Management of invasive bladder cancer in patients who are not candidates for or decline cystectomy

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Abstract: Bladder cancer is a common malignancy seen in older adults with coexisting medical illnesses. The management of patients with muscle invasive disease includes perioperative chemotherapy and radical cystectomy; however, patients may decline surgery and older patients with comorbid conditions may not be candidates for surgery and thus alternative treatment strategies are needed. Trimodality bladder preservation protocols for muscle invasive bladder cancer have generally included only those patients who are candidates for a salvage cystectomy. In this review, we discuss the current status of bladder preservation treatment options for patients with muscle-invasive disease who are not candidates for cystectomy or who decline surgery and highlight the need for clinical trials investigating novel treatment approaches in this older patient population.

Keywords: bladder cancer, bladder preservation, cystectomy, octogenarians, radiation therapy, transitional cell carcinoma, urothelial carcinoma, transurethral resection of bladder tumor, TURBT

Introduction

Bladder cancer is a common malignancy in older adults with a median age of 68 years at diagnosis. An estimated 70,530 new cases and 14,680 deaths are estimated to have occurred in 2010 [American Cancer Society, 2010]. Approximately 70% of patients present with non-muscle-invasive disease (epithelium, Ta; lamina propria, T1; or carcinoma *in situ*, Tis) which is managed with complete transurethral resection of the bladder tumor (TURBT) with or without intravesical therapy [Kirkali *et al.* 2005]. Approximately 20–40% of patients will either present with more advanced disease or progress after treatment for superficial disease. Muscle-invasive bladder cancer is characterized by a distinct biology which includes the structural or functional loss of tumor suppressor genes such as *TP53*, *Rb* and *PTEN* resulting in more than 50% of cases progressing to the lethal phenotype of metastatic disease [Wu, 2005]. Low-grade noninvasive papillary tumors are characterized by mutations in the *HRAS* gene and fibroblast growth factor receptor 3 gene (*FGFR3*) indicating that receptor tyrosine kinase–Ras activation has an early role in bladder cancer tumorigenesis.

Subsequent chromosomal deletions (e.g. 8p-, 11p-, 13q-, 14q-) and/or loss of *TP53* and/or *Rb* have been implicated in the transformation of low-grade superficial disease to invasive and locally advanced disease.

Radical cystectomy with bilateral pelvic lymph node dissection is the gold standard for the management of muscle-invasive bladder cancer and is associated with recurrence-free survival rates at 5 and 10 years of 68% and 66%, respectively [Stein *et al.* 2001]. Lymph node involvement reduces the 5- and 10-year recurrence-free survival rates to 35% and 34%, respectively. In addition to removal of the bladder, radical cystectomy includes resection of the prostate and seminal vesicles in men and *en bloc* resection of the cervix, uterus, fallopian tubes, ovaries and anterior vaginal wall in women. Important surgical factors such as negative margins and the extent of pelvic lymph node dissection (≥ 10 lymph nodes removed) have been associated with an improvement in disease-free and overall survival [Herr *et al.* 2004]. Furthermore, neoadjuvant cisplatin-based chemotherapy prior to radical cystectomy has been shown in a large randomized clinical trial and a

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systematic review and meta-analysis of 11 randomized trials to improve overall survival in patients with muscle-invasive bladder cancer [Advanced Bladder Cancer Meta-analysis Collaboration, 2003; Grossman *et al.* 2003; International Collaboration of Trialists, 1999].

Bladder cancer is a disease of older patients with comorbidities including tobacco-associated lung disease, cardiac disease, renal insufficiency as well as others that may preclude major surgery. The management of muscle-invasive bladder cancer in the older patient is challenging with the need for alternative nonsurgical approaches as well as the development of clinical trials investigating novel management strategies in this patient population.

