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Radical cystectomy versus organ-sparing trimodality treatment in muscle-invasive bladder cancer: A systematic review of clinical trials

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Abstract

Background: Radical cystectomy (RC) represents the mainstay of treatment in patients with muscle-invasive urinary bladder cancer but how it compares with the best organ preservation approach is not known.
Materials and methods: The objective of our review is to compare the 5-year overall survival (OS) rates from retrospective and prospective studies of RC and trimodality treatment (TMT), i.e. concurrent delivery of chemotherapy and radiotherapy after a transurethral resection of bladder tumor (TURBT), involving a total of 10,265 and 3131 patients, respectively. We used random-effect models to pool outcomes across studies and compared event rates of combined outcomes for TMT and RC using an interaction test.
Results: The median 5-year OS rate was 57% in the TMT group, when compared with 52% ($P = 0.04$), 51% ($P = 0.02$) and 53% ($P = 0.38$) in the whole group receiving RC or the group treated with RC alone or RC + chemotherapy, respectively. The hazard risk (HR) of mortality of patients treated with TMT or RC was 1.22 (95% CI = 1.13–1.32) with an absolute benefit of 5% in favor of the former. The HR of mortality from TMT persisted significantly better not only versus the group treated with RC alone (HR = 1.22; 95% CI = 1.12–1.32), but also versus the group receiving RC + chemotherapy (HR = 1.22; 95% CI = 1.09–1.36). Multivariate analysis confirmed TMT as a significant prognostic variable for both RC alone and RC + chemotherapy.
Conclusion: Compared with RC, TMT seems to be associated with a better outcome for patients with muscle-invasive bladder cancer (MIBC). The addition of chemotherapy may improve the RC outcome in some subgroups of patients with a higher probability of micrometastases. Prospective randomized trials are urged to verify these findings and better define the role of organ preservation and radical treatment strategy in the management of patients with MIBC.

Keywords: Muscle-invasive bladder cancer; Trimodality treatment; Radical cystectomy; Chemoradiation; Bladder-sparing

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1. Introduction

Based on the 2012 cancer incidence estimates, urinary bladder cancer represents the fourth most common cancer in men and the 12th most common cancer in women in the United States and Europe [1,2]. A total of 15–25% of bladder tumors are muscle-invasive and require radical treatment. Radical cystectomy (RC), with the primary goal of maximizing survival, represents the mainstay of treatment in these patients and involves removal of the bladder, prostate, seminal vesicles, proximal vas deferens and proximal urethra in men, and bladder, uterus, ovaries, fallopian tubes, urethra and part of vagina in women. However, as in other tumor sites (breast, larynx, anus, prostate, etc.), also in bladder cancer, secondary goals as the organ preservation and the quality of life are increasingly being requested by patients. Trimodality treatment (TMT), based on the concurrent delivery of chemotherapy and radiotherapy after a transurethral resection of a bladder tumor (TURBT), has been largely demonstrated as the most effective bladder sparing treatment (BST) [3–5]. This approach can be considered a competing alternative to RC in muscle-invasive bladder cancer (MIBC), with the advantage of preserving a normal functioning bladder [6] in most of the patients, reserving cystectomy as a salvage option only in cases with a locally confined infiltrating failure. Yet, bladder preservation strategy by TMT is still perceived by many urologists to be inferior in terms of survival when compared with RC, although no randomized trials support this bias. The few attempts of a randomized comparison of RC versus BST have proven to be unfeasible [7]. Indeed, retrospective and prospective non-randomized studies can be affected by several sources of bias including the difference in tumor staging, which is pathological in RC and clinical in TMT. Clinical staging is known to under-stage a large portion of patients compared with surgical staging. The stage discrepancy can occur in up to 50% of patients [8,9], making an appropriate comparison between the two treatment strategies by non randomized studies very difficult. Advanced age, worse performance status and co-morbidities that are more frequent in patients receiving TMT than RC are important variables that can further confound the comparison of the two treatment approaches.

In the absence of controlled randomized trials, regardless of several confounding variables, we investigated the outcomes of patients with MIBC by conducting a systematic review of published prospective and retrospective studies to compare treatment outcomes after TMT or RC.

2. Methods and materials

2.1. Study selection criteria

In order to assess the best-treatment approach for MIBC, a PubMed literature search was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) literature selection process [10]. A search of English medical literature in PubMed from 1990 until 2013 was carried out, using the following terms: bladder cancer, transitional cell carcinoma, urothelial cancer, radical cystectomy, combined chemoradiation treatment, trimodality treatment, bladder preservation, bladder sparing. All prospective and retrospective studies available in full text, involving more than 20 patients with non-metastatic MIBC (T2-4a N0 M0), treated with RC or TMT, reporting 5-year overall survival (OS) rates were selected. Comparative studies (when available) between different treatment strategies (i.e. RC alone or in combination with chemotherapy, different radiotherapy schedules or chemotherapy strategies) were also included in our analysis. Not included were studies on patients with clinically positive regional nodes or distant metastases or non muscle-invasive cancer, or patients receiving partial cystectomy or radiotherapy alone, even if preceded or followed by (neo)-adjuvant chemotherapy. Among trials reporting the results of different therapeutic strategies or including non-muscle infiltrating tumors, when possible only the groups of patients fitting our requirements were selected and included in our analysis. For the aim of this study, patients staged either clinically or pathologically were grouped together.

2.1.1. Outcomes

Due to a large variability in outcome evaluation and reported results, the endpoint of interest for the present analysis was limited to 5-year OS rate. Unfortunately, due to the low number of studies reporting the OS or failure rates at 10 years, it was not possible to do a reliable analysis of the 10-year outcome.

2.1.2. Statistical methods

A descriptive analysis of OS was performed. We used random-effect models to pool outcomes across studies and compare event rates of combined outcomes for TMT and RC using an interaction test. *T*-test was applied to compare groups. The significance level was fixed at $P = 0.05$ and all *P*-values are two-sided unless otherwise stated. Hazard Risk (HR) and 95% confidence interval (95% CI) were calculated by using the 5-year OS projected for the initial number of patients enrolled in each trial. The test for sample heterogeneity was calculated. Investigated variables were treatment type (TMT vs. RC with/without chemotherapy) and stage (T2 or more vs. less than T2). Multivariate logistic regression analysis was performed using variables significant at the univariate analysis. Statistical analysis was conducted using the R-package.

