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REVIEW

Bladder preservation in the treatment of muscle-invasive bladder cancer

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ABSTRACT

Organ preserving strategies are being increasingly utilized in the treatment of solid malignancies with the intent of reducing surgical morbidity and maintaining quality of life. Organ preservation becomes a viable approach only when cancer outcomes are not compromised when compared to radical resection. We reviewed the current literature on bladder preservation for muscle-invasive bladder cancer, focusing on trimodality therapy consisting of complete transurethral resection, radiation therapy, and chemotherapy. Acknowledging the absence of randomized clinical trials, differences in patient selection, and variation in study protocols, trimodality therapy may yield similar 5- and 10-year overall survival rates compared to radical cystectomy alone. This includes the approximately 30% of patients who enter a bladder preservation protocol and undergo salvage radical cystectomy for failure of local control. Currently, bladder preservation appears to be an alternative to radical cystectomy in select patients who have appropriate rigorous surveillance.

Keywords: bladder cancer, trimodality therapy, bladder preservation

INTRODUCTION

Bladder cancer was diagnosed in nearly 71,000 people in the United States and led to approximately 14,000 deaths in 2013 [1]. The incidence of bladder cancer rises with age and affects men three times more often than women. The majority of bladder cancer is of urothelial cell histology. Treatment for non-muscle-invasive disease (Ta, T1, and carcinoma-in-situ (CIS)) is complete transurethral resection followed by adjuvant intravesical administration of Bacillus Calmette-Guérin (BCG) in patients with high-grade disease. For recurrent CIS and high-grade T1, poor pathologic features, or muscle-invasive disease, the standard of care treatment is radical cystectomy with pelvic lymphadenectomy.

Strategies for bladder preservation include limited surgical resection, radiation, and/or chemotherapy. Individually, each modality has been considered inferior to radical cystectomy. Over the last 20 years, the use of combined therapy with transurethral resection of bladder tumor (TURBT), external beam radiation, and chemotherapy for bladder preservation has been investigated. In this article, we review the current state of bladder preservation therapy for muscle-invasive bladder cancer.

The gold standard: radical cystectomy

The long-term outcomes following radical cystectomy have been reported in several large series, with survival and recurrence free outcomes correlating with T stage, extent of nodal disease, and metastases. The University of Southern California experience is one of the largest historical series, including 1054 patients who underwent radical cystectomy for urothelial cell carcinoma during a 26 year period [2]. Recurrence free survival for the entire cohort at 5 and 10 years was 68% and 66% respectively, while overall survival at 5 and 10 years was 60% and 43% respectively. For organ confined (≤ pT3a) node negative bladder cancers, the 5- and 10-year overall survival was 78% and 56% compared to 45% and 37% with lymph node involvement. With locally advanced extravesical disease (pT3b, pT4), 5- and 10-year overall survival dropped to 47% and 27% in node negative and 25% and 17% in node positive tumors. Although bladder cancer recurred in 30% of patients at a median of 12 months, local control was achieved in the majority of patients with an overall pelvic recurrence rate of 9%. Similar survival results have been reported in other large contemporary retrospective cystectomy series (**Table 1**) [2-7]. The 5- and 10-year recurrence free survival rates in these studies have been between 58% to 68% and 50% to 66%, respectively. Overall survival at 5 and 10 years has been reported to be between 45% to 60% and 37% to 45%, respectively. In recent years, the addition of platinum-based neoadjuvant chemotherapy has shown to increase overall 5-year survival by 5% based on the meta-analysis of 11 randomized controlled clinical trials [8]. Maturation of this data may show improved long-term survival of patients undergoing radical cystectomy.