How to define the noncystectomy candidate

Currently, there is no established consensus on how to determine which patients are candidates for cystectomy. Factors often used to determine a patient’s suitability for surgery have included age, functional status, adequacy of social support and psychological state, nutritional status, cognitive status, and medical comorbidities such as cardio-pulmonary disease, diabetes, renal insufficiency, rheumatic disease as well as others (see Table 1). However, the relative weight of these individual factors in determining a patient’s suitability for surgery, and who should make this determination is not at all clear. In a retrospective review of 1142 patients undergoing radical cystectomy at a major cancer center between 1995 and 2005, the rates of major and minor complications as well as bladder-cancer-related deaths were not significantly different in octogenarians as compared with younger patients [Donat *et al.* 2010]. Furthermore, an analysis of 13,796 patients with a diagnosis of bladder cancer in the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) cancer registry between 1988 and 1999, demonstrated that, among patients 80 years or older, radical cystectomy or partial cystectomy had the greatest risk reduction in death from bladder cancer

[Hollenbeck *et al.* 2004]. However, this analysis also found that patients 80 and older were significantly less likely to receive extirpative surgery as compared with younger patients. Comprehensive geriatric assessment tools may aid in clinical decision making for such a heterogeneous patient population. In a prospective study of 84 patients >65 years of age with diffuse large cell lymphoma undergoing treatment at a single institution, a comprehensive geriatric assessment (CGA) tool incorporating age, functional status and number and severity of medical comorbidities classified patients as ‘fit’ or ‘unfit’ for aggressive (curative) chemotherapy [Tucci *et al.* 2009]. Patients were treated according to clinical judgment. All 42 (50%) patients who were classified as ‘fit’ received curative chemotherapy and had significantly better outcomes compared with the ‘unfit’ group. Twenty of the 42 patients classified as ‘unfit’ received curative chemotherapy and experienced similar outcomes compared to the 22 patients receiving palliative chemotherapy. A traditional CGA is often time consuming and a simplified CGA may further enhance clinical decision making in a timely manner. Recently, in a study of 419 patients >70 years of age with solid and hematologic malignancies, the Vulnerable Elders Survey – 13 (VES13), a simplified CGA consisting of a function-based scoring system incorporating age, self-rated health, physical limitations and functional disabilities, was highly predictive of functional status and may be a helpful screening tool prior to undertaking a full CGA [Luciani *et al.* 2010].

Although these reports suggest that many older patients may be considered for surgery, prospective trials that incorporate a multidisciplinary assessment of surgical candidacy and instruments such as a comprehensive geriatric assessment tool to evaluate longitudinal changes in function are most certainly needed.

Bladder preservation strategies

Advancements in the management of cancers such as larynx cancer and anal cancer have led to organ-preserving strategies utilizing chemotherapy and radiation and have been associated with outcomes equivalent to surgery [The Department of Veterans Affairs Laryngeal Cancer Study Group, 1991; Sischy *et al.* 1989]. Although bladder preservation strategies have often been perceived to result in inferior cancer-related outcomes as compared with radical cystectomy, a randomized trial to support this

Table 1. Potential factors to define the cystectomy candidate.

Age	Social Support
Medical (Cardiac, Pulmonary, Renal, Rheumatologic, etc)	Environmental
Nutrition	Economic
Functional (Physical)	Mood
Cognitive	

conclusion does not exist. Historically, bladder preservation protocols have investigated radical TURBT or partial cystectomy alone or in combination with chemotherapy, radiation therapy or concurrent chemoradiotherapy [Yafi *et al.* 2009]. Although no randomized trials have compared bladder-sparing treatment approaches with radical cystectomy, approximately 50% long-term disease-free survival is reported in appropriately selected patients receiving combined modality treatment [Fernando and Sandler, 2007]. A bladder preservation strategy is attractive for older patients with bladder cancer whose comorbidities may place them at greater risk for short- and long-term complications related to surgery; however, the majority of bladder-preservation protocols have included only those patients who are candidates for a salvage cystectomy. These trials have defined appropriate candidates for bladder preservation as those with solitary tumors with small tumor size (<5 cm) without surrounding carcinoma *in situ* (CIS), early tumor stage, a complete TURBT, absence of hydronephrosis and no evidence of pelvic lymph node metastases.