3. Results

Fig. 1 shows the flow diagram of identification and inclusion of trials as recommended by PRISMA [10]. Overall 220 and 293 references were identified and screened for TMT

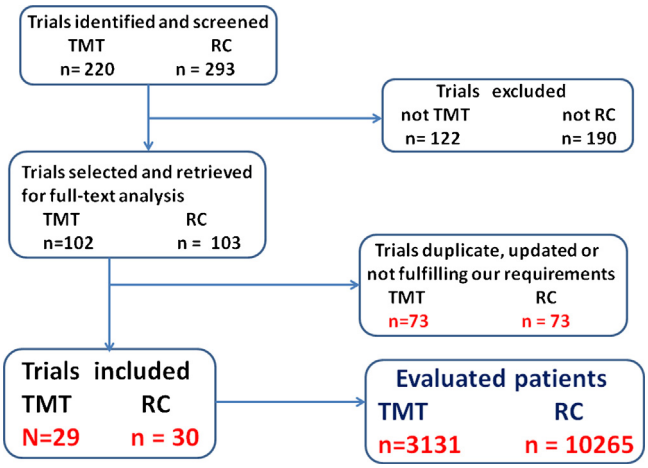

Fig. 1. Flow-chart of the identified and included trials, as recommended by PRISMA.

and RC, respectively. We excluded 122 and 190 papers in the TMT and RC screened groups, respectively, because of stage or treatment not fitting our inclusion criteria, or purposes and outcomes different from our requirements. The remaining 102 and 103 studies were selected and retrieved for full-text analysis. After discarding duplicates and updated papers, as well as the studies not fulfiling our inclusion criteria, the search yielded 29 articles for TMT with a total of 3131 evaluated patients, and 30 articles for RC with a total of 10,265 evaluated patients [3,4,11–68]. The patient sample was largely heterogeneous with regard to tumor stage, prognostic variables, age, outcome evaluation and reporting results, and therefore we decided to group patients staged either clinically or pathologically, and to evaluate only the 5-year OS rates. The patient characteristics of the two treatment groups are summarized in Table 1. Details on treatment, number of patients and 5-year OS rates of each TMT and RC study are reported in Tables 2 and 3, respectively.

The 5-year OS rates of all patients with MIBC undergoing RC or TMT are illustrated in Fig. 2. The median 5-year OS rates were 52 and 57% in the RC and TMT groups, respectively ($P = 0.04$). The lower and higher levels of the boxes represent the 1st and 3rd median quartiles of 5-year OS rates.

Table 1
Patient characteristics of the two treatment strategies.

	TMT	RC
Median age (years)	66	65
Pts.	3131	10,256
Stage [# Pts (%)]		
T2	1510 (48%)	3368 (33%)
>T2	1253 (40%)	6450 (63%)
Unknown	368 (12%)	438 (4%)
Sex		
Male	1941 (62%)	7807 (76%)
Female	477 (15%)	1667 (16%)
Unknown	713 (23%)	791 (8%)

TMT, trimodality treatment; RC, radical cystectomy; # Pts (%), number of patients (percentage of patients).

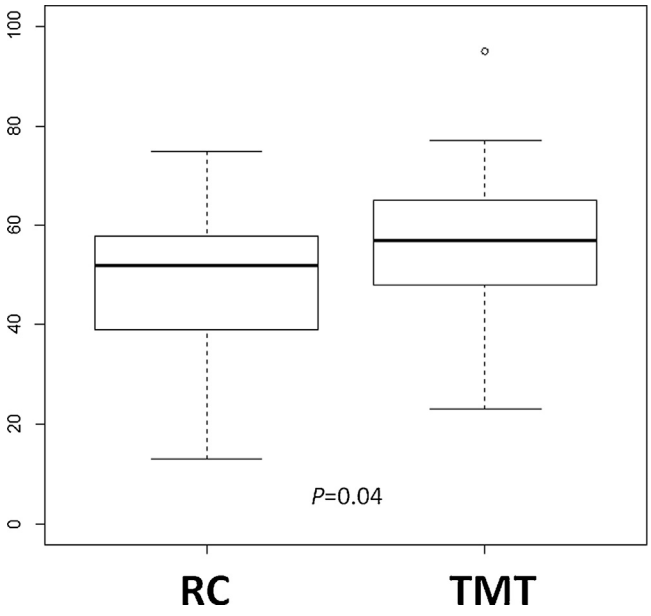

Fig. 2. Boxplot of 5-year OS rates of patients undergoing RC or TMT. In the Box-and-whisker plot, the central box represents the values from the lower-to-upper quartile 25–75 percentile. The middle line represents the median. The vertical line extends from the minimum to the maximum value, excluding circle values, which are displayed as separate points. The outside values are values larger than the upper quartile plus 1.5 times the interquartile range, respectively.

The 5-year OS rates of patients with T2 and >T2 tumor stage, receiving RC or TMT, are illustrated in Fig. 3a and 3b, respectively. The median 5-year OS rates for T2 disease was 61 and 63% for the RC and TMT groups, respectively ($P = 0.30$). The same outcome for patients with >T2 tumor stages was 40 and 45% in the former and latter group, respectively ($P = 0.36$). No difference between the two treatment modalities could be appreciated even in the Forest plot of HRs by separately analyzing the T2 (HR = 1.15, 95% CI = 0.904–1.463), or >T2 stages (HR = 1.126, 95% CI = 0.876–1.448). However, by comparing the mortality rate of the whole group of patients with MIBC, more patients significantly survived at 5 years in the TMT with respect to the RC group (HR = 1.22; 95% CI = 1.13–1.32), with an absolute benefit of 5% (Fig. 4). The test for sample heterogeneity resulted not significant and the results were calculated assuming the random effect model.

Since chemotherapy combined with RC is still controversial, we made a separate comparison of the 5-year OS rates of patients receiving TMT against those undergoing RC alone or RC + chemotherapy (Fig. 5).

The median 5-year OS rate of 57% in patients undergoing TMT was significantly better than the 51% rate in patients receiving RC alone ($P = 0.02$), but not significantly higher than the 53% rate in patients undergoing RC + chemotherapy ($P = 0.38$). However, the HRs and 95% CIs of mortality of patients receiving TMT resulted better than those of patients receiving either RC alone (HR = 1.22; 95% CI = 1.12–1.32) or RC + chemotherapy (HR = 1.22, 95% CI = 1.09–1.36)

Table 2
Number of patients and 5-year overall survival rates of TMT studies selected in our review.

