Long-term Outcomes and Patterns of Failure Following Trimodality Treatment With Bladder Preservation for Invasive Bladder Cancer

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OBJECTIVE	To report long-term results on survival, toxicity, and patterns of failure of 3 different organ-sparing strategies for patients with muscle invasive bladder cancer.
MATERIALS AND METHODS	This is a monoinstitutional prospective analysis of 3 consecutive bladder-sparing protocols combining maximal transurethral resection of bladder tumor (mTURBT), radiotherapy (RT), and cisplatin-based chemotherapy. Protocol 1 consisted of neoadjuvant methotrexate-cisplatin-vinblastine followed by endoscopic re-evaluation and consolidative RT 60 Gy in complete responders. Protocol 2 involved altered-fractionation RT 64.8 Gy and concurrent weekly cisplatin with re-evaluation after 40.8 Gy. Protocol 3 consisted of RT 64.8 Gy with concomitant weekly cisplatin. Nonresponders underwent radical cystectomy. Probabilities for overall survival (OS), cancer-specific survival (CSS), and metastasis-free survival (MFS) were calculated using Kaplan-Meier product limited estimates. A Cox regression multivariate analysis was performed to detect potential risk factors for OS, CSS, and MFS.
RESULTS	The 10-year bladder preservation rate was 79%. The 10-year OS, CSS, and MFS rates were 43.2%, 76.3% and 79.2%, respectively. There was no statistically significant difference in OS between the different treatment protocols. On multivariate analysis, mTURBT of the bladder and the complete response after induction therapy were independent correlates of improved OS and of MFS. The development of invasive bladder recurrence was independently associated with worse CSS and MFS.
CONCLUSION	Ten-year results indicate that bladder-sparing treatment is a successful approach for muscle invasive bladder cancer in selected patients. The mTURBT of the bladder tumor and complete response after induction therapy remain the most relevant predictive factors. UROLOGY 124: 183−190, 2019. © 2018 Elsevier Inc.

Bladder cancer is the fifth most common cause of cancer in Europe and the second most common genitourinary (GU) malignancy.[1,2] Although radical cystectomy (RC) is widely considered the standard of care for muscle invasive bladder cancer (MIBC), combined modality treatments (CMT) have provided with a conservative alternative sparing the morbidity impact on life quality associated with cystectomy.[3]

Despite the lack of randomized clinical trials directly comparing RC with organ preservation strategies in the era of modern surgery and radiotherapy (RT), there is an increasing body of evidence from observational studies and a recent meta-analysis indicating comparable results in selected patients.[4-6]

However, there is still much debate surrounding the effectiveness of organ preservation strategies and concern has been raised regarding the possibility of late recurrences in preserved bladders and the possibility of poorer disease control outcomes.[7]

In this report, we present the long-term results on survival, toxicity, and patterns of failure of a 20-year prospective experience with 3 different bladder-sparing strategies for patients with MIBC. Results on safety and efficacy have been previously reported.[8]

MATERIAL AND METHODS

From 1990 to 2016, 90 patients with MIBC were enrolled in 3 consecutive organ-sparing prospective protocols carried out by

Table 1. Patients' characteristics

	Total (N = 90)
Treatment	90
Protocol 1	42
Protocol 2	38
Protocol 3	10
Median age, years (range)	63 (41-77)
Sex (male/female)	79/11
Median follow-up, months (range)	94 (9-285)
T stage	
T2	50
T3	34
T4	6
N stage	
N0	82
N+	8
Tumor grade (WHO)	
G2	14
G >2	73
Associated Tis	9
TURBT (complete/incomplete)	61/29
Hydronephrosis (present/absent)	8/82
Induction response	
Complete	56
Incomplete	17
Non assessable	17

TURBT, transurethral resection of bladder tumor; WHO, World Health Organization classification.

a dedicated multidisciplinary team of radiation oncologists, clinical oncologists, urologists, and clinical physicists.

Prior to treatment, patients underwent a complete evaluation including physical examination, urinary cytology, random bladder mucosa biopsies, and bimanual examination under anesthesia, complete blood cell count and blood chemistry, chest radiography and computed tomography, or magnetic resonance imaging of the abdomen and pelvis. Patients had to be eligible for RC and able to provide informed consent. Patients were ineligible if there were evidence of distant metastases, prior pelvic irradiation, or contraindication for chemotherapy (CT).

