

Bladder cancer

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Bladder cancer is a heterogeneous disease, with 70% of patients presenting with superficial tumours, which tend to recur but are generally not life threatening, and 30% presenting as muscle-invasive disease associated with a high risk of death from distant metastases. The main presenting symptom of all bladder cancers is painless haematuria, and the diagnosis is established by urinary cytology and transurethral tumour resection. Intravesical treatment is used for carcinoma in situ and other high grade non-muscle-invasive tumours. The standard of care for muscle-invasive disease is radical cystoprostatectomy, and several types of urinary diversions are offered to patients, with quality of life as an important consideration. Bladder preservation with transurethral tumour resection, radiation, and chemotherapy can in some cases be equally curative. Several chemotherapeutic agents have proven to be useful as neoadjuvant or adjuvant treatment and in patients with metastatic disease. We discuss bladder preserving approaches, combination chemotherapy including new agents, targeted therapies, and advances in molecular biology.

Epidemiology

Bladder cancer is the second most common genitourinary malignant disease in the USA, with an expected 69000 newly diagnosed cases in 2008, and 14000 deaths. The incidence of bladder cancer rises with age, peaking between age 50 years and 70 years, and is three times more common in men than in women.¹ Risk factors for the development of bladder cancer can be classified into three subsets; genetic and molecular abnormalities, chemical or environmental exposures, and chronic irritation. Genetic and molecular factors include oncogenes, such as *TP63*,^{2,3} the epidermal growth factor receptors (EGFR),^{4,5} and Ras p21 proteins.⁶ Tumour suppressor genes, including *TP53* and *RB1*,^{7,8} and those newly implicated such as the fragile histidine triad gene,^{9,10} probably play a part in the genetic pathogenesis of bladder cancer. Furthermore, molecular factors are cell cycle regulatory proteins, such as CABLES, Ki67, and cyclin D1.^{11–13} Chemical and environmental exposures include aromatic amines, aniline dyes, nitrites and nitrates, acrolein, coal, and arsenic,^{14,15} but the most important environmental factor is cigarette smoking. Other causal factors include chronic irritation, indwelling catheters, *Schistosoma haematobium* infestation, and pelvic irradiation.¹⁶

Pathophysiology and diagnosis

More than 90% of bladder cancers are transitional cell carcinomas, 5% are squamous cell carcinomas, and less than 2% are adenocarcinomas. The histopathological grading of transitional cell carcinoma of the bladder has historically been grade 1–3 as per the 1973 WHO classification system,¹⁷ but in 1998 a WHO and International Society of Urological Pathology consensus classified urothelial tumours into four categories; papilloma, papillary urothelial neoplasm of low malignant potential, low grade carcinoma, and high grade carcinoma.¹⁸ Histological staging is by the tumour-node-metastasis TNM staging system, in which the tumour (T) stage of the primary tumour is based on the extent of penetration or invasion into the bladder wall.¹⁹

Of all newly diagnosed cases of transitional cell carcinomas, about 70% present as superficial tumours

(stages Ta, T1, or tumours in situ [Tis]), but as many as 50–70% of those superficial tumours will recur and roughly 10–20% will progress to muscularis propria invasive disease (T2–4).²⁰ To predict which patients will progress from superficial to muscularis propria invasive disease remains a challenge. In patients with low grade Ta disease, the 15-year progression-free survival is 95% with no cancer-specific mortality. Patients with high grade Ta tumours had a progression-free survival of 61% and a disease-specific survival of 74%, whereas patients with T1 disease had a progression-free survival of 44% and a disease-specific survival of 62%, lending support to the view that invasion of the lamina propria is a prognostic indicator for risk of disease progression and reduced survival.

The most common presenting symptom of bladder cancer is gross painless haematuria. Additionally, unexplained urinary frequency, urgency, or irritative voiding symptoms should alert the clinician to the possibility of bladder cancer—usually carcinoma in situ. When a diagnosis of transitional cell carcinoma is

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Search strategy and selection criteria

We searched Medline (1996–2008) and PubMed (1993–98), ClinicalTrials.gov, UpToDate database, and the National Cancer Institute Surveillance, Epidemiology and End Results Cancer Statistics Review 1975–2005. We used the search terms “bladder cancer”, “chemotherapy, bladder cancer”, “radiation therapy, bladder cancer”, “bladder presentation, cancer”, “invasive bladder cancer”, “neoadjuvant chemotherapy, bladder cancer”, “adjuvant chemotherapy, bladder cancer”, “chemotherapy, advanced bladder cancer”, and “superficial bladder cancer”. We mostly selected publications from the past 6 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of reports identified by this search strategy and selected those we judged relevant. Reviews and book chapters are cited to provide readers with more detail and references than this Seminar provides. Where appropriate, we excluded non-contemporary series and series with few patients.

suspected, the initial assessment consists of voided urine cytology, cystoscopy, and radiological investigation of the upper tracts. Although the present non-invasive test of choice for diagnosis is voided urine cytology, it has low sensitivity, especially for low grade tumours.²¹ Several new tests have been developed although their value is yet to be established (table 1).