Author	Ref.	# Pts.	OS (%)	Study	Staging	OSt2	OST3-T4
Efastathiou et al. 2012	[3]	343	52	Institutional review	Clinical T2-4 N-	61	41
James et al. 2012	[4]	182	48	Prospective Phase III	Clinical T2-4 N-		
Peyromaure et al. 2004	[11]	43	60	Retrospective monoinstitution	Clinical T2-4 N-		
Mokarim et al. 1997	[12]	35	77	Prospective Phase I-II	Clinical T2-4 N-		
Retz et al. 2000	[13]	53	23	Prospective Phase I-II	Clinical T2-4 N-/+		
Sabaa et al. 2010	[14]	104	55	Retrospective monoinstitution	Clinical T2-3a N-		
Fellin et al. 1997	[15]	56	59	Prospective Phase II	Clinical T2-4 N-		
Zapatero et al. 2012	[16]	39	60	Retrospective monoinstitution	Clinical T2-4 N-		
Chen et al. 2013	[17]	468	57	Multiinstitutional Update	Clinical T2-4 N-		
Miyanaga et al. 2007	[18]	72	66	Retrospective monoinstitution	Clinical T2-3 N-		
Lin et al. 2009	[19]	30	62	Retrospective monoinstitution	Clinical T2-4 N-		
Arias et al. 2000	[20]	50	48	Retrospective monoinstitution	Clinical T2-4 N-		
Caffo et al. 2011	[21]	26	70	Prospective Phase I-II	Clinical ≥T2 N-		
Lagrange et al. 2011	[22]	53	44	Prospective Phase II	Clinical T2-4 N-		
Hara et al. 2011	[23]	82	75	Retrospective monoinstitution	Clinical T2-4 N-	95	63
Hashine et al. 2009	[24]	94	67	Retrospective monoinstitution	Clinical T2-4 N-		
Given et al. 1995	[25]	49	39	Retrospective monoinstitution	Clinical T2-4 Nx		
Choudhury et al. 2011	[26]	50	65	Prospective Phase II	Clinical T2-4 N0		
Krause et al. 2011	[27]	253	48	Institutional review	Clinical T2-4 N0		
Hussain et al. 2004	[28]	41	36	Prospective Phase I-II	Clinical T2-4 N-		
Eapen et al. 2004	[29]	185	48	Prospective Phase I-II	Clinical T2-4 N-/+		
Gogna et al. 2006	[30]	113	50	Prospective Phase II	Clinical T2-4 N-		
Kragelj et al. 2005	[31]	84	42	Prospective Phase II	Clinical T2-4 N-		
Tunio et al. 2012	[32]	230	52	Prospective Phase III	Clinical T2-4 N-		
Radosevic-Jelic et al. 1999	[33]	67	55	Retrospective monoinstitution	Clinical T3 N-		
Perdonà et al. 2008	[34]	78	72	Retrospective monoinstitution	Clinical T2-4 N-		
Danesi et al. 2004	[35]	77	58	Prospective Phase I-II	Clinical T2-4 N-	63	50
Gamal El-Deen et al. 2009	[36]	114	65	Retrospective monoinstitution	Clinical ≥T2 Nx		
George et al. 2004	[37]	60	36	Retrospective monoinstitution	Clinical T2-4 N-/+		

OS (%) Total = 5-year overall survival rates of all patients; OS (%) T2, >T2 = 5-year overall survival rate of patients with the respective tumor stages.

Table 3
Number of patients and 5-year overall survival rates of RC studies selected in our review.

Author	Ref	# Pts.	OS (%) Total	Study	Staging	OS (%) T2	OS (%) >T2
Sherif et al. 2004	[38]	525	50 (Ch+) 48 42 (Ch−)	Prospective Phase III	Clinical T2-4 Nx	63 (Ch+) 60 56 (Ch−)	48 (Ch+) 43 (T3) 37 (Ch−)
van der Steen-Banasik et al. 2009	[39]	65	52	Retrospective monoinstitution	Clinical T2 N-	52	
Grossman et al. 2003	[40]	302	57 (Ch+) 50 43 (Ch−)	Multicenter Phase III	Clinical T2-4 N-	64 (Ch+) 61 57 (Ch−)	52 (Ch+) 43 34 (Ch−)
Takahashi et al. 2004	[41]	518	58	Retrospective multiinstitution	Clinical T2-4 N-/+	67	48
Whoehre et al. 1993	[42]	227	58	Retrospective monoinstitution	Clinical T2-4 N-	63	54
Pollack et al. 1995	[43]	198	52	Retrospective monoinstitution	Clinical T2-4 N-		
Sengelov et al. 2002	[44]	33	58 (Ch+) 52 40 (Ch−)	Prospective randomized	Clinical T2-4 Nx/+		
BA063 2011	[45]	976	49 (Ch+) 46 43 (Ch−)	Prospective multicenter randomized	Clinical T2-4 N-/+		
Munro et al. 2010	[46]	91	37	Retrospective review	Clinical T2-4 Nx		
Cognetti et al. 2012	[47]	183	43 (Ch+) 48 54 (Ch−)	Multicentric Phase III	Pathologic T2-4 N-/+		
Zhender et al. 2011	[48]	959	52	Retrospective multiinstitution	Pathologic T2-3 N-/+		
Scosyrev et al. 2010	[49]	295	62(Ch+) 53 43 (Ch−)	Multicentric Phase III	Clinical T2-4 N-	71 (Ch+) 63 55(Ch−)	55 (CH+) 45 36 (Ch−)
Malmstrom et al. 1996	[50]	253	54 (Ch+) 52 46 (Ch−)	Multicentric randomized	Clinical T2-4 Nx	58 (Ch+) 56 55 (Ch−)	52 (Ch+) 45 37 (Ch−)
Studer et al. 1994	[51]	77	55 (Ch+) 55 55 (Ch−)	Monoinstitution randomized	Pathologic T1-4 N-/+	70 (T1-3a)	40 (>T3a)
Ferreira et al. 2007	[52]	242	55	Retrospective multiinstitution	Pathologic T2-4 N-/+		
Hautmann et al. 2012	[53]	616	53	Retrospective monoinstitution	Pathologic T2-4 N-	57	47
Nishiyama et al. 2004	[54]	762	64	Retrospective multiinstitution	Clinical T2-4 Nx	75	55
Yafi et al. 2014	[55]	1123	39	Retrospective multiinstitution	Pathologic >T2 N-/+		39
Yu et al. 2006	[56]	311	63	Retrospective monoinstitution	Pathologic T2a-b N-/+		
Greven et al. 1992	[57]	55	36	Retrospective monoinstitution	Clinical T2-4 N-/+	50	23
Walz et al. 2008	[58]	265	45	Retrospective multiinstituion	Pathologic T2-4 N-/+		
Lehmann et al. 2006	[59]	49	38 (Ch+) 24 17 (Ch−)	Prospective randomized	Pathologic T2-4 N/-+		
Lehman et al. 2005	[60]	327	46 (Ch+)	Multicentric randomized	Pathologic T2N+ T3-4N-/+		
Martinez-Pineiro et al. 1995	[61]	109	41 (Ch+) 40 38 (Ch−)	Multicentric Phase III	Clinical Tis-4N-/+		