Radical transurethral resection alone

Radical transurethral resection (TUR) alone may represent a bladder-sparing option in patients with solitary tumors at the trigone, posterior, or lateral walls with focal invasion into muscularis propria and has been associated with long-term bladder intact survival of 60–70% in appropriately selected patients (see Table 2). In a retrospective series of 432 patients with muscle-invasive bladder cancer who were referred for definitive management, 151 had either no disease (T0) or T1 tumors after initial TUR. A total of

99 of the 151 patients with no residual invasive disease were followed with active surveillance, and 52 were managed with radical cystectomy. The 10-year cancer-specific survival was similar in these two groups and, furthermore, 57% of those managed with TUR alone survived with their bladders intact [Herr, 2001]. A prospective phase II study of 133 patients with muscle-invasive bladder cancer managed with radical TUR alone demonstrated a 79.5% overall survival and 64.9% bladder-intact survival at 10 years [Solsona *et al.* 2010]. The key inclusion criteria for this trial were no residual tumor (pT0) upon repeat biopsy of the tumor bed and absence of hydronephrosis. Furthermore, the majority of patients had primary unifocal disease without surrounding Tis. In a retrospective review of 327 patients with muscle invasive bladder cancer seen at a large cancer center between 1997 and 2002, only 35 (11%) were eligible for radical TUR and surveillance [Leibovici *et al.* 2007]. Patients with no residual tumor on repeat biopsy of the tumor bed, normal bimanual exam under anesthesia and upper urinary tract findings and no urethral involvement were offered this bladder preserving approach. Of the 27 patients who elected this approach, 15 developed subsequent tumor recurrence and 8 required radical cystectomy. Radical TURBT alone for palliation may represent an option for frail patients who would otherwise not tolerate further treatment.

Partial cystectomy alone

Partial cystectomy, while not necessarily avoiding the perioperative risks associated with radical cystectomy, does preserve urinary and sexual function in selected patients and may avoid

Table 2. Select radical transurethral resection of the bladder tumor studies.

Study	Number of patients	Stage	Inclusion criteria	10-year bladder-intact survival (%)	10-year overall survival (%)
Herr [1987]	45 of 217	T2	<T1 or localized T2 on restaging TUR	67	82 (5.1 years median follow up)
Herr [2001]	99 of 151	T2	T0 or T1 on restaging TUR	57	76
Leibovici <i>et al.</i> [2007]	27 of 327	T2	T0 on restaging TUR, normal EUA and upper urinary tracts	70	81 (2.45 years median follow up)
Solsona <i>et al.</i> [2010]	133	T2	Complete macroscopic resection, Negative biopsies of the depth and tumor periphery, no hydronephrosis	64.9	79.5 (disease specific)
TUR, transurethral resection; EUA, examination under anesthesia.					

long-term morbidity associated with radical cystectomy. Candidates for a partial cystectomy should have solitary tumors with focal muscularis propria invasion located anteriorly or in the bladder dome amenable to removal of a 2 cm margin [Sweeney *et al.* 1992]. A retrospective review of 58 patients undergoing partial cystectomy at a large cancer center demonstrated that an increased risk of local recurrence was associated with the presence of CIS and multifocal disease and an increased risk of advanced recurrence was associated with positive surgical margins and lymph node metastasis [Holzbeierlein *et al.* 2004]. Another retrospective analysis of 25 highly selected patients undergoing partial cystectomy for primary solitary muscle-invasive tumors demonstrated that tumor size at the time of partial cystectomy was significantly associated with the risk of tumor recurrence [Smaldone *et al.* 2008]. In this analysis, all patients underwent preoperative localized radiotherapy, instillation of a single dose of intravesical chemotherapy at the time of surgery, and postoperative bacillus Calmette–Guérin (BCG) therapy. In highly selected patients, partial cystectomy is associated with long-term bladder-intact survival rates of 50–75% [Capitanio *et al.* 2009; Smaldone *et al.* 2008; Kassouf *et al.* 2006; Holzbeierlein *et al.* 2004]. However, a review of the literature indicates that only 5–10% of patients with muscle-invasive bladder cancer are ultimately eligible for this procedure [Holzbeierlein *et al.* 2004; Dandekar *et al.* 1995; Kaneti, 1986; Brannan *et al.* 1978].