Bladder preservation

Monotherapy and dual combined therapy

Radiation therapy and limited surgical resection have been explored

as alternatives to radical cystectomy. Bladder preservation with monotherapy has yielded inferior rates of local control. The 5-year overall survival in radiation therapy series ranges from approximately 25% to 45% [9-13]. Nearly half of these patients require radical cystectomy or further treatment for either residual disease or local relapse in the bladder. The addition of chemotherapy to radiation has been shown to improve response rates and decrease local recurrence [14]. A study from Princess Margaret Hospital reported outcomes with radiotherapy either alone, with concurrent chemotherapy, or with neoadjuvant chemotherapy from 1986 to 1997 [15]. The majority of these patients (73%) underwent radiotherapy alone. The 5- and 10-year overall survival was 32% and 19%, and the relapse free rate was 34% and 32%, respectively. In a subgroup analysis, they identified a favorable cohort of 131 patients who were stage T2 and node negative. The 5-year overall survival for this group was 44% with a local relapse free rate of 49%. Even in this favorable group of patients, the local control and overall survival rates were inferior to those provided by radical cystectomy.

Table 1. Results from contemporary cystectomy series.

Author	No. patients	Pathological stage (%)	% 5 year overall survival	% 10 year overall survival
Stein 2001 [2]	1054	T0,Ta,Tis: 20.2 T1: 19.7 T2: 10.9 T3a: 12.6 T3b: 23.5 T4a: 13.0 N+: 23.0	60.0	43.0
Dalbagni 2001 [3]	300	T0: 10.7 Ta: 2.7 Tis: 12.0 T1: 6.3 T2a: 6.0 T2b: 13.0 T3a: 12.0 T3b: 24.7 T4a: 11.0 T4b: 1.7 N+: 13.0	45.0	-
Madersbacher 2003 [4]	507	Ta, Tis: 3.0 T1: 15.0 T2: 30.0 T3: 36.0 T4: 16.0 N+: 24.0	59.0	37.0
Manoharan 2009 [7]	432	T0: 14.0 Tis: 13.0 Ta: 2.5 T1: 7.0 T2: 24.0 T3: 30.0 T4: 9.5 N+: 21.0	58.0	43.0
Hautmann 2012 [5]	1100	Ta, Tis, T1: 25.8 T2: 36.6 T3: 14.3 T4: 5.1 N+: 18.2	58.0	44.0

Limited surgical resection with either TURBT or partial cystectomy has also been utilized to preserve the bladder. Classic indications for partial cystectomy include a solitary tumor that is located either at the bladder dome or anteriorly, the ability to obtain adequate margins, and the lack of CIS. Effective bladder preservation can be obtained with this technique, however, only a minority of patients presenting with bladder cancer are candidates for partial cystectomy [16-18]. Treatment of muscle-invasive bladder cancer with TURBT alone leads to overall survival rates of approximately 50%. Two large series have reported similar results at 10 years of follow up after radical TURBT in selected patients who do not have evidence of invasive disease on restaging TURBT. Solsona reported disease specific survival and bladder preservation rates of 74.5% and 79.6% respectively at 10 years [19]. Herr reported a 10-year disease specific survival and bladder preservation rates of 76% and 57% [20]. Despite these favorable outcomes, both authors reported a high rate of recurrence and progression, 28% and 34%, respectively. Of patients who recurred, only 29% and 43% of patients were able to be successfully salvaged with radical cystectomy,

respectively. Similar to radiation, chemotherapy has also been combined with TURBT and partial cystectomy. Solsona compared TURBT and chemotherapy with radical cystectomy in a Phase II trial [21]. The 5- and 10-year disease specific survival and overall survival with an intact bladder were 64.5% and 59.8%, and 52.6% and 34.5%, respectively. There were no significant differences in overall survival in the TURBT and chemotherapy arm compared to the radical cystectomy arm. Initial complete response was found to be the only variable that was predictive of survival and bladder preservation. Not surprisingly, local control was poor in the bladder preservation arm, as 56% of patients who achieved a clinical response developed a recurrence or progression, 72% required additional therapy, and 42% required radical cystectomy. Taken together, these results suggest that a select group of patients may be successfully treated using bladder preservation; however, additional salvage therapies may be necessary and strict surveillance is mandatory due to the high rate of local relapse.

Table 2. Results of phase III studies of trimodality treatment.