Table 3 (*Continued*)

Author	Ref	# Pts.	OS (%) Total	Study	Staging	OS (%) T2	OS (%) >T2
Bassi et al. 1999	[62]	257	45	Retrospective monoinstitution	Pathologic T2-4 N-/+	63	39
Stein et al. 2001	[63]	633	47	Retrospective monoinstitution	Pathologic T2-4 N-/+	72	42
Dalbagni et al. 2001	[64]	181	36	Retrospective monoinstitution	Pathologic T2-4 N-/+	60	27
Madersbacher et al. 2003	[65]	413	43	Retrospective monoinstitution	Pathologic T2-4 N-/+	63	32
Schoenberg et al. 1996	[66]	42	54	Retrospective monoinstitution	Pathologic >T2 N-/+	??	54
Freiha et al. 1996	[67]	50	55 (Ch+) 45 35 (Ch−)	Prospective randomized	Pathologic T3b-4N-/+		
Khaushik et al.	[68]	128	13	Retrospective monoinstitution	Paathologic T4a-b N+		

OS (%) Total = 5-year overall survival rates of all patients; OS (%) T2, >T2 = 5-year overall survival rate of patients with the relative tumor stages; Ch+, Ch− = patients receiving or not receiving chemotherapy.

(Fig. 6). The test for sample heterogeneity resulted not significant and the results were calculated assuming the random effect model.

Multivariate analysis for OS, including treatment type (TMT vs. RC with/without chemotherapy), confirmed TMT as a significant prognostic variable in both groups of patients receiving RC alone or RC + chemotherapy ($P = 0.03$) (Table 4).

4. Discussion

Although clinical practice guidelines include both RC and TMT as standard of care [69], RC is still considered the "gold treatment standard" of MIBC. However, a high proportion of these patients do not receive a curative therapy due to advanced age and/or comorbidities that may limit therapeutic options. Age alone should not be the reason for not receiving a potentially curative treatment. Indeed, 25–35% of patients aged between 70 and 80 years and 35–55% aged over 80 years, do not receive curative therapy [70,71]. Although many studies employing radiotherapy alone or in combination with chemotherapy have reported successful results [3–5], only 7–8% of patients receive this treatment [70]. Furthermore, provided the complete tumor eradication remains the primary goal of treatment, organ preservation and the quality of life are increasingly being requested by patients in several tumor sites. Therefore, a more precise evidence on the benefit of TMT as an alternative to RC should be addressed also in patients with MIBC. Unfortunately, phase III randomized trials could never be done or come to an end for several reasons, including the lack of interest of many urologists in recruiting the large number of patients required for such non-inferiority trial, or the problem of randomization between RC and BST and non-adherence to the allocated treatment once the patients were acquainted with the possibility of bladder preservation [7]. Some attempts of comparison by National Cancer Data Base [72] or SEER-medicare database [73] analyses were inconclusive with regard to benefit in terms of survival between RC and TMT.

In the lack of randomized studies, we attempted to compare the treatment outcomes between the radical and organ-sparing treatment by doing a systematic review of published works on MIBC management from January 1990 to December 2013. As already highlighted, the material was largely heterogeneous with regard to patient sample, tumor staging, treatment modality, and data reporting and analysis. In spite of these several variables, we decided to proceed by grouping all patients with MIBC, without distinguishing whether patients were clinically or pathologically staged, and by limiting the analysis to the evaluation of 5-year OS.

By considering the entire group of patients with MIBC, the findings of our systematic review suggest a real advantage in 5-year OS of TMT over RC. We noted a significant survival benefit in patients treated with the bladder-sparing approach, compared with those receiving radical surgery with/without chemotherapy. Unfortunately, the scarcity of studies assessing and reporting the stage-based outcomes made it difficult to assess any significant difference in survival between the two therapeutic modalities in the subgroups of patients with T2 or >T2 tumor stage. However, the lower salvage cystectomy rate reported by several TMT studies in patients who had complete vs. incomplete TURB, which may be considered a surrogate for pT stage [3,27], suggest that RC might be an overtreatment in patients with T2 tumor stage. On the other hand, the more frequent use of chemotherapy reported by RC studies in patients with advanced tumor stages, which are at higher risk of distant progression, might be responsible for the similar 5-year OS rate between the two treatment modalities at >T2 stage. Moreover, the wide CI ranges shown in boxplots, due to the large variation in

