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Review

Management of bladder cancer: A literature review

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ABSTRACT

Cancer bladder represents the fourth most common cancer in men and ninth most common cancer in women. It is the second most prevalent cancer in men 60 years of age or older in United States. Radical cystectomy is the most widely used treatment for invasive bladder cancer. Radical cystectomy and urinary diversion has long-term effects on urinary, gastrointestinal and sexual function, and changes the body image of patients who use incontinent urinary diversions. Five-year specific and overall survival rates are 68% and 40 to 60%, and that is probably dependent upon the existence of micrometastases at the time of diagnosis. Clinical trials in the adjuvant setting require large numbers of patients to detect a survival advantage. It has been difficult to demonstrate a survival benefit from adjuvant chemotherapy. Neo-adjuvant cisplatin-based combination chemotherapy resulted in a significant 14% reduction in the risk of death, which translated into a 5% absolute improvement in five-year OS (from 45 to 50%). In appropriately selected patients, bladder preserving treatment with transurethral resection, radiation therapy and concurrent chemotherapy offers a probability of long term cure and overall survival at 5-years is comparable to cystectomy-based approaches (49 to 63% at 5 years) in patients of similar clinical stage and age. Five-year survival with bladder preservation is 40 to 45%. In addition, these selective bladder-preserving approaches result in approximately 80% of the long-term survivors maintaining a normal functioning bladder.

Keywords: Bladder cancer management, bladder preservation, cystectomy, chemotherapy bladder cancer.

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INTRODUCTION

In the United States, approximately 67,000 individuals (50,000 males and 17,000 females) develop bladder cancer each year, and 13,750 (9630 males and 4120 females) die from this disease (Jemal et al., 2007). Approximately, 80% of cases of bladder cancer are diagnosed in people over the age of 60. It is the second most prevalent cancer in men 60 years of age or older in the United States (Bernard, 2008). Emergence of newer therapeutic approaches has given physicians the scope to offer patients the option of bladder preservation. Also, looking further down, continuing advancements in cancer research could potentially offer more choices for clinician and patient with longer survival and better quality of life.

THE ROLE OF CYSTECTOMY AND BLADDER SPARING SURGERY IN BLADDER CANCER

The initial presentation of bladder cancer ranges from superficial to metastatic disease. For patients with muscle invasive bladder cancer, the most important treatment-related issues include the identification of those who can be adequately managed without total cystectomy, those who need radical cystectomy, and those who require a combined modality approach that includes chemotherapy and/or radiation therapy (RT), keeping our aim to improve patient quality of life treatment satisfaction and survival (Bajorin, 2008).

Radical cystectomy

Radical cystectomy is the most widely used treatment for invasive bladder cancer. It is a major operation, which usually causes loss of sexual function and requires urinary diversion. The morbidity associated with cystectomy can lead to the use of alternative lesser morbid procedures (endoscopic resection, partial cystectomy) or

delays in definitive treatment particularly in the elderly and those with other significant illnesses (Miller et al., 2003).

The alternative techniques are generally thought to have inferior outcomes compared to radical cystectomy when used alone in patients with muscle-invasive disease. However, this has not been proven in a randomized trial. Combining such lesser procedures with chemotherapy and RT may represent an acceptable alternative (Lee et al., 2006).

Indications

Most physicians recommend radical cystectomy in the following circumstances (Bajorin, 2008):

1. Muscle-invasive (≥ T2) disease.
2. Bladder cancer causing symptoms: (e.g., urinary frequency, hemorrhage) that cannot be adequately managed medically.
3. Tis, Ta, or T1 tumors: those are at high-risk for progression to muscle-invasive disease:

a) Patients with multiple tumors or frequent recurrences, particularly when recur within a short period of time despite treatment with intravesical BCG.
b) Superficial tumors of the prostatic urethra, particularly when complete resection cannot be accomplished.
c) Patients with second time recurrent T1 tumors within 6 to 12 months after combined treatment with TURBT and intravesical BCG.

Muscle-invasive tumors

Radical cystectomy with bilateral pelvic lymph node dissection is widely viewed as the treatment of choice for patients with muscle-invasive transitional cell cancers (TCC), including those with either superficial (T2a) or deep muscle invasion (T2b). Cystectomy is the best approach to achieve local control and can be curative even in some patients with nodal metastases (Bajorin, 2008).

The treatment paradigm for muscle-invasive bladder TCC is shifting away from cystectomy alone and leaning towards the use of perioperative chemotherapy. Two large inter-group trials (intergroup trial in the United States and the MRC/EORTC study in Europe) have demonstrated a survival benefit for neoadjuvant chemotherapy compared to cystectomy alone (Hall, 2002). Preoperative RT (40 to 50 Gy) eradicates the tumor in a small proportion of patients who then undergo cystectomy, and a retrospective series suggested improved survival with preoperative RT. However, randomized trials did not confirm a survival benefit compared to cystectomy alone. In addition, preoperative
RT increases the risk of operative complications and makes the creation of an internal urinary reservoir using irradiated bowel more difficult (Wammack et al., 2002).

Surgical technique

In men, radical cystectomy includes en bloc resection of the bladder, prostate, seminal vesicles and proximal urethra, with a wide margin of pelvic adipose tissue and peritoneum (Herr et al., 2004). Loss of sexual function is frequent, although a nerve sparing approach can increase the probability of recovering erectile function (Kessler et al., 2004). Prostate-sparing cystectomy has been explored in young, otherwise healthy men with no involvement of bladder neck or prostatic urethra, no carcinoma *in situ*, and no evidence to suggest prostate cancer. Nieuwenhuijzen et al. (2005) reported 7% local recurrence rate, and three-year disease free survival for organ confined, extravesical, and node-positive disease were 86, 63 and 39%, respectively. Potency was maintained by 78%.