Author	No. Patients	Pathological stage (%)	Treatment (TURBT+)	Complete TURBT (%)	% 5 year overall Survival
James 2012 [23]	182	T2: 84.6 T3a: 5.5 T3b: 6.0 T4a: 3.8	RCT (5-FU, MMC)	56.6	48.0
Tunio 2012 [24]	200	T2: 45.6 T3: 50.0 T4: 4.3	RCT (cisplatin)	76.5	52.0
Shipley 1998 [25]	123	T2: 38.5 T3-T4a: 61.5	+/-Neoadjuvant MCV RCT (cisplatin)	69.0	49.0
Housset 1993 [26]	54	T2: 32.0 T3: 41.0 T4: 27.0	RCT (cisplatin/5-FU)	50.0	59.0 (3yr)

RCT, radiochemotherapy; 5-FU, 5-fluorouracil; MMC, mitomycin C; MCV, methotrexate, cisplatin, vinblastine

Table 3. Results of large retrospective bladder preservation studies.

Author	No. patients	Pathological stage (%)	Radiation therapy alone (%)	Complete TURBT (%)	% 5 year overall survival	% 10 year overall survival
Efstathiou 2012 [27]	348	T2: 54.0 T3: 37.9 T4: 8.1	-	65.2	52.0	35.0
Krause 2011 [30]	473	T1: 23.3 T2/3: 69.3 T4: 7.2 N+: 6.1	30.0	30.0	49.0	30.0
Chung 2007 [15]	340	T1: 10.6 T2a: 25.6 T2b: 19.1 T3b: 25.6 T4a: 7.1 T4b: 12.0 N+: 13.0	72.6	-	19.0	-

Trimodality therapy

The high rates of local recurrence with monotherapy and dual combined therapy have prompted combination of all three modalities. The general approach (**Fig. 1**) involves an initial extensive TURBT to achieve a complete resection. A complete resection is not always possible, and incomplete resection is associated with decreased disease-free survival [22]. This is then followed by a phase of radiation and chemotherapy (induction therapy). Surveillance cystoscopy and biopsy are then performed to assess for clinical response. Complete responders continue with radiation and chemotherapy (consolidation therapy) while non-responders are recommended to undergo immediate radical cystectomy. Cystoscopy and biopsy are again performed after consolidation therapy, and patients with an incomplete response are recommended to undergo radical cystectomy, while patients with a complete response may proceed with adjuvant chemotherapy. In patients who are cystectomy candidates, a key principle of trimodality therapy is that recurrence or failure to respond to radiation and chemotherapy should result in discontinuation of bladder preservation efforts and salvage radical cystectomy should then be performed. Patients who are not cystectomy candidates may not require surveillance cystoscopy performed between induction and

consolidation therapy phases.

In 2012, a multicenter trial in the United Kingdom compared outcomes of patients randomized to trimodality therapy or TURBT followed by radiation therapy alone [23]. Three hundred and sixty patients were randomized to these treatment groups, and the primary outcome was disease free survival at 2 years. The chemoradiation group received fluorouracil on days 1-5 and 16-20 as well as mitomycin on day 1. This study demonstrated that 2-year disease free survival in patients randomized to chemoradiation after TURBT was significantly better than those randomized to receive radiation therapy alone (67% versus 54%, respectively). At 5 years, the disease free survival rates were 48% in the chemoradiation group and 35% in the radiation therapy group; however, these results were not statistically significant. In addition there was a trend towards less salvage radical cystectomy in the chemoradiation group (11.4%) compared to the radiation therapy group (16.8%). Other prospective phase III studies have demonstrated similar results with 5-year overall survival rates of 49% and 52% as well as a 3-year overall survival rate of 59% (**Table 2**) [23-26].