Chemotherapy plus radical TUR or partial cystectomy

Neoadjuvant cisplatin-based chemotherapy prior to cystectomy has been demonstrated to improve survival in patients with muscle-invasive bladder cancer. Selected patients who upon completion of neoadjuvant chemotherapy achieve a complete response on restaging TURBT may defer radical cystectomy and be candidates for bladder-preservation strategies. In a prospective study of 104 patients with muscle-invasive bladder cancer, three cycles of neoadjuvant M-VAC chemotherapy (methotrexate, vinblastine, doxorubicin, and cisplatin) were administered followed by TURBT alone (52 patients), partial cystectomy (3 patients) and cystectomy (39 patients) based on the degree of response to chemotherapy [Sternberg *et al.* 2003]. A total of 29 of 52 patients in the TURBT alone group achieved either a complete response (pT0) or had only

superficial disease (pTa, T1 or CIS). In the TURBT alone group, 44% of patients achieved long-term bladder-intact survival and 67% estimated 5-year overall survival. In a study of 111 cystectomy candidates with T2–T3 invasive bladder cancer receiving neoadjuvant M-VAC chemotherapy, 60 patients achieved a complete response (T0) on restaging TURBT. A total of 43 patients elected for bladder-sparing surgery and 17 patients underwent radical cystectomy. At 10 years, 74% of the patients who selected bladder-sparing surgery were alive and 65% were alive after undergoing a radical cystectomy. In the bladder-sparing group, 58% had intact functioning bladders [Herr *et al.* 1998]. However, a restaging TURBT has limitations in evaluating the extent of disease in the bladder. In the Southwest Oncology Group Trial S0219, 77 patients with T2–T4a bladder cancer were given three cycles of paclitaxel, carboplatin, and gemcitabine, followed by restaging TURBT [de Vere White *et al.* 2009]: 46% of 74 evaluable patients achieved a complete response on restaging TURBT. Of those patients, 10 underwent immediate cystectomy, of whom six patients had persistent tumor in the cystectomy specimen with the authors concluding that patients completing chemotherapy should strongly consider definitive local therapy rather than surveillance regardless of the postchemotherapy cT0 status. Although this trial underscores the importance of cystectomy, the trial did not use a cisplatin-based combination chemotherapy regimen which may have led to an inferior pathological response rate.

Radiation therapy alone

External beam radiation therapy has been widely used as a bladder-sparing strategy in patients who are otherwise not candidates for cystectomy. However, outcomes appear clearly inferior to surgery with 5-year overall survival rates of 20–40% and local control rates of 50% [Pollack and Zagars, 1996; De Neve *et al.* 1995; Mameghan *et al.* 1995; Jenkins *et al.* 1988]. In the 1970s, preoperative radiation therapy was investigated and appeared to provide a benefit as demonstrated by pathological downstaging in a subset of patients with muscle-invasive bladder cancer [Shipley *et al.* 1982; Whitmore *et al.* 1977]. However, subsequent randomized trials demonstrated no benefit in overall survival when compared with radical surgery alone and the use of preoperative radiation complicated the construction of urinary diversions [Cole *et al.* 1995;

Sell *et al.* 1991]. More recently, the synergistic effects of concurrent chemotherapy and radiation has allowed for the reemergence of radiation therapy as a useful tool in the treatment of muscle invasive bladder cancer.