In women, radical cystectomy includes anterior pelvic exenteration to remove the bladder, urethra, uterus, fallopian tubes, ovaries, anterior vaginal wall and surrounding fascia (Kessler et al., 2004).

Lymph node dissection

There is a direct relationship between the tumor (T) stage and lymph nodes (LN) involvement. Nodal positivity was observed in 2, 7, 18, 26, 46 and 42% of patients with pathologic stage T0, T1, T2, T3a, T3b and T4 disease, respectively (Stein et al., 2001). Extended pelvic LN dissection yields more LNs, and a higher likelihood of detecting nodal metastases. More than five studies revealed that the higher number of LNs examined had a favorable impact on survival. Herr et al. (2004) suggested that at least 10 to 14 LNs should be removed. The effort should be made to ensure optimal surgery at the time of radical cystectomy, particularly negative resection margins and a thorough bilateral pelvic lymph node dissection (defined as 10 or more lymph nodes in the pathology specimen) (Bajorin, 2008).

Laparoscopic cystectomy

Laparoscopic radical cystectomy has been proposed as an alternative to open radical cystectomy. Preliminary reports with this technique have demonstrated its feasibility. Although these reports suggest that laparoscopic surgery may decrease operative morbidity and mortality, there is inadequate follow-up (Puppo et al., 2007).

Selective surgical bladder preservation

Partial cystectomy or TURBT have more patient acceptance and satisfaction to treatment and sometimes better quality of life, but it may produce inferior outcomes

compared to radical surgery especially for deep muscle invasive disease. TURBT or partial cystectomy alone may be useful in carefully selected patients (Henry et al., 1988).

Partial cystectomy

Partial cystectomy allows complete pathologic staging of the tumor and pelvic LNs, while preserving bladder and sexual function. It may be useful in elderly or poor-risk patients who cannot tolerate radical cystectomy.

Partial cystectomy may be appropriate in the following conditions (Kassouf et al., 2006):

1. Limited disease to a solitary tumor at the dome, posterior, or anterior or lateral bladder wall. Tumors in the bladder neck or trigone are relative contraindications.
2. Two centimetres margin of normal, non-distended bladder can be removed around the base of the tumor.
3. No history of other TCC and no CIS are present.
4. The bladder has good capacity and normal function.

Local recurrence rate is higher with partial cystectomy (ranges from 38 to 78%). This may be related to inadequate surgical margins, disease in the trigone, multifocal disease, or CIS. In addition, tumor recurrence in the abdominal scar is another complication of partial cystectomy which is uncommon after radical cystectomy and occurs only when the bladder is opened supra-pubically (Hall, 2000).

Transurethral resection of urinary bladder tumor (TURBT)

TURBT alone may be sufficient for carefully selected patients with well differentiated or moderately differentiated (grade 1 or 2), papillary, solitary T2a TCC invading the superficial detrusor muscle only. Such lesions must not be associated with CIS, palpable mass or hydronephrosis (Sharma et al., 2002). If a repeated transurethral resection of the site of the original tumor is negative three weeks after the original TURBT, and if bimanual examination, mucosal biopsies, and urinary cytology are also negative, no further treatment is required. A high proportion of such patients will remain free of invasive cancer (Hall, 2000). Patients require close, life-long cystoscopic follow-up, because of the risk of second bladder tumors. This risk may be as high as 60% and persists for at least 10 years (Zietman et al., 2001).

The main argument against bladder conservation for muscle-invasive bladder TCC is the risk of metachronous bladder cancers. Multifocal urothelial tumors are common since the entire urothelial surface is affected by the same carcinogenic influences (the "field cancerization" effect). The risk of a new bladder tumor after bladder sparing modality is remarkably constant (50 to 60%) and about half of these tumors will be invasive (Kachnic et al., 1997).

ADJUVANT AND NEOADJUVANT CHEMOTHERAPY FOR BLADDER CANCER

The treatment for muscle-invasive bladder cancer is radical cystectomy with bilateral pelvic lymph node dissection. Even with potentially curative surgery, approximately 50% of patients with muscle-invasive TCC develop metastases within two years, and mostly die as a result of their disease (Whitmore, 1983). Five-year survival rates for pT2 and pT4 (pathologic stage T2 and T4) tumors are 60 to 80% versus 0 to 18%, respectively. Patients with lymph node metastases are considered at higher risk for post-cystectomy recurrence. Five-year survival rates up to 57% are reported in patients with clinically unsuspected N1 disease, as compared to 0 to 27% for those with N2 to N3 disease (Stein et al., 2001). The addition of systemic chemotherapy before or after cystectomy may improve the survival for patients with muscle-invasive TCC (Loehrer et al., 1992).

Chemotherapy and bladder cancer

Cisplatin appears to be the most active single agent. In three separate randomized trials, the overall and complete response (CR) rates with cisplatin ranged from 9 to 31% and 3 to 9%, respectively (Loehrer et al., 1992). Single agent carboplatin appears to be less active than cisplatin in patients with advanced urothelial carcinoma, which is true for other older compounds with single-agent activity include methotrexate, vinblastine, doxorubicin, cyclophosphamide, 5-fluorouracil and mitomycin C (Marcuello et al., 1990). Some newer agents possess significant activity for the initial therapy of urothelial carcinoma including gemcitabine (Castagneto et al., 2004), and paclitaxel (Dreicer et al., 1996).