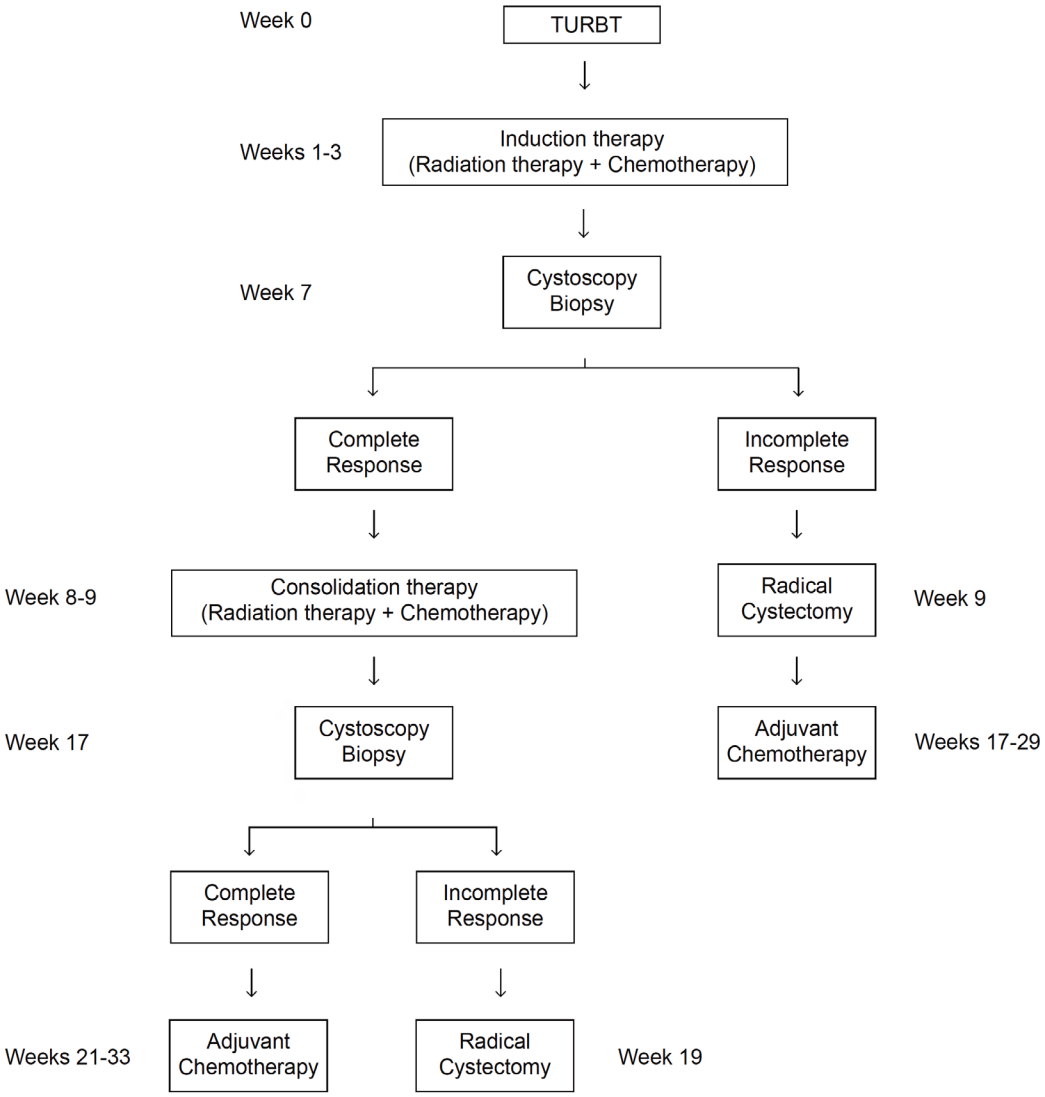

Figure 1. Sample trimodality therapy protocol [37].