Trimodality therapy for bladder preservation

Trimodality therapy incorporating chemotherapy and concurrent radiation therapy following a complete TURBT has been investigated as a strategy to improve outcome in appropriately selected individuals. A number of chemotherapeutic agents have demonstrated radiosensitizing effects including 5-fluorouracil, cisplatin, gemcitabine, paclitaxel and, more recently, cetuximab. Many mechanisms have been proposed to explain the augmented effects of chemotherapy on radiation. Cisplatin, the most commonly used radiosensitizing agent in bladder cancer, may synergize with radiation by interfering with cellular DNA repair after sublethal radiation damage [Coughlin and Richmond, 1989]. The trimodality approach consists of extensive TURBT followed by radiation (40–45 Gy to the pelvis) with concurrent radiosensitizing chemotherapy and an additional radiation boost to the bladder (20–25 Gy) if a complete response is documented on repeat biopsy [Shipley *et al.* 2002, 1998; Coppin *et al.* 1996] (see Table 3). This approach leverages the synergism of chemotherapy and radiation while incorporating an extensive TURBT to allow for maximal focused radiation to the smallest tumor volume with the added potential for eradication of micrometastatic disease using systemic chemotherapy. A maximal TURBT remains a critical component for any successful bladder-preservation strategy and in one multivariable analysis was the only independent prognostic factor for long-term survival [Rodel *et al.* 2002]. Thus, optimal candidates for multimodality therapy are similar to those for radical TURBT and partial cystectomy. Patient selection criteria for a bladder sparing approach should include stage, histology, extent of the primary lesion, hydronephrosis, a palpable mass, the presence or absence of multifocal urothelial cancer or CIS, and the presence of disease outside the bladder that would preclude organ preservation [Rodel *et al.* 2002].

Although the optimal trimodality bladder sparing regimen has not yet been defined, trimodality therapy has been demonstrated to be superior to radiation alone [James *et al.* 2010; Coppin *et al.* 1996]. A recently reported randomized phase III trial from the United Kingdom assigned

patients to radiotherapy alone or chemoradiotherapy with mitomycin plus 5-fluorouracil [James *et al.* 2010]. In this study 360 patients with muscle-invasive bladder cancer were randomized in a 2×2 factorial design to either chemoradiation *versus* radiation alone and standard volume radiation (given as 55 Gy over 20 fractions or 64 Gy over 32 fractions) *versus* reduced high-dose volume radiation to the tumor bed with local–regional disease-free survival (LRDFS) as the primary endpoint. At a median follow up of 40 months, 2-year LRDFS was 67% for chemoradiation and 54% for radiation alone ($p = 0.02$), however there was no significant difference in overall survival. The most active and widely investigated chemotherapeutic agent in bladder cancer is cisplatin and as a result, the majority of trimodality therapy trials in bladder cancer have incorporated concurrent cisplatin with radiation with complete response rates in the 59–75% range, and 5-year survival of approximately 50% [Fernando and Sandler, 2007]. Most of the initial trials investigating trimodality therapy incorporated some form of induction chemotherapy. The approach typically consisted of an extensive TURBT, followed by two cycles of cisplatin-based combination chemotherapy (i.e. M-VAC or CMV [cisplatin, methotrexate, and vinblastine]) and then concurrent pelvic radiation with single-agent cisplatin [Kachnic *et al.* 1997]. The need for induction chemotherapy for successful bladder conservation was directly tested in RTOG trial 89-03. In this trial 123 patients with T2–T4aNx urothelial cancer were randomized to neoadjuvant CMV followed by concurrent RT and cisplatin or concurrent RT and cisplatin alone [Shipley *et al.* 1998]. At a median follow up of 5 years, there were no differences in either overall survival (49% in each group) or survival with an intact bladder (36% *versus* 40%) for induction chemotherapy and chemoradiotherapy alone, respectively. The authors concluded that induction chemotherapy with CMV was not an essential requirement for effective bladder-preservation therapy. The MRC/EORTC trial randomized 975 patients to receive three cycles of CMV chemotherapy or no chemotherapy prior to cystectomy, radiation therapy or pre-operative radiation therapy and cystectomy [Hall, 1996]. In an updated analysis at a median follow up of 4 and 7 years, subset analysis demonstrated no significant difference in overall survival in patients who received neoadjuvant CMV chemotherapy prior to radiation compared with patients who

Table 3. Select trimodality bladder-sparing trials.

