A systematic review and meta-analysis of clinical trials of bladder-sparing trimodality treatment for muscle-invasive bladder cancer (MIBC)

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Accepted 27 November 2014

Abstract

Purpose: Despite the numerous prospective and retrospective studies published during the last 2 decades aiming at testing the safety and the efficacy of trimodality therapy (TMT) as a conservative treatment, an optimal therapeutic strategy has not yet been identified. We made a systematic overview of the 5-year outcomes from 31 trials of combined chemotherapy and radiation (CRT) after transurethral resection of muscle-infiltrating bladder tumours (TURBT), the so-called trimodality therapy. We took into consideration the results of each trial i.e. the rate of complete response (CR), local muscle-invasive local failure (LF), salvage cystectomy (SC), 5-year overall survival (OS) and 5-year bladder intact survival (BIS) from 3315 patients.

Results: About half of the patients were treated with a preliminary induction followed by a consolidation CRT course in CR, or SC in non-CR patients (split treatment). The remaining half of the patients underwent an upfront full-dose CRT course (continuous treatment) with SC reserved to non-CR patients. Excellent results were obtained by trimodality therapy (TMT), with 78% CR, 28% muscle infiltrating LF and 21% SC in patients with MIBC. The 5-year OS and BIS rates were 56% and 42%, respectively. At univariate analysis, CR, and SC rates appeared to be significantly better in the continuous than in the split treatment group. Multivariate analysis confirmed the former regimen as a significant prognostic variables only for CR, while CP-based regimen was a significant prognostic factor for SC. The subgroup analysis revealed a significant improvement in 5-year OS rate of continuous over split treatment in later stage tumours. No relevant benefit was observed with the addition of other drugs to cisplatin (CP) or neo-adjuvant chemotherapy (NATC) to CRT, although, in patients receiving NACT, significantly better CR and OS rates were seen in the continuous than split treatment.

Conclusions: The results of this overview seem to indicate that TMT is able to produce excellent 5-year OS rates, no matter how it is done (continuous or split). No significant difference in 5-year OS rates could be observed between the two treatment regimens, although the continuous may offer some advantage compared to split treatment in terms of higher CR and, likely lower SC rates. The highest benefit might

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http://dx.doi.org/10.1016/j.critrevonc.2014.11.007
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be achieved in later stage tumours, using a total radiation equivalent dose when delivered in 2 Gy/fraction (EQD2) of more than 60 Gy in combination with CP based regimes and preceded by 2–3 NACT cycles. Appropriate randomized trials should be addressed to confirm the results of the present review.

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Keywords: Bladder-sparing trimodality; Radio-chemotherapy; Muscle invasive bladder cancer

1. Introduction

In the last two decades several retrospective and prospective trials have shown that the trimodality therapy (TMT), based on the concurrent delivery of chemotherapy and radiotherapy after muscle-infiltrating bladder tumours (TURBT) can be a safe and effective treatment in the management of muscle-invasive bladder cancer (MIBC). In fact, this strategy has the advantage, with respect to radical cystectomy, of preserving, in most of the patients, a normally functional bladder, reserving cystectomy as a salvage option only in cases with an infiltrating local failure (LF) without distant metastases. The rationale for the combination of chemotherapy and radiotherapy (CRT) is based on two main premises. First, clinical and autopsy data have shown that micrometastases may occur concurrently with MIBC, and their frequency increases with tumour stage [1]. Therefore, it is expected that the addition of chemotherapy to radiotherapy may reduce the probability of distant failure by eradicating occult metastases. Second, some drugs such as fluorouracil, cisplatin, gemcitabine, paclitaxel, etc. act as radio-sensitizers, rendering cancer cells more sensitive to radiation [2]. To avoid a salvage cystectomy (SC), the immediate most important goal of TMT is that of achieving and maintaining the highest rate of CR with the lowest rate of infiltrating LF. Two main different CRT approaches have been employed following TURBT. In protocols developed at the Massachusetts General Hospital (MGH) and adopted in the Radiation Therapy Oncology Group (RTOG) trials, candidates for bladder preservation are selected according to their response to induction CRT, with a cystoscopic assessment of response after a preliminary course. In these protocols, consolidation CRT (split treatment) is given only to completely responding patients, whereas all others undergo SC with a curative intent [3]. The second bladder preservation approach, mainly used in the University of Erlangen [4] and adopted by many European centres, consists of the delivery of an upfront full-dose CRT course (continuous treatment). In this case, patients with an incomplete response and continuing pelvis confined disease at post-treatment evaluation undergo SC. These two therapeutic approaches have been planned with a different intent: to reduce the risk of both uncontrolled loco-regional disease and SC-associated complications, the former approach gives priority to cancer control by carrying out SC in patients with an incomplete response after induction CRT, with a minimal delay after low dose preoperative CRT. The aim of the continuous treatment schedule is that of increasing the chances of bladder preservation by giving a more intensive CRT course and more time for tumours to respond, reserving SC only for patients with an incomplete response and continuing pelvis confined disease.

With the aim of identifying the optimal strategy for bladder sparing in the treatment of MIBC, we performed a systematic review and meta-analysis of the published trials employing TMT.

