with grade III transitional cell carcinoma of the bladder in February 1993. His clinical stage was T4 because the tumour mass was fixed to the pelvic sidewall. He received three courses of 5-FU, α-interferon and cisplatin, which caused his tumour mass to shrink approximately 50%. He then received two courses of methotrexate, vinblastine, doxorubicin and cisplatin, which caused his tumour mass to shrink even further. Finally, following three courses of paclitaxel, methotrexate and cisplatin, his tumour mass, which still measured 4 x 5 x 5cm, became mobile. It now extended to the pelvic sidewall, but was no longer fixed to it. He underwent a radical cystectomy and ileal conduit urinary diversion in February 1994 for what turned out

to be pT3b N0 M0 disease. At last follow-up in June 1999, 63 months after his cystectomy, he was clinically free of disease.

The second patient was a 64-year-old man who was found to have an inflammatory-looking lesion in the bladder during cystoscopy for evaluation of a ureteral calculus. Biopsy revealed anaplastic signet-ring adenocarcinoma. Bimanual examination found a fixed tumour mass and a rectal 'shelf' that was positive on biopsy. The patient received two courses of paclitaxel, methotrexate and cisplatin with no response. He was then given two courses of gemcitabine, ifosfamide and cisplatin, and the tumour mass, which had previously been fixed to the pelvic wall, became mobile. He underwent a third course of gemcitabine, ifosfamide and cisplatin, followed by radical cystectomy in October 1997. There was complete obliteration of all tissue planes by a dense desmoplastic tumour response. Multiple biopsies in the pelvis and on the pelvic sidewall were negative for cancer. A cystectomy was finally performed and revealed poorly differentiated cancer still present in the bladder; one deep surgical margin was positive. The patient received several additional courses of gemcitabine, ifosfamide and cisplatin post-operatively, but experienced recurrent disease in the pelvis eight months later and died 14 months after his radical cystectomy.

Thus it appears that the response to chemotherapy determines the ultimate result. Whether more extensive surgery might improve survival rates for patients who fail in pelvic or retroperitoneal lymph nodes is the subject of a protocol currently underway at MD Anderson Cancer Center. This protocol seeks to determine whether surgical consolidation after response to chemotherapy in patients with positive lymph nodes without other evidence of metastatic disease will improve the survival rate. All urologic oncologists have seen patients who have disease relapse in the pelvic and retroperitoneal lymph nodes after maximum response to chemotherapy. This protocol tests whether aggressive dissection of pelvic or retroperitoneal lymph nodes, or both, may resect occult cancer in some patients and decrease regional relapse. Under this protocol, patients with bladder cancer who have positive retroperitoneal lymph nodes and a clinical complete response to chemotherapy are offered radical cystectomy plus complete pelvic and retroperitoneal lymph-node dissection to the level of the renal vessels. The problem we seek to solve is illustrated by the case of a 68-year-old man who underwent cystectomy in