Study	Number of patients	Clinical stage	Induction treatment	Primary CRT treatment	Complete response pCR [%]	Consolidation CRT for complete responders	5-year overall survival [%]	5-year overall survival with bladder [%]
Kachnic <i>et al.</i> [1997]	106	T2–T4a	TURBT, 2 cycles MCV	39.6 Gy + cisplatin	66	25.2 Gy + cisplatin	52	43
RTOG 85-12 [Tester <i>et al.</i> 1993]	42	T2–T4a	TURBT	40 Gy + cisplatin	66	24 Gy + cisplatin	52	42
RTOG 88-02 [Tester <i>et al.</i> 1996]	91	T2–T4a	TURBT, 2 cycles MCV	39.6 Gy + cisplatin	75	25.2 Gy + cisplatin	62 (median follow-up 4 years)	44 (4 years)
Housset <i>et al.</i> [1997]	120	T2-4	TURBT	24 Gy + cisplatin and 5-FU	77	20 Gy + cisplatin and 5-FU	63	NR
RTOG 89-03 [Shipley <i>et al.</i> 1998]	123	T2–T4a	TURBT, 2 cycles MCV vs. no chemotherapy	39.6 Gy + cisplatin	61 vs. 55	25.2 Gy + cisplatin	49 vs. 48	36 vs. 40
Zietman <i>et al.</i> [1998]	18	T2–T4a	TURBT	42.5 Gy bid fx + 5-FU and cisplatin	78	22.5 Gy bid fx + 5-FU and cisplatin, 3 cycles adjuvant MCV	83 (3 years)	78 (3 years)
RTOG 95-06 [Kaufman <i>et al.</i> 2000]	34	T2–T4a	TURBT	24 Gy bid fx plus 5-FU and cisplatin	67	20 Gy bid fx + FU and cisplatin	83 (3 years)	66 (3 years)
Rodel <i>et al.</i> [2002]	415	T1–T4	TURBT	50.4-59.4 Gy ± carboplatin/cisplatin ± 5-FU	72	–	50	42
RTOG 97-06 [Hagan <i>et al.</i> 2003]	47	T2–T4a	TURBT	40.8 Gy bid fx plus cisplatin	74	24 Gy bid fx + cisplatin, 3 cycles adjuvant MCV	61 (3 years)	48 (3 years)
James <i>et al.</i> [2010]	360	T2–T4a	TURBT, ± induction chemotherapy	55 Gy or 64 Gy plus mitomycin-C + 5-FU vs. RT alone	NR	–	67 vs. 54 2-year LRDFS	NR
RTOG 99-06 [Kaufman <i>et al.</i> 2009]	80	T2–T4a	TURBT	40.3 Gy bid fx + taxol and cisplatin	81	24 Gy BID fx + taxol and cisplatin, 4 cycles adjuvant gemcitabine and cisplatin	56 (actuarial)	NR

CRT, chemoradiation treatment; TURBT, transurethral resection of bladder tumor; MCV, methotrexate, cisplatin, and vinblastine; 5-FU, 5-fluorouracil; bid, twice daily; fx, fraction; pCR, pathologic complete response; NR, not reported; LRDFS, local–regional disease-free survival; RT, radiotherapy.

underwent radiation alone [Hall, 2002; International Collaboration of Trialists, 1999].