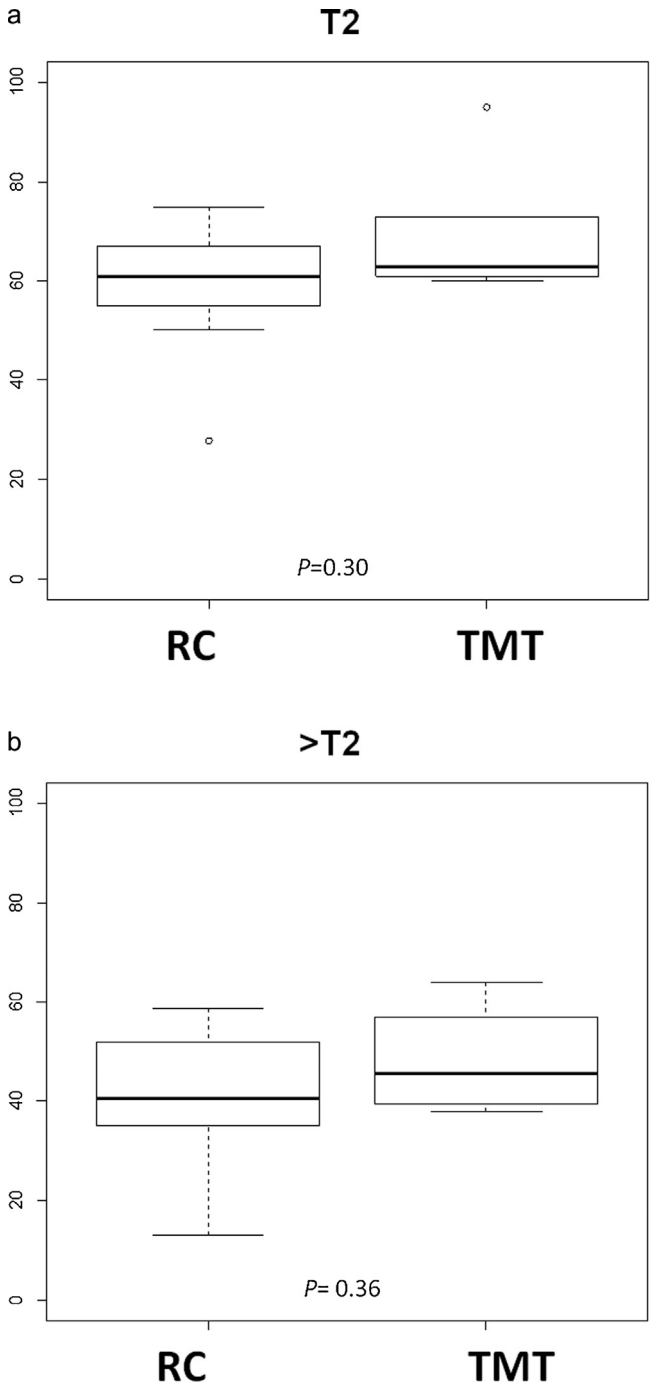

Fig. 3. Boxplot of 5-year OS rates in patients with (a) T2 or (b) >T2 tumor stage treated with RC or TMT. See legend of Fig. 2.

the enrolled patients' number, suggest extreme caution in the interpretation of these results.

Data on the benefit of using adjuvant or neoadjuvant chemotherapy are scarce and inconclusive with some trial showing improved outcomes [45] and some meta-analyses showing insufficient information for a definitive answer [74,75]. Although the value of adjuvant or neoadjuvant chemotherapy is not the aim of the current review, similar

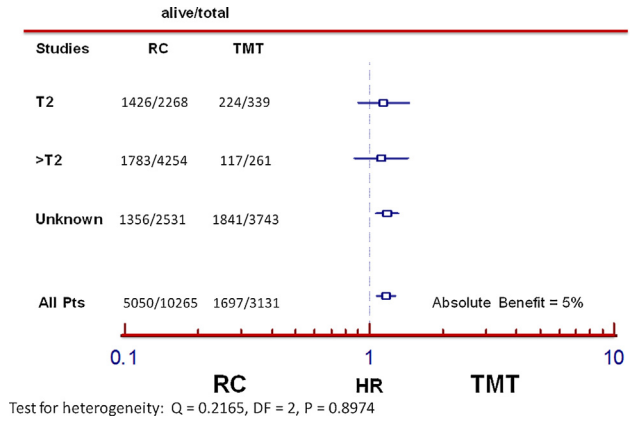

Fig. 4. Forest plot of HRs of 5-year OS rates of the whole group of patients and of patients with T2 or >T2 tumor stage treated with RC or TMT.

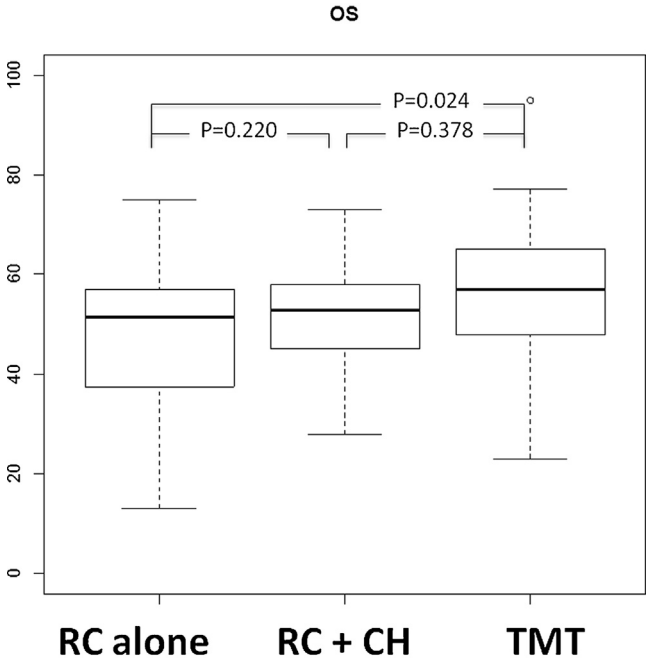

Fig. 5. Boxplot of 5-year OS rates of patients undergoing TMT or RC alone, or RC in combination with chemotherapy. See legend of Fig. 2.

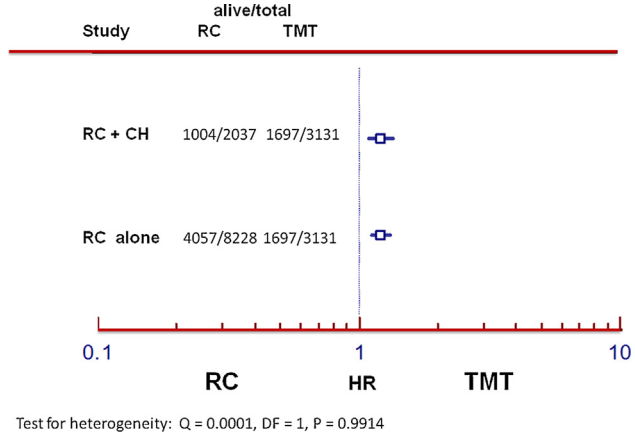

Fig. 6. Forest plot of HRs of 5-year OS rates comparing patients treated with TMT vs. RC alone, and TMT vs. RC + chemotherapy.