The majority of single center trials in the United States have been undertaken at the Massachusetts General Hospital (MGH). Between 1986 and 2006, 348 patients stages T2-T4a were enrolled in various bladder preservation protocols [27]. The overall 5-, 10-, and 15-year survival rates were 52%, 35%, and 22%, respectively. Survival with an intact bladder at 5 and 10 years was 64% and 59%. Multivariate analysis demonstrated that initial complete response as well as clinical T stage were significantly associated with survival outcomes. Overall survival at 5, 10, and 15 years for T2 tumors was 74%, 67%, and 63%, and for T3-T4a tumors overall survival was 41%, 27%, and 16%. Of the complete responders, 29% had a non-invasive recurrence and 16% had an invasive recurrence. Of the 348 patients, 29% of patients (17% incomplete initial responses, 12% recurrences) ultimately underwent radical cystectomy. The 10-year disease specific survival for patients undergoing radical cystectomy was 44%.

In 2002, Rödel published the results of 18 years of bladder preservation therapy at the University of Erlangen in Germany [28]. Four hundred and fifteen patients over an 18 year period were evaluated.

Initially, their bladder preservation protocol included radiation therapy alone after TURBT, but beginning in 1985 chemotherapy with either cisplatin, carboplatin, or cisplatin with 5-FU was incorporated. The overall 5- and 10-year survival for this cohort was 51% (T1 75%, T2 56%, T3 44%, T4 17%) and 31% (T1 51%, T2 32%, T3 26%, T4 9%), respectively. Original stage and completeness of TURBT were significantly associated with clinical response rates and overall survival. Among the 288 initial complete responders, 35% of patients experienced a local recurrence and 11% were muscle-invasive tumors. Only multifocality of primary disease was an independent predictor of relapse. Overall, 83 of 415 (20%) patients underwent radical cystectomy with 5- and 10-year disease specific survival of 50% and 45%. These numbers dropped to 21% and 18% for non-responding patients who were treated with immediate radical cystectomy. In patients undergoing TURBT with cisplatin and 5-FU based chemotherapy and radiation, a 5-year overall survival rate of 74%, with 82% of surviving patients maintaining their bladder was observed [29]. These improved outcomes may be secondary to the choice of chemotherapy, but may also be due to stricter selection criteria for those entering the trial. In 2007, the University of Erlangen outcomes were updated with 15-year follow up data, and they demonstrated that overall survival rates were 49%, 30%, and 19% at 5, 10 and 15 years, respectively [30]. Other large retrospective studies of trimodality therapy have reported 5-year overall survival rates similar to Erlangen (**Table 3**) [15,27,30].

Based on the results from single center studies, the Radiation Therapy Oncology Group (RTOG) has engineered several clinical trials to test the efficacy of trimodality therapy in patients with T2-T4 and N0-NX pathological stages, with the exception of RTOG 8802 and 8512 which included patients with lymph node involvement (**Table 4**). In the first RTOG study, RTOG 8512, patients with T2-T4 bladder cancer were treated with TURBT followed by cisplatin and daily radiation for 4 weeks [31]. The 5-year overall survival was 52%, and 42% of patients survived with an intact bladder. RTOG 8802 and 8903 evaluated the role of neoadjuvant methotrexate, cisplatin and vinblastine (MCV) prior to cisplatin based radiotherapy [32,33]. The 5-year overall survival and survival with an intact bladder were 49% and 38% for patients in both arms. There was no difference between patients receiving neoadjuvant MCV and those who did not. Of note, patients undergoing MCV treatment experienced a high rate of systemic toxicity prompting premature closure of the trial. The subsequent RTOG trials 9506, 9706, and 9906 incorporated various chemotherapy regimens and radiation fractionation schemes in combination with TURBT in adjuvant and neoadjuvant settings in attempts to find the most efficacious and least toxic combination. The RTOG 9506 protocol tested an accelerated hypofractionated radiation scheme in combination with cisplatin and 5-FU. Protocols 9706 and 9906 evaluated a hyperfractionated radiation scheme with either adjuvant MCV (9706) or with cisplatin/paclitaxel radiochemotherapy combined with adjuvant cisplatin and gemcitabine (9906). The overall 3-5 year survival in these trials is reported between 56% to 83% [34-36]. The local recurrence rate reported in all the aforementioned RTOG trials is between 18% and 50%. The majority of these recurrences were treated successfully with TURBT and intravesical chemotherapy with 5- and 10-year survival rates with an intact bladder ranging from 38% to 66%. More recently a multicenter phase II trial, RTOG 0233, examined trimodality therapy with cisplatin combined with either paclitaxel or fluorouracil [37]. Complete response was seen in 72% of patients in the paclitaxel group and 62% of patients in the fluorouracil group, and bladder-intact survival at 5 years was 67% and 71% respectively. Overall treatment completion rates (completion of induction, consolidation, and adjuvant chemotherapy) were 67% in the paclitaxel group and 53% in the fluorouracil group. Of note, the majority of these patients had T2 tumors and good performance status, and they excluded patients that were not acceptable surgery candidates. Despite these various trials, it remains unclear as to which radiation scheme and chemotherapy regimen is superior.