After a urothelial lesion is detected, the diagnosis and clinical stage is established by transurethral resection. This resection should include muscularis propria, especially if the lamina propria is affected or the tumour is high grade. When the transurethral resection shows lamina propria invasion but does not include sufficient muscularis propria in the specimen a repeat resection should be done to rule out muscularis propria invasion. Repeat resection for T1 tumours will identify muscle-invasive disease in 9–53% of tumours that were previously understaged at the initial resection.^{29–32} Furthermore, residual tumour of any stage has been identified in up to 58% of restaging or repeat transurethral resection.^{33,34} In view of these findings, some investigators recommend repeat resection in all high grade T1 tumours.

During transurethral resection, a bimanual examination should be undertaken to assess the degree of mobility of the bladder and pelvic organs. In the setting of muscularis propria invasive disease, a metastatic assessment, including an abdominal and pelvic CT, chest CT, liver function tests, and serum creatinine and electrolytes, should be done. A novel method used to stage bladder cancer is MR lymphangiography, which uses ultrasmall superparamagnetic iron oxide nanoparticles to identify lymph node metastases as small as 2 mm.³⁵ Results of an analysis³⁶ of this technique in patients with transitional cell carcinoma showed a sensitivity of 96% and a specificity of 95% for detection of such metastases. This level of accuracy is a large improvement compared with that achieved with conventional MRI or CT, which rely solely on size criteria for lymph node staging, but this innovative technique needs to be investigated in a large number of patients for validation.

Management

Superficial bladder cancer

The high rate of recurrence is the feature of bladder cancer that makes follow-up a crucial component in effective management. After transurethral resection of the tumour, patients should have cystoscopy and voided urine cytology every 3 months for 2 years, then 6 monthly for 2 years, and then once yearly indefinitely. Upper tract imaging should be done every 12–24 months to establish whether a transitional cell carcinoma is present in the renal collecting system or ureters, because lifetime risk for the development of this upper tract tumour after a diagnosis of bladder cancer is about 5%.³⁷

The initial 3-month follow-up cystoscopy is crucial for the identification of early recurrent disease, which can potentially be the result of incomplete resection or tumour cell reimplantation.³⁸ The frequency of this follow-up schedule can be adjusted on the basis of risk assessment for future recurrence and progression. Several researchers^{39–41} have identified pathological risk factors for recurrence and progression of superficial transitional cell carcinomas, including tumour grade, stage, multifocality, tumour size, and presence of associated Tis. The use of risk assessment tables and statistical nomograms provides clinicians with an improved ability to tailor follow-up for individual patient tumours.^{42,43} A strategy to reduce the rate of recurrence and, potentially, progression of superficial transitional cell carcinomas is the use of intravesical chemotherapy.

Agents used for intravesical therapy are the immunomodulators BCG and interferon alfa, and chemotherapeutic agents such as mitomycin, doxorubicin, thiotepa, and gemcitabine. General complications of intravesical treatment are irritative voiding symptoms such as frequency, urgency, and dysuria, and the long-term potential for bladder fibrosis and contracture. Specific complications related to BCG include fever, arthritis, granulomatous prostatitis, BCG sepsis, disseminated tuberculosis, and death. Additionally, intravesical chemotherapeutic drugs might produce other side-effects, such as myelosuppression with thiotepa, skin desquamation and rash with mitomycin, and gastrointestinal upset and rash with doxorubicin.