Platinum-based combination chemotherapy continues to show a clear and modest benefit for survival and disease-free survival (Advanced Bladder [ABC] Meta-analysis Collaboration, 2005). The MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) regimen has been the standard against which other regimens are compared (Loehrer et al., 1992). Gemcitabine plus cisplatin appears to provide similar efficacy to MVAC in patients with advanced disease, but with a more favorable side effect profile (Von der Maase et al., 2000).

Neoadjuvant chemotherapy

About half of the patients who present with invasive bladder cancer are likely to have occult metastases. Furthermore, patients may best tolerate chemotherapy before they have received potentially debilitating local

treatment with either surgery or radiotherapy. Local treatments may also affect drug delivery by altering blood supply especially to the tissues affected by the tumor. Therefore, neoadjuvant chemotherapy has the potential to deliver the drugs more efficiently and at higher doses than in the adjuvant setting and provides an opportunity to prospectively assess the response to chemotherapy (Neoadjuvant Chemotherapy for Invasive Bladder Cancer, 2004).

The disadvantage of this approach is the marked discordance between clinical and pathologic staging in the assessment of chemotherapy response. In one report, a clinical complete response (CR) (T0 tumor by transurethral resection) was obtained after MVAC in 57%; however, only 30% had pathologic T0 (pT0) disease (pathologic CR) defined at subsequent cystectomy (Scher et al., 1988). In a trial done by Schultz et al. (1994), they reported that the pathologic response rates were related to the stage and size of the primary tumor. The pCR rates after neoadjuvant MVAC in patients with T2/T3a and T3b/T4 tumors were approximately 43 and 9%, respectively. In a report of 125 patients enrolled in trials of cisplatin-based neoadjuvant therapy followed by definitive surgery, at a median follow-up of 25 months, 91% of responders were disease-free in contrast to only 37% of non-responders (Bajorin, 2001). In prospective trial (compared cisplatin plus methotrexate followed by cystectomy with cystectomy alone in 317 patients with T2-4aNxM0 bladder cancer) with a median follow-up of 5.3 years, the difference in five year OS did not reach the level of statistical significance (53% versus 46% for neoadjuvant and control groups, respectively), this may be explained by the inferior chemotherapy regimen chosen (Sherif et al., 2002).

MRC/EORTC trial

The largest trial was performed by the Medical Research Council and the European Organization for Research and Treatment of Cancer. The trial included 491 patients with high-grade T2-T4a, N0-NX, M0 bladder TCC. The patients were randomly assigned to receive three cycles of neoadjuvant CMV (cisplatin, methotrexate and vinblastine) or no chemotherapy, followed by each institution's choice of local management (that is, radical cystectomy or radiation therapy). The pCR rate in the neoadjuvant group was 33%, and the absolute OS benefit from chemotherapy at three years was 5.5% (55.5% versus 50%), which was not significant since the trial was powered to detect a 10% increase in absolute OS (International collaboration of trialists, 1999). Later on, seven years of follow-up reported a 15% OS benefit with neoadjuvant CMV, but it was still not statistically significant (Hall, 2002).

Another sufficiently powered United States Intergroup trial (INT 0080 trial) randomly assigned 317 patients with T2-4a, N0, M0 bladder TCC to cystectomy with or without three preoperative courses of MVAC. Patients treated with MVAC were significantly more likely to have a pCR (38 versus 15%), five year OS (57 versus 43%, $p = 0.06$) were of borderline statistical significance. One-third of the patients receiving neoadjuvant chemotherapy had ≥ grade 3 hematologic or gastrointestinal adverse effects, without treatment-related deaths (Grossman et al., 2003).

Subsequent reports retrospectively assessed whether surgical factors in addition to neoadjuvant chemotherapy had prognostic significance for survival. An optimal cystectomy and thorough pelvic lymph node dissection (defined as negative resection margins and at least 10 lymph nodes in the surgical specimen) was associated with the longest survival. Survival rates were highest in neoadjuvant arm (> 80 versus 39%) in no chemotherapy arm at five years (Dotan et al., 2005).

In an Italian trial, 171 patients with T2-4, N0, M0 bladder TCC were randomly assigned to MVEC (methotrexate, vinblastine, cisplatin plus epirubicin) followed by cystectomy or cystectomy alone. In a preliminary report from 1995 that has never been published in final form, with a median follow-up of 33 months, there were no significant differences in DFS or OS between the groups (Cortesi, 1995).

Although several other randomized trials fail to show a survival benefit for neoadjuvant chemotherapy, this may be resulted from an inadequate number of enrolled patients to demonstrate a statistically valid result, premature closure (Shipley et al., 1998), the use of ineffective chemotherapy (Martinez- Piñeiro et al., 1995), or failure to publish the final results (Shipley et al., 1998).

A survival benefit from neoadjuvant cisplatin-based chemotherapy was demonstrated in a 2005 Cochrane database review that included individual patient data from 3005 individuals enrolled in 11 randomized trials comparing neoadjuvant chemotherapy with local therapy alone. Neoadjuvant cisplatin-based combination chemotherapy resulted in a significant 14% reduction in the risk of death, which translated into a 5% absolute improvement in five-year OS (from 45 to 50%) (Von der Maase et al., 2000). A second meta-analysis included published data from eight randomized trials that compared neoadjuvant cisplatin-based combination therapy to local therapy alone, concluded that there is a 6.5% absolute improvement in five-year OS (from 50 to 56.5%) (Winquist et al., 2004).

The combination of cisplatinum and vinorelbine has demonstrated a favorable response rate in patients with locally advanced bladder cancer along with an acceptable toxicity profile, according to phase II data presented at the 18th International Congress on Anti-Cancer Treatment (ICACT). Overall, 36.7% patients had a partial treatment response, and 10% patients had stable disease. While 3 (10%) patients become operable and had a radical cystectomy that confirmed the down-staging of their tumor, none of them had a pathological

complete response. It is important to note that 47% of patients in series had squamous cell carcinoma, which is more resistant to chemotherapy. There was no grade 3 or 4 non-hematologic toxicity except for nausea and vomiting in 3 (10%) patients. Grade 3 neutropenia occurred in 1 patient (Abd El-Warith et al., 2007).