Treatment Protocols
Treatment details for the first 2 protocols have been previously reported.[8,9]

Neoadjuvant Induction CT. From 1990 to 1999, 42 patients were included in the first protocol (P1). The following eligibility criteria were included: age under 76 years, clinical stage T2-4NxM0 (Union Internationale Contre le Cancer 1989), performance status <2 (Eastern Cooperative Oncology Group), and normal bone marrow and renal function. Treatment consisted of maximal transurethral resection of bladder tumor (mTURBT) and 3 cycles of neoadjuvant methotrexate-cisplatin-vinblastine (MCV) followed by re-evaluation with randomized biopsies and consolidative RT 60 Gy (2 Gy/fraction, 5 fractions/wk) in complete responders. Re-evaluation TURBT was performed as thoroughly as was judged safely possible. Complete response (CR) required the absence of any endoscopically visible tumor and of any microscopic tumor in biopsy specimens. In cases of persistent tumor, RC was recommended.

Concomitant Radiochemotherapy With Split-Course RT. In an attempt to achieve higher rates of CR and local control,

we decided to incorporate induction radiochemotherapy (RCT) in 2000. Thirty-eight patients were treated with this scheme from 2000 to 2010. The inclusion criteria were fundamentally the same as for P1. Additionally, patients with hydronephrosis and absence of a macroscopic complete TURBT (deemed by the treating urologist) were excluded from this protocol. Induction RCT consisted of RT to 40.8 Gy and concurrent weekly cisplatin (40 mg/m^2/iv) prior to re-evaluation TURBT (P2). RT was delivered using accelerated hyperfractionated RT based on Radiation Therapy Oncology Group (RTOG) 99-06 protocol[10] in 26 patients, or normofractionated RT (1.8-2 Gy/fraction) in 12 patients. Response was evaluated by restaging TURBT after a 3-week break. Patients with microscopic CR proceeded to immediate consolidative RCT. Consolidation included 1.5 Gy pelvic RT delivered twice daily to 24 Gy with same chemotherapy scheme for the hyperfractionated scheme (total dose to the bladder 64.8 Gy, total dose to the lymph nodes 45.6 Gy). Whereas for the normofractionated scheme, daily fractions of 1-8-2.0 Gy were delivered (total dose to the bladder ranged from 64 to 66 Gy and to pelvic lymph nodes from 44 to 46 Gy). We made no effort to include the entire bladder when possible. Nonresponder patients underwent RC.

Full-Course RCT. In 2010 after confirming the safety of salvage RC following RCT, we opted for a full-course of RCT prior to re-evaluation. Patients were treated with normofractionated RT (1.8 Gy/fx) to a total dose of 64.8 Gy with 6 cycles of concomitant weekly cisplatin (P3). Ten patients were treated with this protocol from 2010 to 2015. Eligibility criteria for this protocol were identical to those of P2.

Follow-up and Toxicity Assessment
Patients underwent re-evaluation cystoscopy, biopsies of any suspected areas, and urine cytology every 3 months for 2 years after treatment, every 6 months for 5 years, and then annually for a minimum of 10 years. Chest X-ray and abdominal and pelvis computed tomography scans were performed 3 months after the completion of therapy, every 6 months for 5 years, and annually thereafter. In case of suspected relapse, a new TURBT was performed.

Evaluation of late treatment-related toxicity was assessed and reported according to RTOG/European Organisation for Research and Treatment of Cancer (EORTC) and NCI-CTCAE V4.0 criteria.

Statistical Analysis
All living patients have been followed up until March 2017. Primary end points for the analysis were overall survival (OS), cancer-specific survival (CSS), and metastasis-free survival (MFS).