Immediately after transurethral resection, one dose of intravesical chemotherapeutic agent is effective for the reduction of disease recurrence within the first 1–5 years after resection.^{44–47} BCG is not appropriate for this immediate postoperative administration. The most frequently used drug is mitomycin. Although most studies of this practice have been small, Sylvester and co-workers⁴⁸ confirmed the benefit of immediate postoperative intravesical therapy in a meta-analysis of 1476 patients in seven randomised controlled trials with a median follow-up of 3.4 years. However, despite the benefit in prevention of recurrence, a similar benefit for the prevention of progression was not seen. In view of these findings, both the American Urologic Association

| | Mechanism | Sensitivity | Specificity |
|-------------------------------------|--|---|-------------|
| Cytology ^{22,23} | Tumour cells sloughed into urine | 7–17% PNLMP grade 1; 53–90% high grade | 90–98% |
| BTA Stat and BTA TRAK ⁴⁴ | Detects urothelial basement membrane | 50–80% | 50–75% |
| NMP-22 ²⁵ | Nuclear protein released during apoptosis | 50% in non-invasive disease; 90% in invasive disease | 85.7% |
| ImmunoCyt ^{26,27} | Immunofluorescence—three monoclonal antibodies | 50–85% | 62–73% |
| UroVysion ²⁸ | FISH with probes to Chr 3, 7, 17, 9p21 | 70–86% | 66–93% |

BTA=bladder tumour antigen. Stat=signal transducer and activator of transcription (Polymedco, Redmond, WA, USA). TRAK=total reference air kerma. NMP-22=nuclear matrix protein-22 (Matritech, Newton, MA, USA). ImmunoCyt (Diagnocure, Quebec City, Quebec, Canada), UroVysion (Abbott Laboratories, Inc, Des Plaines, IL, USA). PNLMP=papillary urothelial neoplasm of low malignant potential. FISH=fluorescence in-situ hybridisation. Chr=chromosome.

Table 1: Non-invasive diagnostic tests for transitional cell carcinoma

and the European Association of Urology have included in their practice guidelines the recommendation for one immediate postoperative intravesical instillation of chemotherapy for all superficial bladder tumours.

Patients with high risk disease (multifocal Tis, high grade Ta or T1 tumours with associated Tis, and tumours that rapidly recur after transurethral tumour resection) should be regarded as candidates for further adjuvant courses of intravesical drug therapy. Such regimens generally consist of an induction course of treatment once every week for 6 weeks, and then, usually, intermittent maintenance cycles of one installation every week for 3 weeks. This 3-week course is repeated every 4–6 months for up to 2 years. Several investigators^{39–41} compared the effectiveness of these intravesical agents for the prevention of recurrence and progression of transitional cell carcinoma. Their results show that BCG is more effective in the prevention of recurrence than are any of the chemotherapeutic agents,^{49,50} but whether this agent is effective in prevention of disease progression is controversial.⁵¹ Its overall schedule might be important. Investigators of a meta-analysis⁵² of randomised clinical trials identified a reduced risk of disease progression to muscularis propria invasive disease in patients who received maintenance BCG of one course per week for 3 weeks, every 4–6 months. Whether these findings represent a true reduction rather than a further delay of eventual long-term progression is not clear.

Patients who develop rapid recurrence of high risk disease after BCG therapy have a substantially increased risk of progression to muscularis propria invasive disease.⁵³ Those who undergo cystectomy for progression of disease do not seem to have improved survival compared with those who present initially with muscularis propria invasive disease. This absence of survival benefit in high risk patients has encouraged some clinicians to undertake early radical cystectomy before development of invasive disease. 10-year cancer-specific survival outcomes of 80% in patients with superficial disease at the time of cystectomy—as opposed to 50% in those with muscularis propria invasion—might justify this aggressive approach in some high risk patients.⁵⁴ We emphasise, however, that this option will subject many patients whose disease would not have progressed to stage T2 to radical cystectomy.

Muscularis propria invasive disease

The standard of care for bladder cancer invading the muscularis propria is radical cystoprostatectomy for men and anterior exenteration—including the bladder, urethra, uterus, and ventral vaginal wall—for women. In men, a urethrectomy should be done when invasion of the prostatic stroma or concomitant Tis in the urethra is evident.⁵⁵ In some women, in whom an orthotopic continent urinary diversion is planned, and in whom the disease does not involve the uterus, vagina, or urethra, the exenteration can be modified to spare the uterus,

vagina, and urethra. Researchers have reported⁵⁶ an improvement in continence with orthotopic diversion in men after prostate-sparing cystectomy, but the present standard of care calls for prostate resection, and prostate-sparing surgery is still thought of as an investigational approach with the antitumour effect yet to be proven. Partial cystectomy is not standard practice and should be considered only for patients with small unifocal tumours located a sufficient distance from the trigone, such that a 2 cm margin can be obtained.