Neoadjuvant chemotherapy as a component of bladder preservation

Neoadjuvant chemotherapy can be a useful component of strategies aimed at organ preservation. Patients without an appropriate response to neoadjuvant therapy can be referred for radical cystectomy. Non-transitional cell histologies (adenocarcinomas and squamous cell carcinomas) are generally insensitive to chemotherapy, and these patients should not be considered for a neoadjuvant bladder-sparing approach (Bajorin, 2008).

Organ preservation has been investigated in patients with infiltrating TCC of the bladder as an alternative to radical cystectomy. RTOG 88-02 looked at the role of neoadjuvant MCV given immediately following TURBT. It entered 91 patients and reported a 75% response rate treatment-related morbidity and mortality rates, were significantly higher in the neoadjuvant chemotherapy arm. In summary, this trial suggested that two cycles of neoadjuvant MCV were not a necessary component of a bladder preservation strategy. In 1995, the RTOG began phase I to II protocols to evaluate accelerated radiation fractionation schemes in combination with concurrent chemotherapy (Shipley et al., 1998).

Adjuvant chemotherapy

The advantages of adjuvant over neoadjuvant approach in perioperative chemotherapy are mainly summarized in two points (Bajorin, 2008):

1. The administration of chemotherapy following cystectomy allows the treatment decision to be based upon pathologic stage as the indicator of recurrence risk. This reduces overtreatment due to inaccuracies in clinical staging, and avoids treatment-related toxicity in patients who are estimated to have a reasonable outcome from surgery alone (e.g., those with pT2 lesions).
2. The delay in carrying out potentially curative surgery is avoided.

Unfortunately, the evidence for a survival benefit from adjuvant chemotherapy has been less convincing (Lehmann et al., 2006). Two meta-analyses concluded that adjuvant therapy has a modest, statistically significant improvement in survival over surgery alone (Ruggeri et al., 2006). The data are, however, not sufficiently compelling to warrant routine use of adjuvant chemotherapy (Barocas and Clark, 2008). Benefit for adjuvant chemotherapy was initially suggested in a retrospective report from MD Anderson (Logothetis et al., 1988). Suitable patients for chemotherapy were identified based on the presence of nodal metastases, extravesical involvement, lympho-vascular permeation of the primary tumor, and pelvic visceral invasion. Sixty-two patients who met these criteria did not receive chemotherapy (because they were not referred, refused it, or were considered medically unfit) their outcome was compared to that of 71 high-risk patients who received adjuvant cisplatin, doxorubicin and cyclophosphamide (CISCA). They also compared that to an additional 206 low-risk patients who lacked these poor prognostic features and were not offered chemotherapy. The five-year DFS was significantly better for high-risk patients who received chemotherapy compared to those who did not (76% versus 37%), and was strikingly similar to that of the low-risk patients (70%). The problem with this study, which may have impacted the results, was the absence of randomization since patient selection (Bajorin, 2008).

At least five randomized trials have explored adjuvant cisplatin-based chemotherapy following resection of muscle-invasive bladder TCC (Logothetis et al., 1988). Two trials predominantly included patients with organ-confined (pN0) disease, found no significant survival benefit for adjuvant therapy (Skinner et al., 1991). However, there are two other trials that have demonstrated survival benefit in patients with higher risk disease. A survival benefit for adjuvant CISCA was suggested in a study in which 91 patients with pT3-4 or node-positive disease randomly assigned to observation or four cycles of post-cystectomy chemotherapy (Skinner et al., 1991). Patients receiving chemotherapy had a significantly better three year DFS (70% versus 46%) and median OS (4.3 versus 2.4 years). However, this study was flawed by the small number of patients and potential selection bias. Of 498 potentially eligible patients, only 91 chose to participate (Bajorin, 2008).

There is trial that compared MVAC adjuvant regimen (methotrexate, vinblastine, cisplatin plus either doxorubicin or epirubicin) with observation. It was originally designed to detect a 35% improvement in DFS (from 20 to 55%) among 100 patients (Stockle et al., 1992). The study was terminated prematurely after 49 patients with pT3a-4a or node-positive TCC were enrolled, when an interim analysis showed a significant improvement in three year progression-free survival (PFS) with chemotherapy (63 versus 13%). A survival benefit was especially pronounced among patients with node-positive disease; 12 of 13 undergoing cystectomy alone progressed, compared to 3 of 11 receiving adjuvant chemotherapy. A significant PFS benefit was still evident with longer term follow-up, as indicated by a later report of 166 patients (including the originally randomized 49 patients), 80 of whom received three cycles of adjuvant MVAC or MVEC, and 86 who underwent cystectomy alone (Stockle et al., 1996).

In contrast to previous results, another trial of 55

patients with pT3-4 or node-positive TCC who were randomly assigned to four courses of cisplatin, methotrexate, and vinblastine (CMV) or observation following cystectomy failed to show a survival benefit. At a median follow-up of 62 months, adjuvant chemotherapy was associated with a significantly longer median time to progression (37 versus 12 months), but no difference in five-year OS (40 versus 38%) (Freiha and Torti, 1996).