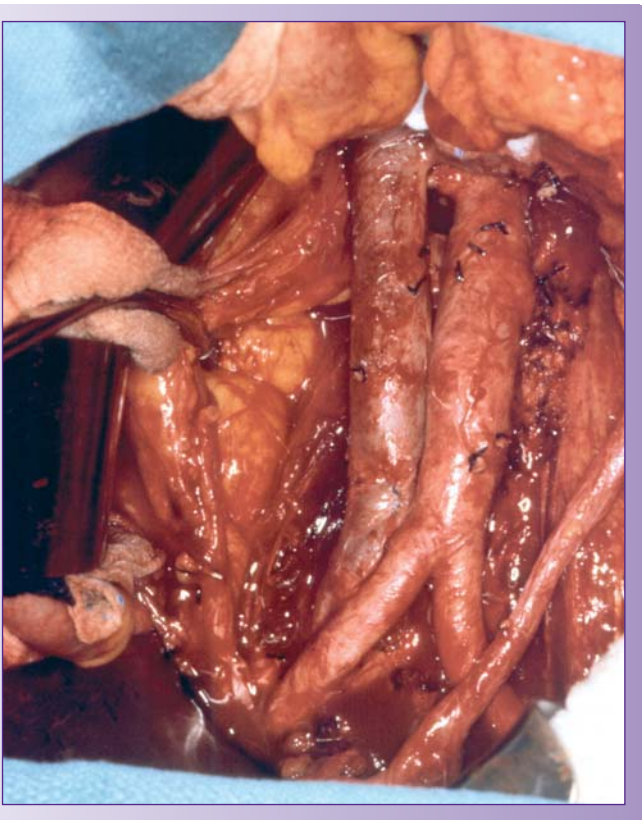

Figure 1: Intra-operative photograph after complete retroperitoneal lymph-node dissection in a patient who had undergone prior radical cystectomy and ileal conduit and multiple courses of chemotherapy.

May 1995 for pT3 N1 bladder cancer. He received four courses of cisplatin, methotrexate and vinblastine as adjuvant therapy, but had disease relapse in the retroperitoneum in December 1995. He then received three courses of paclitaxel, methotrexate and cisplatin alternating with 5-FU, α-interferon, cisplatin and methotrexate with a clinical complete response, although he again had relapse in October 1996. He then received two courses of gemcitabine and cisplatin, again achieving a clinical complete response, and underwent retroperitoneal lymph-node dissection in January 1997, as shown in Figure 1. Twelve of 18 lymph nodes were positive, and the patient received post-operative chemotherapy. In November 1997 he had disease relapse outside of the surgical field, and despite multiple chemotherapy regimens, he experienced rapid progression, including liver metastases, in late 1998 and died. It should be stressed that such an aggressive surgical

approach, even in a salvage setting, is best performed only when there is a protocol to evaluate such an approach.

Technical considerations for salvage cystectomy

Experience with 158 patients who had salvage cystectomy performed by urologists at MD Anderson Cancer Center between 1969 and 1987 (114 patients) and between 1993 and 1998 (42 patients), as well as the additional 55 patients shown in Table 5 who had cystectomy between 1993 and 1998, forms the basis of our conclusions on how to avoid some of the surgical complications associated with salvage cystectomy. It is apparent to us that many of the complications are the result of obliterated tissue planes following prior surgery, prior irradiation, prior chemotherapy, or combinations thereof. Some of the dense desmoplastic reaction may be due to obliteration of tumour, some due to healing from prior injury, and some due to ischaemic changes because of injury to small blood vessels.

We believe that the risk of these complications can be reduced by several modifications in technique. First, minimize blunt dissection. Although many surgeons, myself included, are accustomed to opening up tissue planes by finger dissection, with or without using a sponge-stick for assistance, during salvage cystectomy such manoevres are more likely to tear structures randomly, frequently where you don't want them to tear. This may include blood vessels or the rectal wall. Second, be alert to anatomic distortions. The obturator nerve, particularly if the space of Retzius is dissected bluntly, may not be found in its accustomed position on the pelvic sidewall because it may adhere to the bladder wall after

Table 5: Prior therapy in 55 patients who underwent contemporary salvage-equivalent cystectomy after non-definitive therapy or definitive therapy for non-urothelial cancers

Urothelial cancers
23 patients had received neo-adjuvant chemotherapy (two courses)
16 patients had received ≤50 Gy irradiation (plus chemotherapy in five)
Other cancers
10 patients had received ≥65Gy (plus chemotherapy in three)
6 patients had received chemotherapy (plus ≤50 Gy in three)

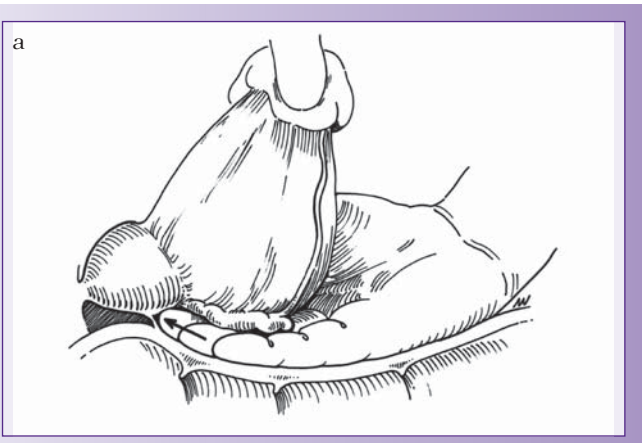

Figure 2: Dissection of the bladder and prostate off the anterior rectal wall.