Pelvic lymphadenectomy should be standard practice in all cases of radical cystectomy. The limits of dissection of the standard pelvic lymphadenectomy are the genitofemoral nerve laterally, the bladder medially, the bifurcation of the common ileac artery cephalad, and the endopelvic fascia caudad. Many researchers now recommend an extended lymphadenectomy with the cephalad limits of dissection extending up to the aortic bifurcation and including caudally the presacral nodes. Not only does an extended lymph node dissection provide additional data for tumour staging, but also survival might be improved by this technique.^{57–60}

After radical cystectomy, urinary diversion is done in either a non-continent or continent way, with a segment of bowel. The simplest form is the non-continent ileal conduit. A continent urinary diversion can be either an orthotopic neobladder or an abdominal pouch. In both diversions a segment of bowel is made into a detubularised spherical form, with continence in the abdominal pouch relying on a catheterisable continent stoma and on the patient's striated urethral sphincter in the orthotopic neobladder. Potential metabolic and surgical complications of intestinal segments for urinary diversion are hyperchloraemic metabolic acidosis and other electrolyte abnormalities, renal calculi, bacteriuria, sepsis, malabsorption of vitamin B12, fat-soluble vitamins and bile salts, short bowel syndrome, urine leak, ureteral obstruction, renal deterioration, and bowel obstruction. One or more metabolic complications are more likely to happen in continent diversions than in non-continent urinary diversions.⁶¹

The ileal conduit is the urinary diversion done most frequently and is the standard to which other forms of urinary diversion should be compared. The continent diversion is technically complex and needs a longer operative time than does the non-continent type, but it can improve quality of life in some patients.⁶² Although no randomised clinical trials comparing the orthotopic neobladder with the ileal conduit have been done, results of several retrospective analyses^{63–65} have not shown substantial differences in overall surgical complication rates. The ileal conduit is often undertaken in elderly patients (eg, over age 65 years) with severe comorbidities and heightened operative risk, whereas the continent diversion is often used in young, healthy patients. In a multivariate retrospective analysis⁶⁶ comparing the ileal conduit with continent urinary diversion, investigators

| | Treatment | Number of patients | 5 year survival |
|-----------------------|--------------------------------|--------------------|-----------------|
| Italian ⁷⁴ | Cystectomy± NCT | 206 | 54% |
| RTOG ^{*75} | TURBT, XRT Cisplatin±NCT | 123 | 49% |
| SWOG ^{*76} | TURBT, XRT plus Cisplatin+5-FU | 25 | 45% |
| SWOG ⁷⁷ | Cystectomy± NCT | 317 | 47% |

All studies were in operable patients with muscle-invasive bladder cancer of similar clinical stage. NCT=neoadjuvant chemotherapy. TURBT=transurethral resection of the bladder tumour. XRT=external beam irradiation. 5-FU=fluorouracil. SWOG=Southwest Oncology Group. RTOG=Radiation Therapy Oncology Group. *All patients were cystectomy candidates.

Table 2: Survival in cystectomy series versus bladder-sparing therapy

noted that a high American Society of Anesthesiologists score was the only clinically significant predictor of early major complications.

Selective bladder-preserving approaches

In North America, bladder-sparing protocols have been done mainly by the Radiation Therapy Oncology Group (RTOG).⁶⁷ From 1995, RTOG trials incorporated concurrent cisplatin with twice daily radiation for induction and consolidation for complete responders. Beginning in 1999, paclitaxel as a radiosensitiser was tested. Adjuvant chemotherapy with cisplatin (70 mg/m² on day 1) and gemcitabine (1000 mg/m²) on days 1, 8, and 15 was tested. The results of RTOG protocol 99-06⁶⁸ were reported with more than 4 years of median follow-up in 80 patients, showing an 81% complete response rate and actuarial 5-year overall and disease-specific survival rates of 56% and 71%, respectively.

RTOG has completed accrual to a randomised phase II study designed to identify the optimum concurrent chemotherapy regimen in conjunction with radiation treatment. Patients were randomised to radiation twice daily with either concurrent paclitaxel and cisplatin or concurrent infusional fluorouracil and cisplatin during the induction and consolidation phases. Additionally, the adjuvant chemotherapy triplet regimen of gemcitabine (1000 mg/m² on days 1 and 8), paclitaxel (50 mg/m² on days 1 and 8), and cisplatin (75 mg/m² on days 1 and 8) is being investigated. This triplet regimen was based on the protocol piloted by Bellmunt and co-workers⁶⁹ and tested in a phase III trial led by the European Organisation for Research and Treatment of Cancer (EORTC) and the Southwest Oncology Group.⁷⁰