There is no widely accepted standard of care for postoperative chemotherapy in the treatment of muscle-invasive bladder cancer. Interpretation of the available data has resulted in divergent opinions about the possible benefit of chemotherapy in this setting. The likelihood of cure is probably greatest in patients with both good performance status (reflecting lower tumor burden) and disease that is restricted to LNs. Using these data to guide conventional therapy policy at Memorial Sloan Kettering, patients who have advanced TCC (extravesical extension, > pT2 , or node-positive) after cystectomy and pelvic lymph node dissection are considered for adjuvant chemotherapy. Four cycles of either MVAC or gemcitabine/cisplatin are recommended only for patients who are likely to tolerate a cisplatin-based regimen (that is, satisfactory performance status, adequate renal function, and acceptable medical comorbidity). If cisplatin-based therapy is not possible, or if disease is less extensive, observation is recommended (Bajorin, 2008).

MVAC may be the most effective regimen based upon randomized comparisons to cisplatin and to the combination of cyclophosphamide, doxorubicin and cisplatin (Saxman et al., 1997). However, cisplatin plus gemcitabine is a reasonable alternative based on similar efficacy far less toxicity (Neoadjuvant Chemotherapy for Invasive Bladder Cancer, 2004). Clinical trials in the adjuvant setting require large numbers of patients to detect a survival advantage. Because measurable disease is absent, surrogate end points such as an objective response cannot be used as therapeutic end points, so it has been difficult to demonstrate a survival benefit from adjuvant chemotherapy (Bajorin, 2008).

Neoadjuvant versus adjuvant therapy

There are no trials directly comparing neoadjuvant with adjuvant chemotherapy in patients undergoing cystectomy. One study addressed the optimal timing of perioperative chemotherapy by randomly assigning 140 patients with locally advanced TCC to two preoperative plus three postoperative courses of MVAC, or five postoperative courses following cystectomy and pelvic lymph node dissection. At an average follow-up of 6.8 years, the median survival for the entire group was four years, and patients underwent postoperative chemo-therapy alone had similar DFS (60 versus 56%) as those receiving neoadjuvant plus adjuvant chemotherapy (Millikan et al., 2001). Although 9% of the cohort died during treatment, there was no significant difference in treatment tolerance and perioperative morbidity between the two groups. Patients who underwent neoadjuvant chemotherapy had a lower rate of positive surgical margins than those who received all of their chemotherapy postoperatively (2 versus 11%), and a lower incidence of pelvic lymph node metastasis at exploration (36 versus 22%).

RISK-DIRECTED CLINICAL TRIALS

Among the new prognostic factors for patients with bladder TCC are mutations in the p53 tumor suppressor gene. P53 mutations confer a poor prognosis in muscle-invasive TCC of urinary bladder (Sarkis et al., 1995). In one analysis of 243 patients undergoing cystectomy, the risk of both disease recurrence and death was significantly higher in patients whose tumors contained mutant p53 (Esrig et al., 1994). Recurrence rates for tumors with and without detectable p53 mutation were 62 versus 7% for pT1 tumors, 56 versus 12% for pT2 tumors, and 80 versus 11% for pT3 tumors. It was difficult to separate the influence of p53 overexpression from tumor stage (Tsuji et al., 1997).

In a recent study done by Ecke et al. (2008) for tumor invasion and p53 mutation, the frequency in P53 mutation was 44.6% in non-invasive tumors, while for invasive bladder cancer it was 84.2%. In a report of 90 patients that underwent neoadjuvant MVAC chemotherapy, patients with mutant p53 were three times more likely to die from their disease than those with wild-type p53 (Sarkis et al., 1995). The impact of p53 over expression on survival was predominantly in T2 and T3a tumors (Garcia del Muro et al., 2002).

Aggressive TURBT and neoadjuvant chemotherapy was used to facilitate bladder preservation, in patients with both favorable biological features (wild-type p53 inferred from IHC staining) and clinical features (muscle-invasive, organ-confined disease without hydronephrosis). Results suggested that the bladder may be preserved for up to ten years in patients with wild-type p53 tumors that are confined to the bladder wall (stage T2) (Takata et al., 2005).

A different hypothesis was tested at the University of Southern California; the data suggested that adjuvant chemotherapy may enhance survival in patients with p53 mutant tumors (Cote et al., 1997). Future individualization of therapy, whether or not the response to neoadjuvant chemotherapy may be predicted based upon an individual tumor's gene expression pattern, is an area of great interest. Such work is in its infancy, but holds promise (Takata et al., 2005).

RADIATION THERAPY AND BLADDER CANCER

Radiotherapy as a radical treatment for bladder cancer has declined in many parts of the world because of:

1. The perception that radical cystectomy is more effective in controlling the primary tumor and preventing the development of new bladder tumors.
2. Improvements in surgical techniques for radical cystectomy.
3. The availability of more acceptable alternatives for urinary diversion, include stomal and orthotopic neobladders, which reduced the need for bladder conservation.

However, parallel advances in radiation treatment planning and delivery, along with an improved understanding of radiobiology, have reinforced the important role that radiotherapy plays in the treatment of patients with this disease (Milosevic et al., 2007).

Preoperative radiotherapy

Multiple studies have tried to answer the question about the benefit of preoperative radiotherapy. The largest single-institution experience with preoperative radiotherapy for bladder cancer reported at the MD Anderson Cancer Center. Among 338 patients with T2 to T4 disease, pathologic down-staging was observed as a result of radiotherapy in 65% of cases, and 42% had no tumor cells remaining in the surgical specimen. Overall survival at 5 years was 44%. Pelvic and distant recurrence rates were 16 and 43%, respectively. Preoperative radiotherapy appeared to improve pelvic control in patients with T3b disease at presentation (Pollack et al., 1994).