5-year OS rates could be observed in the RC series with or without the addition of chemotherapy. By calculating the median 5-year OS rates reported in each study, independent of the number of enrolled patients, TMT showed results similar to those of RC + chemotherapy but significantly better than those of RC alone. However, when the analysis was performed by HRs on the total number of patients recruited for the trials, survival rates of the TMT group appeared significantly better than those of both RC alone or RC + chemotherapy. Multivariate analysis confirmed TMT as a significant prognostic variable for all patients. Some subgroup of patients, such as those with later tumor stages, having a higher probability of micrometastases, could perhaps benefit from adding chemotherapy to RC, thereby reducing the risk of distant disease progression. This may explain the lack of significance in median OS rates between TMT and RC + chemotherapy group. Unfortunately, the number of studies correctly assessing and reporting cause-specific and metastasis-free survival is not adequate to obtain a reliable analysis of these latter outcomes.

Owing to the heterogeneity of reported data, our findings could have been confounded by selection bias. Furthermore, the comparison of outcomes, not within but only across studies raises further concern about the absence of prognostic balance between TMT and RC. Furthermore, patients with a more advanced age or co-morbidities, having a shorter life expectancy, were more likely selected for TMT, thus contributing to a reduced OS rate in this group.

Appropriate randomized trials with specific objectives are urged to give patients with MIBC definitive answers on the possibility of choosing the most appropriate individual treatment. Presently, despite the presence of confounding variables (mostly against TMT), the comparison of 5-year OS rates reported in the TMT and RC series suggests that TMT might be associated with better outcome in patients with MIBC. Furthermore, after TMT, approximately 75% of surviving patients maintain an intact and functional urinary bladder and approximately 21% of patients undergo salvage cystectomy for a local infiltrating failure [5,6] without having compromised their survival probability. Since patients with MIBC can undergo serious physical, functional and psychosocial disease-related detriments and experience side effects of treatment, an accurate evaluation of these outcomes would be of paramount importance for assessing treatment options. Therefore, TMT should be seriously considered as a treatment option rather than an alternative to RC until a definitive answer on the best-treatment strategy for MIBC is proved by appropriately conducted, phase III randomized trials. The possibility of a well-informed choice between the two treatment approaches offering similar (although slightly better in favor of TMT) survival rates between radical and conservative strategies should be given to patients according to their individual preferences and needs. Furthermore, urologists should be aware of the potential curability of MIBC by TMT also in consideration of the large number of patients not eligible for cystectomy who are not yet receiving any curative treatment at all, resulting in inadequate patient care for this aggressive, life-threatening cancer [70,71].

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Conflict of interest

The authors have declared no conflicts of interest.

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References

[1] Siegel R, Naishadham D, Jemal A. Cancer statistics 2013. CA Cancer J Clin 2013;63:11–30.
[2] Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality in Europe: estimates for 40 countries in 2012. Eur J Cancer 2013;49(6):1374–403.
[3] Efstathiou JA, Spiegel DY, Shipley WU, et al. Long-term outcomes of selective bladder preservation by combined-modality therapy for invasive bladder cancer: the MGH experience. Eur Urol 2012;61:705–11.
[4] James ND, Hussain SA, Hall E, et al. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. New Engl J Med 2012;366:1477–88.
[5] Arcangeli G, Arcangeli S, Strigari L. Systemic review of clinical trials of bladder-sparing trimodality treatment for muscle-invasive bladder cancer (MIBC). Crit Rev Oncol Hematol 2015;94(1):105–15, http://dx.doi.org/10.1016/j.critrevonc.2014.11.007. Epub 2014 Dec 4.
[6] Zietman AL, Sacco D, Skowronski U, et al. Organ conservation by transurethral resection, chemotherapy and radiation: results of a urodynamic and quality of life study on long-term survivors. J Urol 2003;170:1772–6.
[7] Huddart R, Birtle A, Lewis R, et al. Results of the SPARE feasibility study-Selective bladder preservation against radical excision in muscle-invasive T2/T3 transitional cell carcinoma of the bladder (CRUK/07/011). Int J Radiat Oncol Biol Phys 2012;84(3S):S119.
[8] Svatek RS, Shariat SF, Novara G, et al. Discrepancy between clinical and pathological stage:external validation of the impact on prognosis in an international radical cystectomy cohort. BJU Int 2011;107:898–904.
[9] Gray PJ, Lin CC, Jemal A, et al. Clinical-pathologic stage discrepancy in bladder cancer patients treated with radical cystectomy: results from the National Cancer Data Base. Int J Radiat Oncol Biol Phys 2014;88:1048–56.
[10] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analysis that evaluate health care interventions: explanation and elaboration. Ann Intern Med 2009;151(4):W65–94.
[11] Peyromaure M, Slama J, Beuzeboc P, et al. Concurrent chemoradiotherapy for clinical stage T2 bladder cancer: report of a single institution. Urology 2004;63:73–7.