Cisplatin cannot be used in patients with impaired kidney function, and hence a British group⁷¹ undertook a phase I and II study of the chemoradiation combination fluorouracil and mitomycin with pelvic radiotherapy. They reported a complete response rate of 70% in patients receiving mitomycin 12 mg/m² day 1 and fluorouracil 500 mg/m² given days 1–5 on weeks 1 and 4 in combination with external beam radiation to 55 Gy and 20 fractions.⁷¹ James and Hussaid⁷² are testing in a phase III trial this chemoradiation regimen compared

with radiation therapy alone. Their trial incorporates quality of life, bladder capacity measurements, and cancer control endpoints.⁷²

To make a comparison between the results of selective bladder-preserving approaches and radical cystectomy series is difficult for several reasons. Perhaps the most important reason is that such comparisons are confounded by discordance between the clinical and pathological staging of both the primary tumour and pelvic lymph nodes in these series. Clinical staging used in bladder-preserving approaches is more likely to underestimate the extent of disease penetration into the muscularis propria or beyond (including spread to pelvic lymph nodes) than is pathological staging, which is possible with cystectomy.⁷³ Thus, any positive outcome bias that might exist is in favour of the pathologically reported radical cystectomy series.

The optimum way to compare outcomes of selective bladder-preserving approaches with cystectomy series is to compare the outcomes of prospective protocols in which eligibility is based on clinical staging, all patients are cystectomy candidates, and all entered patients are reported for outcome whether or not they completed treatment (table 2).^{74–77} Thus, the survival outcomes of contemporary cystectomy and bladder-sparing therapy protocols in patients with muscle-invasive cancer of similar clinical stage—all of whom were potential candidates for cystectomy—were similar, with overall survival rates ranging between 45% and 54% (table 2). No strong evidence exists to show that modern selective bladder-preserving and cystectomy approaches in muscularis-propria-invasive bladder cancer are comparable because no randomised phase III trial has yet been done. However, selective bladder-preserving treatment with cystectomy for failure compared with cystectomy is being investigated in a randomised study undertaken by the Medical Research Council in the UK.

Candidates for bladder preservation with the highest success rate are patients with solitary T2 or early T3 tumours less than 6 cm, no tumour-associated hydro-nephrosis, tumours allowing a visibly complete trans-urethral tumour resection, invasive tumours not associated with extensive carcinoma in situ, and adequate renal function for administration of cisplatin to be given concurrently with radiation. Our recommendation for bladder-preserving treatment off protocol includes daily fractions of radiation to the bladder and pelvic lymph nodes of 40 Gy, with a boost to the bladder tumour to a total of 64 Gy. The concurrent chemotherapy we recommend is one of two potent radiosensitisers, cisplatin or paclitaxel—either cisplatin given days 1–3 in weeks 1, 4, and 7 at 15 mg/m², or for patients judged unsuitable for cisplatin, paclitaxel 50 mg/m² day 1 of weeks 1, 4, and 7.⁷⁸ On the basis of reported studies, neoadjuvant chemotherapy cannot be regarded as standard care.

An important concern with bladder-sparing therapy is the risk of subsequent superficial tumour relapses within

the intact bladder, which could in some cases progress to life-threatening malignant disease. In the Massachusetts General Hospital series,⁷⁹ 26% of 121 patients with complete responses developed a recurrent superficial tumour. Overall survival in people with superficial recurrence was the same as for those without, although cystectomy was eventually needed in ten patients. Superficial relapse is usually adequately managed by transurethral resection and intravesical BCG therapy. The optimum regimen of combined radiation and chemotherapy continues to be investigated, as does the addition of rational molecular targeted therapy. Successful bladder preservation requires a skilled multidisciplinary team of radiation oncologists, medical oncologists, and urological surgeons, and motivated patients who are committed to lifelong cystoscopic surveillance and cystectomy for residual or recurrent invasive tumour.

Neoadjuvant chemotherapy

Interest in neoadjuvant chemotherapy arose because of the failure rates of 30–45% after surgery alone in muscle-invasive bladder cancer⁸⁰ and the reported chemoresponsiveness of metastatic bladder cancer to several drugs, both single agent and, with better results, in combination. The rationale has been that drugs proven to be effective in advanced metastatic disease might have a heightened effect when given in the neoadjuvant setting, in which with careful staging, treatment can be restricted to patients thought likely to have micrometastases. Unfortunately, despite more than 20 years of clinical investigations of neoadjuvant chemotherapy, uncertainty still exists as to whether neoadjuvant treatment affects survival favourably.