Successful bladder-sparing strategies will ultimately hinge on the development of new drug combinations and radiation techniques as well as the development of targeted therapies based on a growing knowledge of bladder cancer pathogenesis. More aggressive trimodality therapies combining additional agents with cisplatin and those utilizing hyperfractionated radiotherapy have been associated with higher responses [Kaufman *et al.* 2009; Danesi *et al.* 2004; Varveris *et al.* 1997; Cole *et al.* 1992]. RTOG 99-06 investigated twice daily (hyperfractionated) irradiation and concomitant cisplatin and paclitaxel followed by four cycles of adjuvant gemcitabine and cisplatin. A total of 81% of patients achieved a complete response following induction chemoradiotherapy and, in a preliminary report, the 2-year survival with an intact bladder was 69% [Kaufman *et al.* 2008]. At a median follow up of 49 months, 5-year actuarial overall survival and disease-specific survival were 56% and 71%, respectively [Kaufman *et al.* 2009].

Cisplatin, while it remains the most active drug in the treatment of bladder cancer, is associated with significant toxicities such as nausea and vomiting, myelosuppression, nephrotoxicity, neurotoxicity, ototoxicity as well as others. Older patients who are not candidates for cystectomy may similarly not be candidates for cisplatin-based trimodality therapy due to coexistent medical illnesses such as renal insufficiency and cardiovascular disease. There is a growing interest in the development of non-cisplatin based radiosensitizers for invasive bladder cancer. Gemcitabine, when used as a single agent, has minimal toxicity and may be a suitable alternative in non-cisplatin candidates [Lichtman and Boparai, 2008]. A phase I study evaluating trimodality therapy with gemcitabine with concurrent radiation demonstrated a high rate of bladder preservation and was well tolerated but was associated with late local failures [Oh *et al.* 2009; Kent *et al.* 2004]. At 5 years, 62% survived with an intact bladder with overall and disease-specific survival rates of 76% and 82%, respectively. Importantly, there was no statistically significant difference in quality-of-life measurements before, during or following therapy in patients other than those who received higher gemcitabine doses [Herman *et al.* 2004].

Current studies are now focused on identifying driver genetic alterations that predict both response and resistance to novel agents to allow for patient-specific therapy and ultimately improve outcomes. A recent RTOG study demonstrated that HER2 expression correlated with inferior tumor responses, and epidermal growth factor expression was associated with improved disease-free and overall survival [Chakravarti *et al.* 2005]. The RTOG 0524 trial is currently evaluating concurrent paclitaxel with daily radiation and trastuzumab in patients with Her2/Neu overexpressing muscle-invasive bladder cancer who are not candidates for cystectomy.

Furthermore, improvements in radiation delivery including intensity modulated radiation and image-guided techniques may allow for optimal delivery of higher doses of radiation to tumor tissue with minimal exposure to adjacent normal tissue thereby reducing toxicity and increasing efficacy. Targeted delivery of chemotherapy to tumor tissue may also lead to less toxicity and enhanced effectiveness. A recently reported trial in elderly patients comparing cystectomy with a novel bladder-preservation approach investigating the use of balloon-occluded intra-arterial infusion of gemcitabine and cisplatin with concomitant hemodialysis and concurrent radiation therapy demonstrated an 89% complete remission rate and 91% 5-year overall survival rate [Azuma *et al.* 2011].

Conclusion

An important first step in the development of effective treatment strategies for muscle-invasive bladder cancer in the noncystectomy candidate is to develop a consensus definition for the noncystectomy candidate. The incorporation of comprehensive geriatric assessment tools that include assessments of functional status, cognition and medical comorbidities that ultimately lead to a better understanding of competing risks will help to better define the surgical candidate. Furthermore, while established bladder-sparing approaches are appropriate for selected noncystectomy candidates (see Figure 1) prospective clinical trials evaluating similar approaches in noncystectomy candidates are needed including those evaluating novel radiation techniques and the utilization of alternative non-cisplatin radiosensitizing agents. Novel agents targeting driver genetic alterations that are currently under investigation in advanced bladder cancer patients should be evaluated in the initial management

Figure 1. Options for the management of invasive bladder cancer in patients who are not candidates for cystectomy.

of patients with muscle-invasive disease including those patients who are not candidates for radical cystectomy.

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None declared.

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