Table 2. Definitive model for multivariate analyses

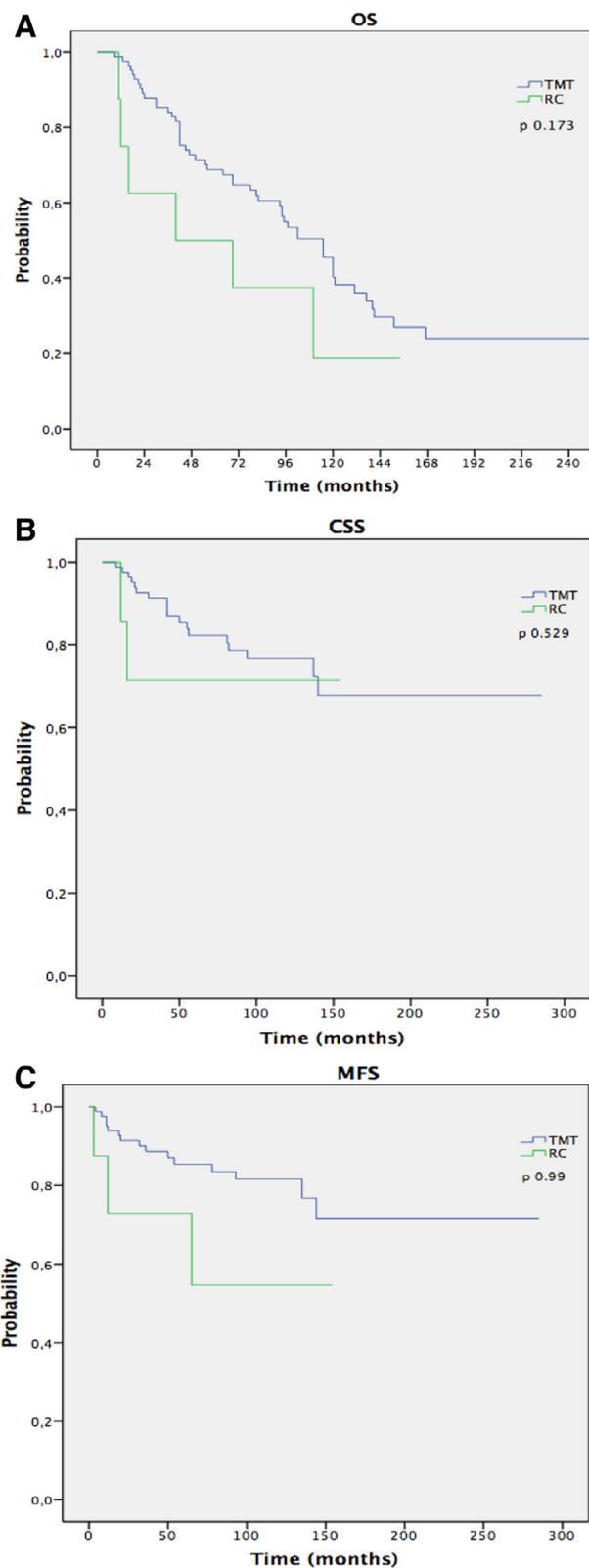| End Point	Variable	HR (CI 95%)	P
OS	mTURBT	0.44 (0.23-0.84)	.012
	Invasive relapse	1.89 (0.93-3.84)	.076
	Complete response	0.47 (0.24-0.96)	.039
CSS	mTURBT	0.32 (0.11-0.948)	.039
	Invasive relapse	6.16 (2.12-17.96)	.001
MFS	mTURBT	0.30 (0.11-0.83)	.021
	Invasive relapse	3.50 (1.26-9.72)	.015
	Complete response	0.30 (0.11-0.84)	.022