A large randomised trial⁸¹ assessed the effect of neoadjuvant chemotherapy on survival in patients treated either by radical cystectomy or bladder irradiation as part of a bladder-sparing approach. This study is weakened by the fact that 11 years were taken to accrue 317 patients from 126 institutions and during that time diagnostic standards, patient care—including supportive care during chemotherapy—and surgery had changed. Furthermore, some difficulties associated with large cooperative studies are evident. For example, central pathological review was not possible in 46 cases because slides were not available and muscle invasion could not be confirmed by central review in 17 patients. Another concern is the wide 95% CI, 25–60 months in the median survival of 46 months in the cystectomy group and 55–104 months in the 77-month survival of the chemotherapy plus cystectomy group.

Results of this clinical trial are suggestive that neoadjuvant chemotherapy of methotrexate, vinblastine, doxorubicin, and cisplatin is better than is cystectomy only. However, although this study alone does not make the case convincingly for this neoadjuvant combination to be declared the standard treatment before cystectomy in muscularis propria invasive bladder cancer, for medical

oncologists and urologists to discuss with patients the pros and cons of this approach would be reasonable on the basis of these data.

In 1989, the Medical Research Council and the EORTC⁸² began a prospective randomised trial of neoadjuvant cisplatin, methotrexate, and vinblastine in patients undergoing cystectomy or full-dose external beam radiotherapy for muscularis propria bladder cancer. This study was updated in 2002⁸³ with a median follow-up of 7.4 years. This trial had a statistically significant 5-year survival improvement for patients who received neoadjuvant chemotherapy compared with those who did not; $p=0.048$, hazard ratio (HR)=0.85 (95% CI 0.72–1.00).⁸⁴

Black and colleagues⁸⁵ make the case for risk-adapted neoadjuvant chemotherapy, ie, offering neoadjuvant chemotherapy to patients at highest risk and most likely to respond to treatment. In this context, risk is established by the anatomical extent of disease, tumour biology and grade, histological subtype, and biomarkers. Extent of disease includes size, clinical tumour-node-metastases stage, location in the bladder, ureteral obstruction, and extravesical extension.⁸⁵ A surrogate endpoint of major importance is achievement of a complete pathological response to neoadjuvant chemotherapy. Such responses have been assessed in a large cooperative trial⁸⁶ with cisplatin based combinations showing complete pathological response rates of 14–38%. In a meta-analysis by Winkvist and colleagues,⁸⁷ this response status was the only factor independently predictive of overall survival in multivariate analyses of four trials (786 patients).

The issue remaining to be addressed is whether a regimen that produces high rates of complete pathological response in the neoadjuvant setting will result in improved rates of long-term cure after cystectomy. The Advanced Bladder Cancer (ABC) Meta-analysis Collaboration undertook a meta-analysis⁸⁸ of all completed randomised trials of neoadjuvant chemotherapy for invasive bladder cancer. Updated results are from 11 trials and 3005 patients. They showed a 5% absolute improvement in survival at 5 years. Although the study lends support to the idea that platinum based neoadjuvant chemotherapy is of value, this conclusion is not widely accepted. Some cogent criticisms are based on the fact that the patient population in the trials might not be truly representative of the population with bladder cancer in the Surveillance, Epidemiology and End Results (SEER) database^{89,90} in which a third of patients would have been ineligible for treatment by virtue of advanced age, inadequate renal function, or poor performance status.

Takata and colleagues⁹¹ studied gene expression profiles from biopsy samples before neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin was given and identified 14 genes that were expressed differently in responders and non-responders. *TP53* gene, angiogenesis factor expression (VEGF), EGRF, ERBB2 (HER2) protein, and lymphovascular invasion have all

been investigated retrospectively, but the true importance of these and other factors awaits results from large prospective studies.

Adjuvant chemotherapy

The obvious advantage of adjuvant—as opposed to neoadjuvant chemotherapy—is that pathological staging enables improved accuracy for patient selection. Adjuvant treatment facilitates the separation of patients in pathological stage T2 from those in stages T3, T4, or node positive disease—all at high risk of progression. The major disadvantage is the delay in systemic therapy for occult metastases while the primary tumour is being treated. To assess response to treatment is difficult because the only clinical endpoint is disease progression.