Toxicity

When embarking upon bladder preservation protocols, acute and long term toxicities must be considered. The RTOG 8903 trial was stopped short of its projected accrual due to significant MCV toxicity which included 3 treatment related deaths [25]. In the subsequent RTOG 9506, 21% of patients developed grade 3 and 4 hematologic toxicity [34]. In RTOG 9706, 11% of patients experienced grade 3 and 4 toxicity during induction and 35% had grade 3 toxicity when taking adjuvant chemotherapy [35]. The RTOG 0233 trial demonstrated that paclitaxel was associated with grade 3-4 toxicity in 35% of patients during induction, 24% of patients during consolidation, and 85% of patients during adjuvant chemotherapy [37]. Fluorouracil was associated with grade 3-4 toxicity in 19% of patients during induction, 26% of patients during consolidation, and 76% of patients during adjuvant chemotherapy. The Erlangen group has reported lower rates of toxicity. In their review of 415 patients, 3-13% experienced grade 3 toxicity, 0-3% had grade 4 toxicity, and there was 1 treatment related death [29]. Efstathiou reported late grade 3+ pelvic toxicity occurring more than 6 months after chemoradiation in patients enrolled in various RTOG protocols (RTOG 8903, 9506, 9706, 9906) to be 7% [38]. There were no late grade 4 toxicities or treatment related deaths. Grade 3 toxicity only persisted in 1 patient; however, these results demonstrate that there are potential delayed side effects associated with bladder preservation. Late grade 3-4 toxicities in the RTOG 0233 study occurred in 11% of patients receiving paclitaxel and 6% of patients receiving fluorouracil, most of which were also related to bladder preservation (hematuria or contracted bladder) [37]. Late toxicities of the other RTOG studies are summarized in **Table 4**. On the other hand, the perioperative mortality and complication rate for radical cystectomy have been reported to be between 2-5% and 25-30% respectively [2,4,5,7]. The potential the additive morbidity associated with salvage cystectomy should be taken into account when pursuing bladder preservation therapy as well.

Quality of life

An assumed benefit of bladder preservation is improved quality of life by maintaining ones own bladder. To our knowledge, there are no prospective studies that have compared quality of life after bladder preservation to radical cystectomy. Wright recently reported on the difficulty of assessing bladder cancer quality of life outcomes due to limitations in study design and the use of varied and non-validated questionnaires [39]. Despite these limitations, patients who undergo radical cystectomy tend to report a good overall quality of life [40-43]. Henningsohn reported that quality of life in patients undergoing radical cystectomy with orthotopic neobladder was not significantly different from age matched controls [44]. Approximately 94% of patients following radical cystectomy reported erectile dysfunction compared to 48% of controls. Sexual dysfunction was also reported in a majority of patients who underwent radical cystectomy in a recent survey by

the French Association of Urology. In addition, they also reported that nearly 83% of patients with a neobladder experienced nighttime incontinence, with 32% reporting that it interfered with sleep. Despite these symptoms, 93% of patients were satisfied with their diversion, suggesting that patients eventually adapt and adjust to their situation. Zietman reported quality of life and urodynamic outcomes of 32 long term survivors of trimodality therapy from MGH [45]. A majority of patients (24/32) had normal bladders based on urodynamics. Patients complained of flow symptoms (6%), urgency (15%), and control problems (19%); however, distress from these symptoms was rare. Only 8% of patients were dissatisfied with their sex life and 54% were able to achieve an erection suitable for vaginal penetration. In this small cohort, global health-related quality of life was high in this group of patients, however direct comparison to radical cystectomy has yet to be performed.