CI, confidence interval; CSS, cancer-specific survival; HR, hazard ratio; MFS, metastasis-free survival; OS, overall survival.
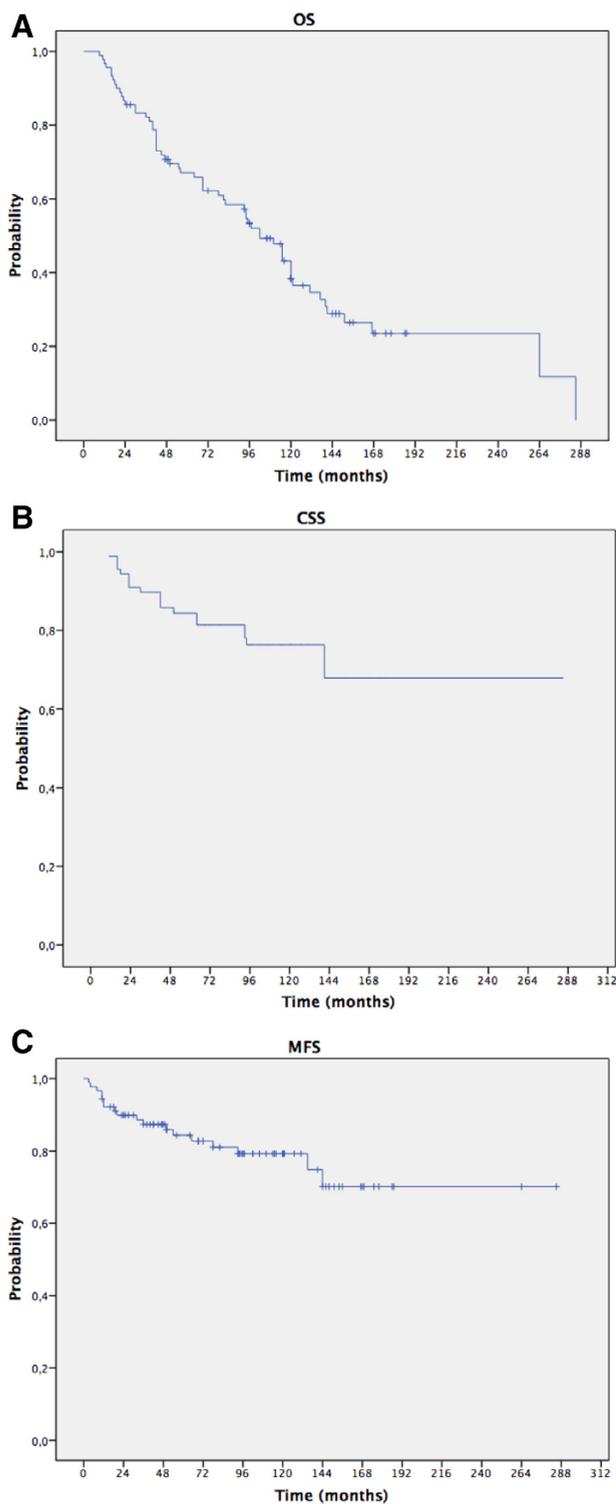
Figure 1. Kaplan-Meyer curves for overall survival (OS) (**A**), cancer-specific survival (CSS) (**B**), and metastasis-free survival (MFS) (**C**). (Color version available online.)

Figure 2. Kaplan-Meyer curves for overall survival (OS) (**A**), cancer-specific survival (CSS) (**B**), and metastasis-free survival (MFS) (**C**) by primary treatment. RC, radical cystectomy; TMT, trimodality treatment. (Color version available online.)

Organ preservation, pattern of failure analysis, and late toxicity evaluation were secondary end points.

Probabilities for OS, CSS, and MFS were calculated using Kaplan-Meier product limited estimates. Actuarial survival rates were calculated from the date of first diagnostic TURBT to last follow-up (FU) or death. Patients dead due to unrelated causes were censored at death. CSS was calculated from date of first TURBT till death due to MIBC. MFS was defined as the probability of remaining free from distant metastasis. Differences were

tested by the log-rank test. The chi-square test (2-tailed) was used to determine statistical significance between proportions. Superficial relapse was defined as presence of non-MIBC (including in situ recurrence—Tis and T1) during the FU time. Invasive disease was defined as the presence of MIBC (T2 or greater).

A univariate analysis was used to detect potential risk factors for OS, CSS, and MFS. The following variables were included in the analyses: patient age, sex, treatment protocol, T-stage, tumor grade, multicentricity, bladder Tis, presence of hydronephrosis, extension of initial TURBT (macroscopically complete resection deemed by the treating urologist vs residual tumor), clinical response after induction treatment, invasive vs superficial relapse, RT dose and RT fractionation, RC vs RT as primary local treatment after induction treatment. Variables with a statistical significance of < 0.05 in the univariate analysis and those considered of clinical relevance were included in the multivariate model. A Cox multivariate logistic regression analysis was used to calculate hazards ratios (HRs). A $P < .05$ significance level (2-sided) was considered for all statistical tests. Statistical analysis was performed using SPSS version 10.0 (SPSS, Chicago, IL).