The role of adjuvant chemotherapy after cystectomy is not clear, because several of the reported studies were small phase II trials using various chemotherapeutic regimens. Many early studies used drug combinations now little used since combinations of new drugs have come to the forefront. Investigators generally agree that for patients with positive nodes and even with negative nodes and high pathological stage of the primary tumour, adjuvant chemotherapy is probably important to improve survival. Of the adjuvant studies in bladder cancer, five randomised trials used adjuvant chemotherapy.^{92–94}

In an important review of the present status of adjuvant chemotherapy in muscle-invasive bladder cancer, the (ABC) Meta-analysis Collaboration⁹⁵ examined 491 patients from six trials, representing 90% of all patients randomised in cisplatin based combination chemotherapy trials. They concluded that insufficient evidence exists on which to base reliable treatment decisions and recommended further research. The EORTC 30994 trial is appropriately designed to lead to valid conclusions and the results of that study are awaited.⁹⁴ The ABC investigators believe that consideration should be given to the participation of urologists in existing and future randomised trials of adjuvant chemotherapy.⁹⁶

An example of the convergence of biological predictors and chemotherapy in the search for improved treatment of bladder cancer is the important adjuvant multi-institutional Southwest Oncology Group (SWOG) phase III trial.⁹⁷ The aim of the study is to assess the therapeutic and prognostic significance of altered *TP53* expression by the tumour *TP53* after radical cystectomy in patients whose tumours are pathological stage T1 or T2 and assessed for *TP53* status. For patients with *TP53*-negative tumours the treatment is observation. Those with *TP53*-positive tumours are randomised to methotrexate, vinblastine, doxorubicin, and cisplatin treatment or observation. The effect of other genes, including *CDKN1A*, *RBI*, *ERBB2*, might prove important in relation to prognosis and possible benefit for chemotherapy after cystectomy.⁹⁸ Until completion of this study and other sufficiently powered clinical trials, the place of adjuvant chemotherapy will remain uncertain. The role of new

drug combinations already identified as active in advanced bladder cancer is yet to be established.

Chemotherapy for metastatic disease

An estimated 12 500 deaths per year in the USA are attributable to metastatic bladder cancer.⁸⁹ The initial spread of bladder cancer is typically to pelvic lymph nodes, but via lymphatic and haematogenous channels it often metastasises to other organs—most frequently the lungs and bones, but also the liver and brain. Prognosis is poor with cures rarely achieved. The median survival of patients with metastatic cancer of bladder origin is 12 months.

Compared with other solid tumour malignant diseases, transitional cell carcinoma of bladder origin is especially chemosensitive. In several phase II and III trials of combination chemotherapy, response rates greater than 50% have been reported, although most responses were partial rather than complete. Three phase II studies^{99–101} investigated combination gemcitabine and cisplatin in metastatic bladder cancer. Gemcitabine (1000 mg/m²) was given on days 1, 8, and 15, every 4 weeks. Cisplatin was given once every 4 weeks either on day 1 or 2 (70–75 mg/m²), or on days 1, 8, and 15 (35 mg/m²) of a 28-day cycle. In total, 116 patients were treated in the three studies with this doublet, with a response rate of 42–66% and a complete response rate of 18–28%. The median survival was 12.5–14.3 months.^{99–101} Primary toxicity was haematological and generally easily managed, with rare admissions for febrile neutropenia and no toxic deaths.

Because of this doublet's apparently comparable efficacy and improved tolerability, gemcitabine and cisplatin was compared with standard methotrexate, vinblastine, doxorubicin, and cisplatin in a multicentre phase III study.⁹⁹ No substantial difference was seen in time to progression or treatment failure, but patients treated with the doublet had measurably reduced toxicity and improved tolerability. As a result of this study, gemcitabine and cisplatin is regarded by some clinicians as the new standard of care for metastatic bladder cancer, but methotrexate, vinblastine, doxorubicin, and cisplatin is still thought of as a co-standard regimen.

Single agent paclitaxel resulted in clinically significant responses in advanced metastatic bladder cancer^{102,103} and the combination of the doublets paclitaxel and gemcitabine,^{104–106} cisplatin and docetaxel,^{107–109} gemcitabine and cisplatin,^{110,111} and cisplatin and paclitaxel,¹¹² and the triplets gemcitabine, paclitaxel, and cisplatin,¹¹³ and paclitaxel, carboplatin and gemcitabine,¹¹⁴ have all led to response rates better than those seen with any single agents, including gemcitabine alone, cisplatin alone, and paclitaxel alone. Results of a phase III study¹¹⁵ comparing methotrexate, vinblastine, doxorubicin, and cisplatin with gemcitabine and cisplatin showed no difference in response rate or duration of response, but the doublet had fewer toxic effects.