[12] Mokarim A, Uetani M, Hayashi N, et al. Combined intra-arterial chemotherapy in the treatment of bladder carcinoma. Cancer 1997;80:1776–85.
[13] Retz M, Lehmann J, Tocha C, et al. Long-term follow-up of combined radiochemotherapy for locally advanced bladder carcinoma. Cancer 2000;89:1089–94.
[14] Sabaa MA, El-Gamal OM, Abo-Elenen M, et al. Combined modality treatment with bladder preservation for muscle invasive bladder cancer. Urol Oncol Sem Orig Invest 2010;28:14–20.
[15] Fellin G, Graffer U, Bolner A, et al. Combined chemotherapy and radiation with selective organ preservation for muscle-invasive bladder carcinoma. A single institution phase II study. Br J Urol 1997;80: 44–9.
[16] Zapatero A, De Vldales CM, Arellano R, et al. Long-term results of two prospective bladder-sparing trimodality approaches for invasive bladder cancer: neoadjuvant chemotherapy and concurrent radiochemotherapy. Urology 2012;80:1056–62.
[17] Chen RC, Shipley WU, Efstathiou JA, Zietman AL. Trimodality bladder preservation therapy for muscle-invasive bladder cancer. J Natl Compr Cancer Netw 2013;11:952–60.
[18] Miyanaga N, Akaza H, Hinotsu S, et al. Background variables for the patients with invasive bladder cancer suitable for bladder-preserving therapy. Jpn J Clin Oncol 2007;37:852–7.
[19] Lin CC, Hsu CH, Cheng JC, et al. Induction cisplatin and fluorouracil-based chemotherapy followed by concurrent chemoradiation for muscle-invasive bladder cancer. Int J Radiat Oncol Biol Phys 2009;75:442–8.
[20] Arias F, Dominguez MA, Martinez E, et al. Chemoradiotherapy for muscle-invading bladder carcinoma. Final report of a single institutional organ-sparing program. Int J Radiat Oncol Biol Phys 2000;47:373–8.
[21] Caffo O, Fellin G, Graffer U, et al. Gemcitabine and radiotherapy plus cisplatin after transurethral resection as conservative treatment for infiltrating bladder cancer. Cancer 2011;117:1190–6.
[22] Lagrange JL, Bascoul-Mollevi C, Geoffrois L, et al. Quality of life assessment after concurrent chemoradiation for invasive bladder cancer: results of a multicenter prospective study(GETUG 97-015). Int J Radiat Oncol Biol Phys 2011;79:172–8.
[23] Hara T, Nishijima J, Miyachika Y, et al. Primary cT2 bladder cancer: a good candidate for radiotherapy combined with cisplatin for bladder preservation. Jpn J Clin Oncol 2011;41:902–7.
[24] Hashine K, Kusuhara Y, Miura N, et al. Bladder preservation therapy conducted by intra-arterial chemotherapy and radiotherapy for muscle invasive bladder cancer. Jpn J Clin Oncol 2009;39:381–6.
[25] Given RW, Parsons JT, McCarley D, Wajsman Z. Bladder-sparing multimodality treatment of muscle-invasive bladder cancer: a five-year follow-up. Urology 1995;46:499–505.
[26] Choudhury A, Swindell R, Logue JP, et al. Phase II study of conformal hypofractionated radiotherapy with concurrent gemcitabine in muscle-invasive bladder cancer. J Clin Oncol 2011;29:733–8.
[27] Krause FS, Walter B, Ott OJ, et al. 15-year survival rates after transurethral resection and radiochemotherapy or radiation in bladder cancer treatment. Anticancer Res 2011;31:985–90.
[28] Hussain SA, Stoken DD, Glaholm JG, et al. Long-term results of a phase II study of synchronous chemoradiotherapy in advanced muscle invasive bladder cancer. Br J Cancer 2004;90:2106–11.
[29] Eapen L, Stewart D, Collins J, Peterson R. Effective bladder sparing therapy with intra-arterial cisplatin and radiotherapy for localized bladder cancer. J Urol 2004;172:1276–80.
[30] Gogna NK, Matthews JHL, Turner SL, et al. Efficacy and tolerability of concurrent weekly low dose cisplatin during radiation treatment of localized muscle invasive bladder transitional cell carcinoma: a report of two sequential phase II studies from Trans Tasman Radiation Oncology Group. Radiother Oncol 2006;81:9–17.
[31] Kragelj B, Zaletel-Kragelj L, Sedmak B, et al. Phase II study of radiochemotherapy with vinblastine in invasive bladder cancer. Radiother Oncol 2005;75:44–7.
[32] Tunio MA, Hashmi A, Qayyum A, et al. Whole-pelvis or bladder-only chemoradiation for lymph node-negative invasive bladder cancer: single-institution experience. Int J Radiat Oncol Biol Phys 2012;82:e457–62.
[33] Radosevic-Jelic L, Pekmezovic T, Pavlovic-Cvwtkovic L, et al. Concomitant radiotherapy and carboplatin in locally advanced bladder cancer. Eur Urol 1999;36:401–5.
[34] Perdonà S, Autorino R, Damiano R, et al. Bladder-sparing, combined-modality approach for muscle-invasive bladder cancer. A multi-institutional, long-term experience. Cancer 2008;112:75–83.
[35] Tirindelli-Danesi D, Arcangeli G, Cruciani E, et al. Conservative treatment of invasive bladder carcinoma by transurethral resection, protracted intravenous infusion chemotherapy, and hyperfractionated radiotherapy. Cancer 2004;101:2540–8.
[36] Gamal E-Deen HSH, Elshazly HF, Abo Zeina EA. Clinical experience with radiotherapy alone and radiochemotherapy with platin based regimens in organ-sparing treatment of invasive bladder cancer. J Egypt Ntl Cancer Inst 2009;21:59–70.
[37] George L, Bladou F, Bardou VJ, et al. Clinical outcome in patients with locally advanced bladder carcinoma treated with conservative multimodality therapy. Urology 2004;64:488–93.
[38] Sherif a Holmberg L, Rintala E, et al. Neoadjuvant cisplatinum based combination chemotherapy in patients with invasive bladder cancer: a combined analysis of two nordic studies. Eur Urol 2004;45:297–303.
[39] van der Steen-Banasik E, Ploeg M, Witjes JA, et al. Radiotherapy versus cystectomy in solitary bladder cancer: a case control, multicentre East-Netherland study. Radiother Oncol 2009;93:352–7.
[40] Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. New Engl J Med 2003;349:859–66.
[41] Takahashi A, Tsukamoto T, Tobisu K, et al. Radical cystectomy for invasive bladder cancer: results of multi-institutional pooled analysis. Jpn J Clin Oncol 2004;34:14–9.
[42] Woehre H, Ous S, Klevmark B, et al. A bladder cancer multi-institutional experience with total cystectomy for muscle-invasive bladder cancer. Cancer 1993;72:3044–51.
[43] Pollack A, Zagars GK, Cole CJ, et al. The relationship of local control to distant metastasis in muscle invasive bladder cancer. J Urol 1995;154:2059–64.
[44] Sengelov L, von der Maase H, Lundbeck F, et al. Neoadjuvant chemotherapy with cisplatin and methotrexate in patients with muscle-invasive bladder tumours. Acta Oncol 2002;41:447–56.
[45] International Collaboration of Trialists. International phase III trial assessing neoadjuvant cisplatin, methotrexate and vinblastin chemotherapy for muscle-invasive bladder cancer: long-term results of BA063 0894 trial. J Clin Oncol 2011;29:2171–7.
[46] Munro NP, Sundaram SK, Weston PMT, et al. A 1-year retrospective review of a nonrandomized cohort of 458 patients undergoing radical radiotherapy or cystectomy in Yorkshire, UK. Int J Radiat Oncol Biol Phys 2010;77:119–24.
[47] Cognetti F, Ruggeri EM, Felici A, et al. Adjuvant chemotherapy with cisplatin and gemcitabine versus chemotherapy at relapse in patients with muscle-invasive bladder cancer submitted to radical cystectomy: an Italian, multicenter, randomized, phase III trial. Ann Oncol 2012;23:695–700.
[48] Zhender P, Studer UE, Skinner EC, et al. Super extended versus extended pelvic lymph node dissection in patients undergoing radical cystectomy for bladder cancer: a comparative study. J Urol 2011;186:1261–8.
[49] Scosyrev E, Messing EM, et al. Do mixed histological features affect survival benefit from neoadjuvant platinum-based combination chemotherapy in patients with locally advanced bladder cancer? A secondary analysis of Southwest Oncology Group-Directed Intergroup Study (S8710). BJU Int 2010;108:693–700.
[50] Malmstrom PU, Rintala E, Wahlqvist R, et al. Five-year follow up of prospective trial of radical cystectomy and neoadjuvant chemotherapy: a nordic cystectomy trial I. J Urol 1996;155:1903–6.