RESULTS

Patient Characteristics
Patient and treatment's characteristics are summarized in Table 1. The median age was 63 years (range 41-77), the median FU of the whole series was 94 months (range 9-285 months), and the median FU for surviving patients was 115 months (range 25-187 months). Median FU for protocol 1, 2, and 3 were 99.5, 87.5, and 55.5 months, respectively.

Outcomes
Descriptive Bladder-Sparing Results and Pattern of Failure. Seventy-one (79%) patients preserved their bladder: 34 of 42 patients (81%) in P1, 28 of 38 (74%) in P2, and 9 of 10 (90%) in P3. Out of these 71 patients, 25 (35%) remain alive and free of disease, 14 (20%) have died from bladder cancer, and 32 (45%) died from other causes with bladder tumor controlled. Among the 71 patients with bladder preserved, 3 patients (4%) experienced invasive relapse alone and were successfully rescued by RC, 11 patients (15%) experienced superficial relapses, 8 patients (11%) distant metastases alone, and 3 patients (4%) developed both, distant and invasive relapse.

Of the 11 patients who developed superficial relapse, 5 patients are alive and free of disease, 4 patients died from other causes with tumor controlled after successful local therapy, and 2 patients died from bladder cancer (1 developed distant metastasis and 1 experienced invasive locoregional relapse).

An extensive TURBT ($P = .007$) and a CR at re-evaluation ($P = .055$) were significantly associated with a lower incidence of invasive relapse after bladder preserving treatment. The most intensive protocol P2 had a borderline impact ($P = .061$).

Descriptive RC Results. Nineteen patients (21%) ultimately required RC: 4 patients for less than CR after induction with CT alone, 14 patients in a prompt salvage approach following chemoradiation, and 1 patient as the result of radiation toxicity with the bladder tumor controlled. Of the 18 patients treated with salvage RC for bladder relapse, 14 had pT2b-T4 tumors (2 patients had also N1 disease), 3 had pT0/Tis, and 1 patient had pT1N0. Six out of the 19 cystectomy patients remain alive and free of disease, 6 patients died from bladder cancer, and 7 died from other causes with their bladder tumor controlled, 1 of them from urinary sepsis 5 months following cystectomy. Of the 19 patients treated with RC, 7 (37%) experienced distant metastasis.

Survival Outcomes
In the whole series, 20 patients (22%) died from bladder cancer, 31 patients (35%) remain alive and free of disease, and 39 (43%) died from other causes with their bladder tumor controlled. Thirteen patients died from secondary tumors, mainly lung cancer (6 patients), but also colorectal cancer (3 cases), hepatocarcinoma (1 case), leiomyosarcoma of the bladder (1 case), late ureteral urothelial carcinoma 20 years later (1 patient), or glioblastoma (1 patient).

The corresponding 5 and 10-year OS, CSS, and MFS for the whole series were 67.1% and 43.2% for OS, 81.4% and 76.3% for CSS, and 84.4% and 79.2% for MFS, respectively (Fig. 1). There were no statistically significant differences in outcomes regarding treatment protocol or local treatment (cystectomy vs RCT with bladder sparing; Fig. 2).

Univariate and Multivariate Analysis
The results of univariate analysis for OS, CSS, and MFS are summarized in Supplementary Figure 1. The mTURBT of the bladder, absence of hydronephrosis, a CR at re-evaluation, and noninvasive bladder relapse were significantly associated with an improved OS, CSE, and MFS. Other relevant factors affecting favorably the outcome were a younger patient age (ie, < 65 years old) for OS and a bladder preservation approach for MFS.

The results of multivariate analysis are illustrated in Table 2. An mTURBT and the development of a ≥ T2 bladder relapse were the most relevant factors associated with OS (mTURBT: HR = 0.444, $P = .012$; invasive relapse: HR = 1.894, $P = .076$), CSS (mTURBT: HR = 0.328, $P = .039$; invasive relapse: HR = 6.164, $P = .001$), and MFS (mTURBT: HR = 0.303, $P = .021$; invasive relapse: HR = 3.504, $P = .015$). A CR after re-evaluation was also significantly associated with OS ($P = .039$, HR = 0.478) and MFS (HR = 0.300, $P = .022$).