Pemetrexed used as a single agent has proved to be safe and active as second-line treatment in patients with transitional cell carcinoma of the urothelium. Sweeney and co-workers¹¹⁶ reported results of 47 patients in an intent-to-treat efficacy analysis. Three patients had complete responses (6.4%) and ten had partial responses (21.3%), with an overall response rate of 27.7%. The median duration of response was 5 months. Patients with impaired renal function who are not candidates for cisplatin might benefit from combinations such as gemcitabine and paclitaxel¹¹⁷ or carboplatin-containing regimens.¹¹⁸ Elderly patients, who cannot tolerate the most aggressive combination of chemotherapeutic agents, might achieve responses—albeit partial—from single agent chemotherapy with paclitaxel or gemcitabine, or the combination of gemcitabine and vinorelbine.¹¹⁹

Molecular biology and targeted therapies

Variations in chromosomal alterations arise at several points along the pathogenesis of transitional cell carcinoma. The loss of 9q seems to happen early in tumour development¹²⁰ whereas the loss of 17p, 3p, 13q, 18q, and 10q is noted more frequently in high than in low grade and stage disease.¹²¹ When the range of genetic alterations in the pathogenesis of transitional cell carcinoma is compared, gains and amplifications are more frequent in advanced than in early stage disease, whereas deletions generally arise in early stages.¹²² This pattern suggests that loss of tumour suppressor genes represent an early event in the pathway of transitional cell carcinoma progression, and the activation of oncogenes takes place in late stages.

Tumour suppressor genes such as *TP53* and *RB1* have been studied in detail in bladder cancer, but both markers have led to contradictory data in assessment of risk for disease progression and survival.¹²³ Cell cycle regulatory proteins p27 and Ki-67 might predict recurrence and disease progression but are not yet clinically applicable.^{124–126} Another protein that might show promise as a urine and tissue biomarker for transitional cell carcinoma is cystatin B. Its expression in urine correlates with disease recurrence and stage or grade progression, and intensity of expression in tissue correlates with tumour grade.¹²⁷

The tumour's pretreatment apoptotic index or altered expression of the *RB1* and *BCL2* genes might alter tumour response to radiation therapy.^{128–130} RTOG¹³¹ investigated the outcomes of 73 patients treated in four RTOG bladder-preserving protocols and noted in patients treated with transurethral surgery, concurrent chemotherapy, and radiation that altered expression of p53, CDKN2A, and retinoblastoma had no prognostic significance, but that overexpression of ERBB2 correlated with a significantly reduced complete response rate (50% vs 81%, $p=0.026$).

The aim of targeted therapies is to interfere with molecular events related to tumour growth. Examples of

these therapies are: cetuximab, an antiEGFR monoclonal antibody; gefitinib and erlotinib, EGFR-specific tyrosine kinase inhibitors; trastuzumab, an antihuman EGFR type 2 (ERBB2)-related monoclonal antibody; lapatinib, a dual inhibitor of EGFR-associated and ERBB2-associated tyrosine kinases; and bevacizumab, a VEGF monoclonal antibody.¹³² On the basis of preclinical and clinical evidence, EGFR, ERBB2, and VEGF are validated targets for cancer therapy and remain the subject of intense investigation. Both EGFR and ERBB2 are targets identified on cancer cells, whereas VEGF is a target that acts in the tumour microenvironment.¹³²

Black and colleagues¹³³ investigated targeting growth factors and receptors in bladder cancer. From their important preclinical studies they concluded that clinical efficacy was disappointing. Osai and co-workers¹³⁴ reported a substantial response to bevacizumab in one patient with poorly differentiated transitional cell carcinoma originating in the bulbar urethra with inguinal node metastases. Jalali Nadoushan and colleagues¹³⁵ showed that expression of the *ERBB2* oncogene has a direct relation with the grade of the bladder transitional cell carcinoma, suggesting the possibility that expression might be a prognostic factor. Several investigators^{136–138} have attempted to show this relation, but their results are preliminary.

Results of some studies^{139–141} have shown a reduced complete response rate when ERBB2 is overexpressed. These results have led to a new RTOG protocol (RTOG-0524) for patients with muscle-invasive bladder cancer who are not fit for cystectomy. This phase I and II trial investigates paclitaxel and daily radiation therapy, with trastuzumab given to patients whose tumours overexpress ERBB2. This study is the first example of molecular targeted therapy being added to treatment for patients with localised bladder cancer. With an enhanced understanding of the molecular pathophysiology of bladder cancer, we move toward an improved ability to predict which patients will progress to invasive disease, on the basis of tumour biology, enabling improved patient selection for definitive treatment and specific targeted molecular therapy for those with advanced disease.

Contributors

DSK, WUS, and ASF contributed equally to the researching and writing of this report. DSK served as senior author, reviewing, and finalising each draft.

Conflicts of interest

WUS declares that his family has substantial stock ownership in Pfizer. DSK and ASF declare that they have no conflicts of interest.

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