Figure 2a: Blunt dissection with the surgeon's hand may establish the correct plane in patients without prior treatment.

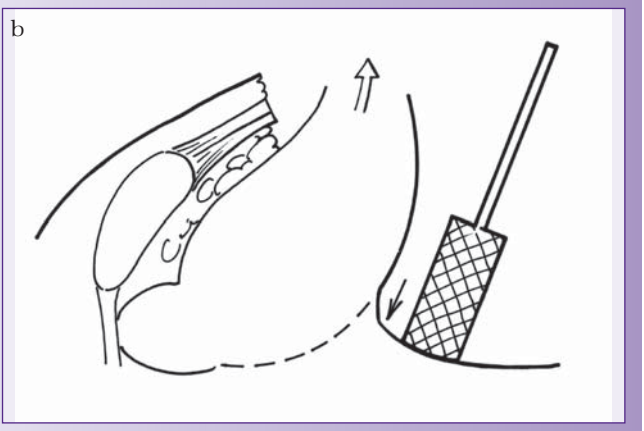

Figure 2b: In patients undergoing salvage cystectomy, the plane between the posterior bladder wall and the anterior rectal wall is frequently obliterated by a dense desmoplastic reaction. Depress the rectal wall with a sponge-stick and cut immediately adjacent to the bladder wall (small arrow) instead of using blunt dissection.

prior irradiation, chemotherapy, or surgery, exposing it to risks during the dissection. Third, dissect tissue planes sharply. This is the corollary to minimizing blunt dissection, of course, but it is offered to emphasize the importance of visualizing where you want to dissect and then doing so sharply with scissors or knife. Use counter-traction to help visualize the correct planes. These last two points are illustrated by Figures 2a and 2b.

Although the dissection between the rectum and the posterior bladder wall can frequently be performed bluntly in the patient who has had no prior therapy (as illustrated in Figure 2a), it is much more likely that you

will find the posterior bladder wall densely adherent to the rectum, as illustrated in Figure 2b. To minimize the risk of injury to the rectal wall, use a sponge-stick to depress the rectal wall at the same time the bladder is lifted up, and then use scissors to cut immediately adjacent to the posterior bladder wall; then push *gently*, if possible, to reveal the next point that should be cut. The proper technique requires the surgeon to visualize to the fullest extent possible the juncture of posterior bladder wall and rectum, cut and *gently* push to see if the dissection proceeds easily, and then repeat the cycle as many times as is necessary. As you approach the prostate itself, it is often easier to complete the dissection following incision of the endopelvic fascia. This may enable you to get down behind the prostate and work in a retrograde manner. It may be optimal to alternate these two approaches: cut and push gently in an antegrade direction, and then try working in a retrograde direction to complete the dissection of the posterior bladder wall and prostate off the rectum.

The distal ureters are frequently very fibrotic because of changes secondary to radiation therapy or chemotherapy. We find it helpful to ligate the ureters as soon as they are cut and to allow them to dilate. Observe the dilation of the ureter. You may find, as illustrated in Figure 3, that a portion of the distal ureter does not dilate. This portion is fibrotic secondary to vascular compromise and should not be used for your urinary diversion. Cut and use only the dilated portion of the ureter to help ensure sufficient blood supply and to minimize the chance that you will get a late stenosis of the anastomosis of the ureter to the bowel.