Table 4. Results of RTOG bladder preservation studies – late toxicity.

RTOG Protocol	No. patients	Pathological stage (%)	Treatment (TURBT+)	% 5 year overall survival	Late Toxicity (% Grade 3+)	
					GU	GI
8512 (Tester 1993) [31]	42	T2: 25.0 T3: 56.0 T4: 19.0 N+: 9.0	RCT (CP)	52.0 (4 yrs)	2.0	2.0
8802 (Tester 1996) [32]	91	T2: 24.0 T3a: 54.0 T3b: 12.0 T4a: 10.0 N+: 6.0	+/- Neoadjuvant MCV RCT (CP)	62.0 (4 yrs)	3.0	1.0
8903 (Shipley 1998) [25]	123	T2: 38.5 T3-T4a: 61.5	+/- Neoadjuvant MCV RCT (CP)	50.0	13.0	8.0
9506 (Kaufman 2000) [34]	34	T2: 76.0 T3: 21.0 T4: 3.0	RCT (CP and 5-FU)	83.0 (3 yrs)	6.0	15.0
9706 (Hagan 2003) [35]	47	T2: 66.0 T3a: 25.0 T3b: 9.0	RCT (RT BID + CP) Adjuvant MCV	61.0 (3 yrs)	6.0	3.0
9906 (Kaufman 2009) [36]	81	T2: 88.0 T3a: 11.0 T3b: 1.0	RCT (RT BID + P, CP) Adjuvant G, CP	56.0	4.0	0.0
0233 (Mitin 2013) [37]	93	T2: 95.0 T3-T4: 5.0	RCT (CP, P vs. CP,5-FU) Adjuvant G, CP, P	73.0	5.0	1.0

RCT, radiochemotherapy; CP, cisplatin; MCV, methotrexate, cisplatin, vinblastine; 5-FU, 5-fluorouracil; RT, radiation therapy; BID, twice daily; G, gemcitabine; P, paclitaxel

DISCUSSION

The primary goals for cancer therapy should be to maximize patient survival, minimize cancer recurrence, and optimize quality of life. In the case of bladder cancer, an ongoing challenge and area of controversy lies in determining which patients may be appropriate candidates to preserve their bladders. Survival in radical cystectomy series has remained relatively constant throughout the years, and survival outcomes in both radical cystectomy and bladder preservation series are significantly dependent on TNM stage. In contemporary series, 5- and 10-year overall survival for radical cystectomy is reported between 45% to 60% and 37% to 45%, respectively [2-7]. The 5-year overall survival for bladder preservation using trimodality therapy falls within a similar range at 36-74% [25,27-29,33,36,37,46-50]. Currently, bladder preservation appears to be a viable alternative to radical cystectomy in patients who may be poor surgical candidates or in those who may opt not to undergo radical cystectomy. However, it is difficult to compare data on trimodality therapy and radical cystectomy secondary to study variations in patient populations and selection biases. For instance, whether or not a patient is fit for surgery has been shown to be a predictor of overall survival among patient undergoing trimodality therapy [51,52]. Furthermore, contemporary radical cystectomy outcomes incorporating the increased utilization of neoadjuvant chemotherapy and the potential benefits of extended node dissection, may be distinct from the long-term, single-center retrospective studies that have been published, and thus using historical series to compare present day treatment options may prove inaccurate. Until randomized controlled trials comparing trimodality bladder preservation treatments with radical cystectomy are performed, comparisons of cancer control and quality of life parameters will be limited due to selection biases and other confounding factors among disparate studies.