At least 3 other randomized phase III studies have been conducted to compare planned preoperative radiotherapy plus cystectomy with cystectomy alone. The problem with these studies included patients with early-stage disease who were unlikely to benefit from preoperative radiation. In addition to the use of relatively low doses of radiation and infrequent reporting of local control (Milosevic et al., 2007), only one of the studies individually showed a survival advantage in favor of preoperative radiotherapy, and it included a high proportion of patients with schistosomiasis (Ghoneim and Awaad, 1985). The meta-analysis of the combined data from the previous studies found no effect of preoperative radiotherapy on survival (Huncharek and Geschwind, 1998).

In most randomized trials, preoperative RT significantly improved local control but not survival when compared to cystectomy alone (Shipley et al., 1999). However, the results of RT alone for operable patients (five year survival 20 to 40%, local control rate 50%) are inferior to those reported with radical surgery, at least because of the inclusion of patients with clinically occult extravesical disease (Zelefsky, 2008).

Combined treatment with radiotherapy and chemotherapy (Table 1)

With the effectiveness of chemotherapy for bladder TCC, and its synergistic effect with radiation, RT has re-emerged as an integral component of bladder conserving approaches for patients with muscle-invasive disease (Rödel et al., 2002). Radiotherapy has been combined with chemotherapy to treat bladder cancer in many studies, with the aim to enhance local tumor control, reduce metastasis development, and improve patient survival.

Cisplatin is the most active single agent in the treatment of patients with bladder cancer, and it has been shown in preclinical studies to enhance the cytotoxic effects of radiation under both oxic and hypoxic conditions. Numerous case series and phase III randomized trials support the use of radiation and chemotherapy together in patients with muscle-invasive disease (Milosevic et al., 2007).

There are no randomized data to compare radiotherapy (RT) and surgery, but a study of patients recruited from one geographic area within the United Kingdom has shown similar outcomes, including cause-specific survival rates of approximately 50% at 5 years from either modality (Kotwal et al., 2008). When transurethral resection of a bladder tumor (TURBT), radiation and multi-agent chemotherapy are combined, complete response rates of 70% have been achieved. Most chemo-radiation regimens for MIBC employ concurrent cisplatinum in various doses and schedules (Dunst et al., 1994; Kaufman et al., 1993; Housset et al., 1993; Eapen et al., 1989).

In the Massachusetts General Hospital, series of 190 patients treated by tri-modality therapy between 1986 and 1998, 63% exhibited a CR (Shipley et al., 2002). In another series from Germany and Spain, CR was 80 and 89%, respectively (Sauer et al., 1998; Zapatero et al., 2010). The radiotherapy oncology group (RTOG) trials demonstrated a CR rate after induction in 75 and 59% of the patients (Shipley et al., 1998). RTOG twice daily protocol revealed 81% CR after induction phase (Kaufman et al., 2009).

The long-term outcome data published by Shipley et al. (2002) suggested that the expected complete response rate with TURBT, chemotherapy, and external beam RT is approximately 65 to 70%, five-year survival rates are approximately 50 to 60%, and approximately 35 to 40% of patients survive five years with an intact bladder (Shipley et al., 2002). In the majority of this group of selected patients, normal bladder function is maintained for long-term. These long-term survival rates are similar to those reported in most cystectomy series, although no randomized trials directly comparing cystectomy with combined modality therapy are available (Zelefsky, 2008).

In case of bladder preservation, there has been reluctance to recommend chemoradiotherapy (CRT) for bladder cancer due to the impression that such treatment would be associated with a higher likelihood of bladder contractures and intractable hematuria. However, late complications are infrequent with meticulous attention to

Table 1. Clinical trials for combined treatment with radiotherapy and chemotherapy in urinary bladder preservation.

Investigator (publication year)	No. patients	Clinical stage	Induction therapy		CR (%)	Consolidative therapy		5-year OS (%)	5-year BIS (%)
			Neoadjuvant	CRT regimen		CRT regimen	Adjuvant		
Given et al. (1995)	93	T2-4	2 or 3 cycles MVAC or MCV	64.8 Gy + cisplatin	63	-	-	39	NA
Tester et al. (1996)	91	T2-4a	2 cycles MCV	39.6 Gy + cisplatin	75	25.2 Gy + cisplatin	-	62 (4-year)	44 (4-year)
Housset et al. (1997)	120	T2-4	TURBT	24 Gy+cisplatin and 5-FU	77	20 Gy+cisplatin and 5-FU	-	63	NR
Kachnic et al. (1997)	106	T2-4a	2 cycles MCV	39.6 Gy + cisplatin	66	25.2 Gy + cisplatin	-	52	43
Fellin et al. (1997)	56	T2-4	2 cycles MCV	40 Gy + cisplatin	50	24 Gy + cisplatin	-	55	41
Shipley et al. (1998)	123	T2-4a	2 cycles MCV vs. no chemotherapy	39.6 Gy + cisplatin	61 vs. 55	25.2 Gy + cisplatin	-	49 vs. 48	36 vs. 40
Rodel et al. (2002)	415	T1-4	-	50.4–59.4 Gy + cisplatin or carboplatin (+ FU)	72	-	-	50	42
Danesi et al. (2004)	77	T2-4	2 cycles MCV	69 Gy + cisplatin/FU	90	-	-	58	47
Dunst et al. (2005)	68	T2-4	-	50.4–59 Gy + cisplatin or paclitaxel	87	-	-	45	NA
Weiss et al. (2007)	112	T1-4	-	55.8–59.4 Gy + cisplatin/FU	88.4	-	-	74	61
Perdonà et al. (2008)	121	T2-4	2 cycles MCV	65 Gy + no vs. cisplatin or carboplatin	74.4 vs. 89.7	-	-	60.4 vs. 71.8	46.5 vs. 53.8
Aboziada et al. (2009)	50	T2-3b	TURBT	44 Gy +cisplatin	70	20 Gy + cisplatin	-	NA	NA
Kaufman et al. (2009)	80	T2-4a	-	40.3 Gy + cisplatin/ paclitaxel	0.81	24 Gy + cisplatin/paclitaxel	4 or 6 cycles GC	56	47
James et al. (2010)	360	T2-4a	TURBT ± induction chemotherapy	55 Gy or 64 Gy plus mitomycin- C+ 5-FU vs. RT alone	NR	-	-	67 vs. 54 2-year LRDFS	NR
Sabaa et al. (2010)	104	T2-3a	3 cycles GC	60 – 65 Gy + cisplatin	78.8	-	-	54.8	NA