Toxicity
Among the 71 patients with CMT and bladder preservation, 14 patients (20%) experienced grade ≥ 2 late GU complications (1 grade 3 and 1 grade 4). A significantly higher GU grade ≥ 2 toxicity was observed in patients treated with hyperfractionated RT scheme compared to those treated with normofractionation ($P = .003$). Five patients (7%) developed grade ≥ 2 late intestinal complications (3 grade 2 and 2 grade 4).

Regarding the 19 patients treated with RC, 8 patients (42%) developed grade ≥ 2 GU toxicity (5 grade 3 and 1 grade 4), while only 1 patient developed grade 2 Gastro-intestinal (GI) complications.

DISCUSSION

In this study, we present the long-term results of a prospective study of CMT with bladder preservation for the management of MIBC. The 10-year OS, CSS, and MFS

rates were 43.2%, 76.3%, and 79.2%, respectively, and the long-term bladder preservation rate was 71 per 90 (79%). These data are similar to previous CMT studies and confirm that organ preservation strategies are feasible and effective achieving survival outcomes comparable to RC published series. The results are also consistent with other series in the modern era of RT and surgery reporting 5-year OS results on different CMT and RC regimens that range from 40% to 60% and 47% to 60%, respectively.[5,11,12] The most notable feature of our series is the long FU, one of the longest published so far. Interestingly, our long-term results are still similar to previous reported experience. In a pooled analysis of different CMT protocols conducted at the Massachusetts General Hospital, Giacalone et al reported 10 and 15-year OS and CSS rates of 39%, 25%, and 59% and 56%, respectively, whereas the 10 and 15-year OS in the series published by Krause et al were 30% and 19%, respectively.[12,13]

Despite these data, the question on whether CMT offers similar outcomes to RC in the management of MIBC remains unanswered, due to the lack of randomized evidence comparing both approaches. Selective bladder Preservation Against Radical Excision (SPARE) was a randomized phase III trial designed to compare RC and CMT after neoadjuvant CT, unfortunately the trial was closed due to recruitment difficulties and noncompliance to the assigned treatment.[14] Therefore, we have to rely on observational evidence subject to different biases, and data are rather contradictory. Three different analyses of big databases and meta-analyses have been recently published, and are particularly relevant. Seisen et al performed a comparative analysis of the US National Cancer Database assessing the effectiveness of trimodality treatment (TMT) vs RC for MIBC. They found no difference in median OS between the 2 modalities. Nonetheless, TMT had a negative impact on OS after 25 months of FU (HR 1.4, $P > .001$), although this effect decreased significantly with age.[7] In the authors' opinion, these results suggest that the potential long-term benefit of RC could be diminished by the risk of postoperative mortality. Also, older patients may not live enough to benefit from a surgical approach. Unfortunately, no CSS or toxicity assessment was performed. It is important to note that the authors could not account for important prognostic factors in this series, such as completeness of TURBT or the presence of hydronephrosis.[15] On the other hand, Vashistha et al[4] reported the results of meta-analyses of different observational and randomized studies including >12,000 patients treated either with RC or TMT. They found no statistically significant differences in 5 and 10-year OS or CSS. Recently, Fahmy et al published the result of a meta-analysis including data of over 30,000 patients and assessing the results of different TMT and RC with or without neoadjuvant CT.[16] Similar to Seisen et al, they could not find a significant difference in 10-year OS or CSS (mean 10-year OS for TMT 30.9% vs 35.1% for RC $P = .32$; mean 10-year CSS for TMT 50.9% vs 57.8% for RC $P = .26$).

These data support bladder-sparing strategies in the management of MIBC but patient selection is crucial and the results are applicable to a specific subset of patients. Traditionally, patients showing high-risk features (ie, cT4 or node positive disease, carcinoma in situ associated, multifocal disease, presence of hydronephrosis, incomplete TURBT, or aggressive histology) have been considered poor candidates for organ-sparing protocols.[17] In our risk factors analysis, we confirmed that the presence of hydronephrosis and a complete TURBT are significantly associated with outcomes. This stresses the importance of achieving an mTURBT prior to chemoradiation.