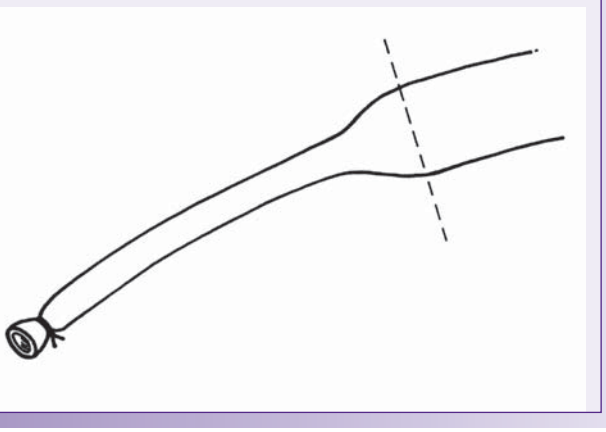

Figure 3: The distal ureter may be fibrotic after irradiation. Cut (dotted line) and use only the dilated portion of the ureter.

When selecting bowel for the urinary diversion, avoid unhealthy looking bowel. If portions of the small bowel look very leathery, with multiple adhesions and very friable serosa, consider more proximal segments, since the last 45–60cm of the ileum is usually the worst. To minimize further injury to the bowel, avoid handling tissues unnecessarily. Furthermore, when handling the ureter, do not take even the vascular forceps and grasp the full thickness of the ureteral wall. Try to pick up only adventitia or periureteral tissue so as not to injure already compromised tiny vessels even more. When selecting a segment of bowel, be sure to protect compulsively against injuring the blood supply to the selected segment of bowel. Although it is mostly the small vessels that have been injured by pre-operative therapy, this places increased importance on maintaining a good blood supply with the larger vessels. Avoid injury to any of the vessels at all costs.

Given the high morbidity rate for salvage cystectomies, even with ileal conduits, it should not be surprising that alternative diversions were not recommended until relatively recently. Bochner *et al.*, from the University of Southern California, reported in 1998 that 18 patients had construction of an orthotopic neo-bladder following salvage cystectomy for disease recurrence after receiving at least 60 Gy of radiation for either bladder or prostate cancer.[20] They noted good continence during the day and night in 67% and 56% respectively of irradiated patients. Similarly, Gschwend *et al.*, from the University of Ulm, performed orthotopic urinary diversions in 11 patients after high-dose pelvic irradiation, with 'satisfactory results' in seven patients.[21] They did see a neovesical-peritoneal fistula in one woman 10 months after surgery, which was repaired during laparotomy, and a neovesical-vaginal fistula that required a supravesical urinary diversion in a second woman. They concluded that high-dose pelvic irradiation should not be a primary contra-indication for orthotopic urinary diversion using segments of small intestine. However, they felt that the indication for orthotopic bladder replacement should be considered critically in patients who undergo combined external and interstitial radiotherapy.

In our experience, we performed either orthotopic neo-bladder diversion or continent cutaneous diversion on 21 of the 97 patients who had had various types of therapy before cystectomy.[7,14] Considering only the 42 patients who underwent 'true' salvage cystectomy, 35 had ileal conduits constructed, two had continent cutaneous diversions, and five had Studer ileal neo-bladders constructed. Although one patient undergoing continent

cutaneous diversion died post-operatively, this death was attributed to a pulmonary embolus and not urinary diversion. No specific complications were attributable to the urinary diversion, and we believe our experience supports that of others who have concluded that alternatives to ileal conduit can be performed safely in carefully selected patients, despite prior irradiation or chemotherapy, or both.

Conclusions

We conclude that salvage cystectomy can be performed safely after radiation, chemotherapy, or both. The success of salvage cystectomy depends highly on meticulous surgical technique and strict adherence to standard surgical principles. The results in selected patients justify its use, particularly after radiation therapy alone. The results in patients who have undergone definitive chemotherapy appear to depend more on the response to systemic therapy than on the surgical intervention, although the role of surgery has not yet been fully defined. We believe that diversions other than ileal conduit are possible in selected patients despite heavy pre-treatment with radiation, chemotherapy, or both.

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