Outcomes in bladder preservation incorporate patients who have undergone treatment of local recurrences and salvage radical cystectomy. Up to 50% of patients undergoing bladder preservation with trimodal-

ity therapy will have local recurrences. The majority of local bladder recurrences tend to be superficial and can be treated conservatively [53,54]. Patients with higher stage and multifocal disease are more likely to recur. However, approximately 30% of patients eventually undergo radical cystectomy either due to initial incomplete response or recurrence. These patients may have a worse prognosis, as Rödel and Shipley reported long-term disease specific survival of 48-50% and 41-45% at 5 and 10 years for patients salvaged with radical cystectomy [28,55]. Furthermore, Eswara reported a 90-day complication rate of 69% in patients at MGH who underwent salvage radical cystectomy after trimodality therapy [56]. Of these complications, 16% had major complications (Clavien grade 3+) and the 90-day perioperative mortality rate was 2.2% The difference in outcomes of salvage radical cystectomy and primary radical cystectomy therefore confounds the comparison of trimodality therapy and radical cystectomy given that many patients undergoing trimodality therapy end up having salvage radical cystectomy.

Proper patient selection for bladder preservation is critical to ensure the best outcomes. The European Association of Urology guidelines state that the optimal candidates for bladder preservation are patients with T2NX or N0M0 disease without tumor related hydronephrosis, prostatic invasion, or extensive CIS [57]. Patients who have superior outcomes with bladder preservation tend to be younger, have small or unifocal tumors, and lack hydronephrosis. Renal function is also important with respect to outcomes as a creatinine clearance over 50 ml/min is necessary to complete platinum-based chemotherapy. Bladder preservation studies consistently demonstrate an association between initial response and survival as well as recurrence rates. Rödel showed that overall survival in patients who underwent cystectomy for incomplete initial response to induction radiochemotherapy was worse than those who were salvaged after initially responding [28]. Chakravarti showed that of patients who were enrolled in various RTOG protocols, those with epidermal growth factor receptor (EGFR) positive tumors had improved overall survival, disease specific survival, and disease specific survival with an intact bladder [58]. Alternatively, those with Her-2 positive tumors had significantly reduced complete response rates. A phase II study has demonstrated that targeted therapy with Trastuzumab, a humanized monoclonal antibody that binds to Her-2, is a feasible addition to trimodality therapy protocols in patients with bladder tumors that overexpress Her-2 [59]. Future trimodality therapy protocols may and incorporate Her-2 overexpression in patient selection and randomize patients to treatment with Trastuzumab. Expression of DNA damage signalling proteins may also correlate with disease specific survival. High expression of MRE11 in bladder tumors was found to be associated with improved disease-specific survival in patients undergoing radiotherapy compared to those undergoing radical cystectomy [60]. The association between high MRE11 expression and improved disease specific survival was also validated in a study in which the majority of patients undergoing radiotherapy received concurrent chemotherapy [61]. These results exemplify the heterogeneity of bladder cancer and their spectrum of aggressiveness. We must continue to utilize basic and translational research to identify which patients will respond to which type of therapy based on individual tumor characteristics, genetic, and epigenetic influences. In doing so, we can target those who will most likely respond to radiation or chemotherapy, choose appropriate drug regimens, avoid unnecessary toxicities, and avert treatment delays for individuals who will likely require radical surgery.

CONCLUSIONS

Bladder preservation using trimodality therapy is a suitable alternative to radical cystectomy in highly selected patients with muscle-invasive urothelial cell carcinoma. Patients who enter into a bladder preservation protocol should be highly compliant, as lifelong surveillance is necessary, and they should be made aware that there is approximately a 30% chance that they may eventually require radical cystectomy. In addition, the acute and delayed toxicities associated with chemoradiation as well as the cumulative risk associated with potential salvage therapies must be considered. An integrated team of radiation oncologists, medical oncologists, and urologists need to closely follow patients who undergo bladder preservation in order to optimize outcomes.

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