BIS: bladder intact survival.

technique and the use of newer RT methodologies such as three-dimensional conformal and intensity-modulated RT (Zelefsky, 2008).

A study done by Aboziada et al. (2009), included 50 bladder cancer patients (T2a 4%, T2b 44%, T3a 28% and T3b 24%). The patients underwent maximum TURBT, and then they received combined chemo-radiotherapy. They reported 70% CR. They reported that trimodality treatment (TURBT and chemo-radiotherapy) may be a reasonable alternative to classical surgical approach in selected group of patients (Aboziada et al., 2009).

Hyperfractionated (twice daily) RT regimens appear to further improve the likelihood of local tumor control in this setting. In one study in which hyperfractionated RT was combined with infusional cisplatin/5-FU-based chemotherapy and a TURBT, 90% of treated patients achieved a clinical complete response, and the five-year likelihood of surviving with an intact bladder was 47% (Danesi et al., 2004).

Newer drug regimens and combinations are being explored as well as new approaches in RT. Paclitaxel-based regimens with or without platinum are under study in an effort to further enhance the radiation response and improve local control (Zelefsky, 2008).

Targeted therapy in bladder cancer

Due to the poor prognosis of advanced bladder carcinoma and the insufficient effects of the chemotherapeutic agents for this disease, the investigation of the novel genetic and pharmacologic agents including anti-angiogenic agents that can target pathway-specific molecules

has been the subject of several publications especially for the last 2 years (Silay and Miroglu, 2007). Targeted therapy with novel agents may have the potential to improve management of patients with bladder cancer.

Epidermal growth factor receptor (EGFR)

EGFR is over-expressed in the majority of patients with urothelial carcinoma of the bladder (Kassouf and Tuziak, 2007). This over-expression correlates not only to tumor stage and grade (Sriplakich and Karlsson, 1999), but also to patient survival (Mellon et al., 1995).

Furthermore, EGFR inhibitors have been shown to have a clear anti-proliferative and anti-angiogenic effects in preclinical models (Kassouf and Brown, 2005). EGFR-targeted agents, including the tyrosine kinase inhibitor erlotinib and the monoclonal antibody cetuximab, are FDA approved and continue to be investigated in NSCLC (Shepherd et al., 2005), colorectal carcinoma (Cunningham et al., 2004), pancreatic carcinoma (Moore et al., 2007), head and neck tumors (Bonner et al., 2006), and other malignancies.

EGFR-targeted treatment of bladder cancer is currently being investigated in several clinical trials. These trials cover a broad spectrum of strategies for different disease states. For example, gefitinib is being used together with gemcitabine and cisplatin for metastatic disease. There are two running trials in MD Anderson cancer center, the first is comparing consolidation treatment with docetaxel alone versus docetaxel and gefitinib in advanced disease. In the second trial, erlotinib is being given preoperatively (Peter and Colin, 2007).

One challenge to EGFR-targeted therapy is its significant cytostatic effect that may abrogate the efficacy of chemotherapeutic agents such as taxanes that act on cell cycle progression. The sequence of delivery of these agents when used in combination is critical. Gefitinib in this setting should be given concurrently or after docetaxel (Kassouf et al., 2006).

Human EGF receptor 2 (HER2)

Humanized monoclonal antibody to HER2 (trastuzumab) offers a survival advantage in HER2-positive breast cancer patients when given in the metastatic or adjuvant settings. The success and safety of trastuzumab in breast cancer (Piccart-Gebhart et al., 2005) have raised the question if it is possible to be used in other solid tumors.

Varied results have been reported on the significance of HER2 expression in urothelial carcinoma (Jimenez et al., 2001), with studies linking over-expression to both adverse (Krüger et al., 2002) and improved outcome (Gandour-Edwards et al., 2002). Other studies revealed no correlation between HER2 expression and stage, grade or survival (Piccart-Gebhart et al., 2005). Some of this variability is likely related to patient selection and the different techniques used to determine HER2 expression.

Despite these mixed findings in bladder cancer, clinical trials have been initiated to investigate the efficacy of trastuzumab in this disease. The results of a Phase II trial investigating trastuzumab together with combination chemotherapy (paclitaxel, carboplatin, and gemcitabine) was reported at the 2005 meeting of the American Society of Clinical Oncology (ASCO) (Hussain et al., 2007). This treatment proved to be feasible in patients with locally recurrent or metastatic urothelial carcinoma over-expressing HER2. There was a 73% response rate and a median survival of 15.2 months. The conclusion of this study was that this combination warrants investigation in a Phase III trial.

In a second trial, the response rate reported was 70%, and the median survival was 14.1 months. Although it appears that the addition of trastuzumab to the triplet did not significantly alter the response rate or the median survival. However, such comparison should be made with caution, given the potential for selection bias (Vaughn, 2007).

Vascular endothelial growth factor (VEGF)

In a cohort of 64 patients with high-risk localized bladder cancer, it was reported that patients with increased VEGF expression by *in situ* hybridization had a significantly decreased survival compared with those with normal levels of expression (Slaton et al., 2004).