[51] Studer UE, Bacchi M, Biederman C, et al. Adjuvant cisplatin chemotherapy following cystectomy for bladder cancer: results of a prospective randomized trial. J Urol 1994;152:81–4.
[52] Ferreira U, Matheus WE, Pedro RN, et al. Primary invasive versus progressive invasive transitional cell bladder cancer: multicentric study of overall survival rate. Urol Int 2007;79:200–3.
[53] Hautmann RE, de Petriconi RC, Pfeiffer C, et al. Radical cystectomy for urothelial carcinoma of the bladder without neoadjuvant or adjuvant therapy: long-term results in 1100 patients. Eur Urol 2012;61:1039–47.
[54] Nishiyama H, Habuchi T, Watanabe J, et al. Clinical outcome of a large-scale multi-institutional retrospective study for locally advanced bladder cancer: a survey including 1131 patients treated during 1990–2000 in Japan. Eur Urol 2004;45:176–81.
[55] Yafi FA, Aprikian AG, Chin JL, et al. Contemporary outcome of 2287 patients with bladder cancer who were treated with radical cystectomy: a Canadian multicenter experience. BJU Int 2010;108:539–45.
[56] Yu RG, Stein JP, Cai J, et al. Superficial (pT2a) and deep/pT2b) muscle invasion in pathological staging of bladder cancer following radical cystectomy. J Urol 2006;176:493–9.
[57] Greven KM, Spera JA, Solin LJ, et al. Local recurrence after cystectomy alone for bladder carcinoma. Cancer 1992;69:2767–70.
[58] Walz J, Shariat SF, Suardi N, et al. Adjuvant chemotherapy for bladder cancer does not alter cancer-specific survival after cystectomy in a matched-case control study. BJU Int 2008;101:1356–61.
[59] Lehmann J, Franzaring L, Thuroff J, et al. Complete long-term survival data from a trial of adjuvant chemotherapy vs control after radical cystectomy for locally advanced bladder cancer. BJU Int 2006;97:42–7.
[60] Lehmann J, Rez M, Wiemers C, et al. Adjuvant cisplatin plus methotrexate versus methotrexate, vinblastine, epirubicin and cisplatin in locally advanced bladder cancer: results of a randomized, multicenter phase III trial (AUO-AB 05/95). J Clin Oncol 2005;23:4963–74.
[61] Martinez-Pineiro JA, Gonzalez Martin M, Arocena F, et al. Neoadjuvant cisplatin chemotherapy before radical cystectomy in invasive transitional cell carcinoma of the bladder: a prospective randomized phase III study. J Urol 1995;153:964–73.
[62] Bassi P, Drago Ferrante G, Piazza N, et al. Prognostic factors of outcome after radical cystectomy for bladder cancer: a retrospective study of a homogeneous patient cohort. J Urol 1999;161:1494–7.
[63] Stein JP, Liesvkovsky G, Cote R, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol 2001;19:666–75.
[64] Dalbagni G, Genega E, Hashibe M, et al. Cystectomy for bladder cancer: a contemporary series. J Urol 2001;165:111–6.
[65] Madersbacher S, Hochreiter W, Burkhard F, et al. Radical cystectomy for bladder cancer today: a homogeneous series without neoadjuvant chemotherapy. J Clin Oncol 2003;21:690–6.
[66] Schoenberg MP, Walsh PC, Breazeale DR, et al. Local recurrence and survival following nerve sparing radical cystoprostatectomy for bladder cancer: 10 year follow-up. J Urol 1996;155:490–4.
[67] Freiha F, Reese J, Torti FM. A randomized trial of radical cystectomy versus radical cystectomy plus cisplatin, vinblastine and methotrexate chemotherapy for muscle-invasive bladder cancer. J Urol 1996;155:495–500.
[68] Khaushik D, Frank I, Eisenberg MS, et al. Gender-specific survival following radical cystectomy for pT4 bladder cancer. World J Urol 2014;32(6):1433–9.
[69] NCCN Guidelines Version 2.2014: Bladder Cancer. 2014. http://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf (accessed 06.14).
[70] Gray PJ, Fedewa SA, Shipley WU, et al. Use of potentially curative therapies for muscle-invasive bladder cancer in the United States: results from the National Cancer Data Base. Eur Urol 2013;63:823–9.
[71] Noon AP, Albertsen PC, Thomas F, et al. Competing mortality in patient diagnosed with bladder cancer: evidence of undertreatment in the elderly and female patients. Br J Cancer 2013;108:1534–40.
[72] Smith AB, Deal AM, Woods ME, et al. Muscle-invasive bladder cancer; evaluating treatment and survival in the National Cancer Data Base. BJU Int 2014;114(5):719–26.
[73] Bekelman JE, Handorf EA, Guzzo T, et al. Radical cystectomy versus bladder-preserving therapy for muscle-invasive urothelial carcinoma: examining confounding and misclassification bias in cancer observational comparative effectiveness research. Value Health 2013;16(4):610–8.
[74] Advanced Bladder Meta-Analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data. Eur Urol 2005;48:202–6.
[75] Advanced Bladder Meta-Analysis Collaboration. Adjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis of individual patient data. Eur Urol 2005;48:189–201.