Selection of the optimal regime is also an important issue, still controversial. The use of cisplatin as radiosensitizer with or without neoadjuvant MCV has been traditionally the most accepted approach.[18] Despite positive evidence from meta-analyses, the use of neoadjuvant MCV has been neglected due to the lack of benefit in randomized clinical trials and the significant toxicity associated.[19] The combination of RT and different agents such as taxanes and gemcitabine or new targeted drugs is under study and might further improve outcomes in organ preservation strategies.[20,21] We failed to show significant differences among RCT protocols regarding OS, MFS, or CSS. Nonetheless, the comparison of the 3 protocols was out of the purpose of this study and this result should be considered cautiously. Interestingly, the lack of difference among RT protocols compared to the results published by Fahmy et al.[16]

One of the drawbacks of bladder-sparing approaches is the continuous potential risk of bladder relapses or "de novo" superficial carcinomas. TURBT with or without intravesical therapy has proved to be a safe approach for the management of Ta-Tis and T1 recurrence with a reported overall outcome similar to that of patients not experiencing recurrences, although with a smaller chance of bladder preservation.[22,23] In the present study, of the 71 patients with CMT, 11 patients developed Ta-Tis and T1 relapses successfully managed with intravesical therapies in 9 cases; however, 2 patients finally progressed despite local treatment and died from BC. These findings are consistent with prior studies and underscore the need of aggressive cystoscopic FU.[3] Moreover, there is a higher concern regarding ≥T2 bladder recurrences after bladder-sparing treatments. A systematic review of 17 studies analyzing the prevalence and management of local recurrences after bladder-sparing treatments reported a lower OS and MFS despite salvage cystectomy in patients experiencing invasive recurrence.[24] In our series, patients treated with RC showed a higher distant-metastasis rate (37%) compared to those treated with CMT (17%). Whether this data reflects a more aggressive or advanced disease in the RC patients or the benefit of longer duration of CT in the bladder preserving therapy is unclear and needs further research.

Salvage RC after CMT failure is crucial to improve outcomes despite that the reported complications rate could be higher than with early cystectomy. Among those who

underwent RC in our series, 13 of 18 patients (66%) remained disease free, with a grade ≥ 2 GU toxicity of 42%, suggesting that surgical salvage has a curative role within bladder preservation protocols and highlights the need for multidisciplinary and highly specialized teams when assessing bladder-sparing approach.

RCT treatment was fairly well tolerated with few patients developing grade 3 or greater GU or GI toxicity. Only 1 patient needed RC due exclusively to distressing bladder symptoms (contracted bladder), while 79% retained a functional bladder. These results compared to those published by other authors.[25,26] In this series, RT was administered using 3D techniques. One might argue that the use of intensity modulated radiation therapy and image guidance allowing focal boosts and dose sparing in healthy bladder could further reduced GU toxicity incidence. Considering the extensive evidence reporting RC toxicity and its impact on quality of life,[27,28] treatment toxicity profile and patient preferences should be a cornerstone when discussing treatment options for MIBC.

The authors acknowledge the inherent limitations of this observational study, specially the small sample size and the inclusion bias. Also, the widespread recruitment time and the heterogeneous cohort with the use of 3 different organ-sparing protocols add some uncertainties to the final analysis limiting drawing more solid conclusions. The main strength of our study is the long-term FU data with available results on local recurrences and RC outcomes.

Results of ongoing studies will hopefully bring light to the management of MIBC. The role of the PD1-PDL1 immune checkpoint is being investigated in different MIBC stages.[29-31] It will be interesting to explore the hypothetical benefits of combined treatments given the potential synergistic effect of radiation therapy and immune targeted new drugs. Another area of interest with promising impact is the potential benefit of targeted Her-2 therapies.[32]

CONCLUSION

Our long-term results confirm that organ-sparing strategies are a successful approach in the management of MIBC. A CR after induction therapy and an mTURBT remain the most significant predictive clinical factors. Patient selection is crucial and there is an urgent need for randomized data in order to further improve results and help us select the most appropriate strategy for each patient.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.urology.2018.07.058.