Bevacizumab is an FDA-approved monoclonal antibody against VEGF that has proven benefit in multiple solid tumors including metastatic colorectal cancer (Hurwitz et al., 2004), breast cancer (Miller and Gralow, 2005), NSCLC (Sandler et al., 2006), and renal cell carcinoma (Yang et al., 2003). MD Anderson Cancer Center is currently processing a Phase II clinical trial of neoadjuvant chemotherapy with dose dense MVAC plus bevacizumab in patients with locally advanced urothelial cancer. The primary outcome measures will be down-staging to pT1N0 or lower in the cystectomy specimen and 4-year disease-free survival. Secondary outcome measures will include perioperative morbidity and mortality, gastrointestinal perforation and wound dehiscence, which have been reported to occur at a higher rate after treatment with bevacizumab (Scappaticci et al., 2005).

Multi-kinase inhibitors

A key to the success of targeted therapy in the future may be the combination of multiple inhibitors against different targets, or the use of single inhibitors directed against two or more targets. The multi-kinase inhibitors, sorafenib and sunitinib, are the most extensively

Table 2. Clinical trials of targeted agents for urothelial cancers.

Drug	Reference	Phase and setting	Treatment	Response rate	Median OS (months)	Median PFS (months)	Comments
Bevacizumab	Hahn et al.	Phase II: 1st line advanced UC	GC + Bev	CR: 9/43 pts (21%) PR: 22/43 (51%)	20.4	8.2	Grade 3-4 non-hematologic toxicity included: DVT/PE 21%, hemorrhage 7%, hypertension 5%, proteinuria 2%.
Aflibertcept	Twardowski et al.	Phase II: 2nd line advanced UC	Single-agent aflibercept	PR: 1/22 (4.5%)	NA	2.79	Similar toxicity as other VEGF inhibitors: hyper-tension, proteinuriea, he-morrhage (Bajorin, 2001).
Sorafenib	Sridhar et al.	Phase II: 1st line advanced UC	Single-agent sorafenib	OR: none SD ×3 mo: 1/17 (6%) SD <3 mo: 3/17 (18%)	5.9	1.9	Most common 3+ toxicities: abdominal pain, back pain, hand foot reaction, bladder infection.
	Dreicer et al.	Phase II: 2nd line advanced UC	Single-agent sorafenib	OR: none	6.8	4-month PFS: 9.5%	Most common 3+ toxicities: fatigue, hand-foot reaction.
	Krege et al.	Phase II: 1st line advanced UC	GC +/− sorafenib	NA	NA	NA	42% received only 1-2 cycles of chemotherapy Similar toxicity between arms: 43% (placebo) vs. 49% (sorafenib)
Sunitinib	Gallagher et al.	Phase II: 2nd line advanced UC	Single-agent sunitinib, either 4 wk on/2 wk off (cohort A) or continuous dosing (cohort B)	PR cohort A: 3/45 pts (7%) PR cohort B: 1/32 (3%) PR + SD: 33/77 (43%)	7.1 vs. 6.0 (A vs. B)	2.4 vs. 2.3 (A vs. B)	Included 26% renal pelvis or ureter primary urothelial tumors 61% experienced grade 3-4 toxicity
	Galsky et al.	Phase II: 1st line advanced UC	GC + sunitinib (up to 6 cycles), followed by daily sunitinib until progression	PR: 8/15 pts (53%) SD: 1/15 (7%)	NA	NA	Significant toxicity: 40% discontinued tx <3 cycles. Neutropenia (80%), 1 septic death.

	Bradley et al.	Phase II: Maintenance advanced UC with CR/PR/SD following 4-6 cycles of CT	sunitinib vs. placebo, 4 wk on/2 wk off	SD ×24 wk: 2/7 (29%) PR ×60 wk: 1/7 (14%)	NA	2.2 (on open-label sunitinib)	No grade 4-5 adverse events.
	Bellmunt et al.	Phase II: 1st line advanced UC, ineligible for cisplatin	sunitinib, 4 wk on/2 wk off	PR: 2/16 (8%) SD ×>3mon: 8/16 (50%)	NA	5.9	
Pazopanib	Necchi et al.	Phase II: 2nd line advanced UC	single-agent pazopanib	PR: 4/18 (22%) SD: 11/18 (61%)	NA	NA	Results after median follow-up of 3 months.

investigated agents of this class, and they have had a profound impact on the management of renal cell carcinoma (Pasche, 2006).

Sorafenib is a raf-kinase inhibitor that also inhibits VEGFR-2, VEGFR-3 and PDGFR-β (Platelet derived growth factor receptor β). Sunitinib targets VEGFR-2 and PDGFR-β (Wilhelm et al., 2004). This combination of targets appears promising in the context of the preclinical results (Peter and Colin, 2007). Both inhibitors are FDA approved and have begun clinical investigation in bladder cancer.

Princess Margaret Hospital in Toronto is leading a Phase II multi-center trial of sorafenib in advanced or metastatic urothelial carcinoma. Memorial Sloan-Kettering Cancer Center is conducting a Phase II trial using sunitinib as second line therapy for progressive metastatic urothelial carcinoma (Peter and Colin, 2007).

The results of clinical trials of targeted agents for urothelial cancers published thus far have generally been disappointing, and to date, no biologic agents have been approved either as monotherapy or in combination with cytotoxic chemotherapy for advanced urothelial carcinoma. Despite the identification of genetic alterations thought to drive high-grade, muscle-invasive disease, these aberrations have not successfully predicted response to targeted treatment (Table 2) (Guancial et al., 2011).

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