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10 years in surviving patients, they report 10-year bladder preservation rates of 79% and cause-specific survival of 76%. These results complement the long-term experience of other institutions.[3]

While their relatively small cohort over 3 decades raises the possibility of selection bias, their mature TMT results contribute to a growing body of literature demonstrating comparable long-term outcomes to upfront RC for MIBC in appropriately selected patients. With the randomized selective bladder preservation against radical excision trial closing early due to poor accrual (partly explained by patient preference for TMT),[4] alternative analyses have compared the 2 treatments. A recent propensity-score analysis matching RC and TMT patients treated in a multidisciplinary setting found no survival difference, nor did a systematic review and meta-analysis.[5,6] Two retrospective large database studies using the National Cancer Database and the Surveillance, Epidemiology and End Results-Medicare database found inferior survival for patients treated with TMT vs RC.[7,8] However, in such analyses using population-level data, many important confounders go unaccounted for making results hard to interpret, such as the validity of chemoradiation data (adequate dose, etc), and whether patients undergoing TMT fit the recommended selection criteria or were simply unfit for surgery.

If survival data are equivalent in appropriately selected patients, the different morbidity profiles of TMT and RC become essential to consider. With over 80% of patients undergoing TMT retaining their native bladder nowadays, there are potential quality-adjusted life year gains with TMT and the quality-of-life (QOL) implications of the strategies need further investigation. One study using validated QOL instruments from 226 patients found that TMT was associated with superior general and sexual QOL.[9] At the least, respect for patient autonomy dictates that they can be made aware of acceptable alternative treatments options during the supported decision-making process.[10]

The key to successful TMT is well-coordinated multidisciplinary care and the careful selection of appropriate candidates. The urologist is essential to introducing and leading patients through a bladder-sparing approach, highlighted by a maximal transurethral resection being a strong predictor of success,[3] the importance of salvage cystectomy, and the need for lifelong cystoscopic surveillance. With TMT ready for "prime-time," it is being investigated in the immunotherapy era through SWOG/NRG 1806, a phase III randomized trial of TMT +/− the PD-L1 inhibitor atezolizumab. Those eligible may stand to benefit in certain QOL domains and, as shown by Büchser et al, 80% may preserve their bladder. After all, a functioning bladder is a bladder well worth saving.

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EDITORIAL COMMENT

Bladder-sparing trimodality therapy (TMT) as an acceptable alternative to radical cystectomy (RC) for the treatment of muscle invasive bladder cancer (MIBC) is the product of consecutive institutional and national protocols over decades and across continents. RC and TMT are now recognized as bona fide treatment options for MIBC by multiple international guidelines.[1,2]

In this issue, Büchser et al contribute their institution's experience with TMT. Having treated 90 MIBC patients eligible for RC from 1990 to 2016, with a median follow-up of almost

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AUTHOR REPLY

As has been discussed in our work and the related Editorial Comment, there is now a mounting evidence supporting combined modality treatments in the management of muscle invasive bladder cancer as an acceptable alternative to radical cystectomy.[1-3] In this context, patient selection acquires particular significance.

The results of our study with a median FU of 115 months showed a 10-year bladder preservation rate of 79% and 10-year OS, CSS, and MFS rates were 43.2%, 76.3%, and 79.2%, respectively. These data are particularly relevant in a clinical scenario where randomized information is nonexistent and there is little hope of having it in the medium or long term. In this setting, we should make a special effort in producing high-quality observational studies intending to identify predictive and prognostic factors associated with each treatment. This will allow professionals to assign each patient to the most appropriate treatment and provide accurate information, so a fully informed decision can be made.

Although our data is subjected to some limitations given the small sample size, we could not observe significant differences in survival between treatment protocols. However, from our point of view, the data seem to support the use of a more convenient scheme (transurethral resection and chemoradiation: 64.8 Gy with 6 cycles of concomitant weekly cisplatin) for both patients and physicians. This protocol entails a shorter period of treatment, less complications (ie, toxicity) and slightly better bladder preservation rate (90% vs 81% and 74% in the other 2 protocols). In this setting we should underline the relevant role of urologists' expertise in performing successful salvage radical cystectomies after full-course of radiochemotherapy.

We can only agree with the editorial comment on the utter importance of the multidisciplinary approach in the management of muscle invasive bladder cancer. Considering the impact on quality of life of each treatment[4,5] and the high likelihood of retaining a functional bladder after combined modality treatments in well selected and informed patients, it is our opinion that organ sparing approaches should be always discussed in a multidisciplinary team, where the need for an intensive cystoscopic FU and the possibility of a salvage cystectomy should be considered as well.

Finally, we cannot obviate the high expectations derived from emerging role of immunotherapy in bladder preserving approaches.

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