2. Methods and material

2.1. Study selection criteria

In order to assess the different strategies of TMT of MIBC, we conducted a PubMed literature review using the preferred reporting items for systematic reviews and meta-analyses (PRISMA) literature selection process [5]. English medical literature from 1990 until 2013 was searched in PubMed using the terms bladder cancer, urothelial carcinoma, combined chemo-radiation treatment, TMT, bladder preservation, organ sparing. We selected all published full articles written in English, prospective and retrospective studies on more than 20 patients with non-metastatic MIBC, treated with trimodality bladder preservation therapy (i.e. TURBT, followed by neoadjuvant chemotherapy and/or concomitant CRT, with SC at local infiltrating failure in cases without distant relapses) reporting CR and 5-year OS rates. Comparative studies (when available) between different radiotherapy or chemotherapy strategies were also included in our analysis. Not included in our analysis were studies on patients with non muscle-invasive cancer and/or receiving partial cystectomy, or studies delivering radiotherapy alone, even if preceded by neoadjuvant chemotherapy. Few papers reported an exhaustive evaluation of all relevant endpoints, therefore for 3/26 studies we calculated the BIS rates (referred to 5 year-cancer-specific survival) using the same percentage applied to the 5 year-OS rate. For the same reason, a study selection was also made for subgroup analyses. Among trials reporting the results of different therapeutic strategies or including non-muscle infiltrating tumours, when possible, we selected and included in our analysis only the groups of patients fitting our requirements. Studies not having a sufficient follow-up for the primary objective analysis were included only for the CR evaluation. Of the individual or pooled studies variously reported over time, we only considered the most updated endpoint results. Therefore, some studies reporting different endpoint results in different periods were selected more than once.
2.2. Outcomes

The primary endpoint of interest was the 5-year OS rate. Other clinical outcomes were also evaluated, such as CR, infiltrating LF, SC, and 5-year BIS rate, classified as the rate of patients who survive with their own functioning bladder. Because of incomplete or lack of report in most trials, an accurate analysis of distant relapse and 10-year OS rates was not possible.

2.3. Statistical methods

The linear-quadratic formula was used to express the total dose of each RT fractionation schedule in terms of equivalent dose when delivered in 2 Gy/fraction (EQD2).

The EQD2 was calculated as follows:

$$EQD_2 = \frac{BED}{1 + (2/\alpha/\beta)}$$

The BED was calculated using the following formula:

$$BED = D \left[1 + \frac{d}{(\alpha/\beta)}\right]$$

where $D =$ total dose; $d =$ dose per fraction and $\alpha/\beta = 10$ Gy for the tumour.

We evaluated the associations between the types of treatment (or the EQD2 value) and the investigated clinical end-points, calculating the hazard risk (HR) and 95% confidence intervals (CIs). We also performed a stratification analyses by clinical T-stage and hydrenephrosis. For split treatment, being CR evaluated at the end of the induction CRT course, EQD2 was calculated based on the dose delivered at this time point; while for 5-year OS the EQD2 was calculated as the sum of both induction and consolidation doses. A chi-square test was performed to compare groups. A pooled estimate of the HR was computed according to the inverse variance method. A HR > 1 favours the split course, whereas a HR < 1 favours continuous treatment. When the pooled results were significant, the absolute risk difference was calculated. For all analyses, a forest plot was generated to display the results. Variables significantly associated with outcomes at the univariate analysis were included in the multivariate analysis to identify independent prognostic factors. A significant level of $p < 0.05$ was chosen for univariate analysis and corrected for multiple comparison. We conducted all analyses with R-package.

3. Results

Table 1

<table>
<thead>
<tr>
<th>Patient characteristics of the two treatment strategies.</th>
<th>Continuous</th>
<th>Split</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)</td>
<td>67.25</td>
<td>65</td>
</tr>
<tr>
<td>Pts.</td>
<td>1820</td>
<td>1495</td>
</tr>
<tr>
<td>Stage [no. Pts (%)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>778 (43%)</td>
<td>854 (57%)</td>
</tr>
<tr>
<td>&gt;T2</td>
<td>652 (36%)</td>
<td>641 (43%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>390 (21%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Hydrenephrosis [no. Pts (%)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>213 (12%)</td>
<td>67 (5%)</td>
</tr>
<tr>
<td>No</td>
<td>693 (38%)</td>
<td>616 (41%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>914 (50%)</td>
<td>912 (54%)</td>
</tr>
<tr>
<td>TURB [no. Pts (%)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>358 (20%)</td>
<td>60 (4%)</td>
</tr>
<tr>
<td>Incomplete</td>
<td>251 (14%)</td>
<td>39 (3%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1211 (66%)</td>
<td>1396 (93%)</td>
</tr>
</tbody>
</table>

Fig. 2a shows the cumulative results from the evaluated trials. CR was observed in 78% of patients. LF, i.e. tumours not achieving CR plus later muscle-infiltrating recurrences, occurred in 28% of cases. SC was necessary in 21% of patients. At 5 years, OS and BIS rates were 56% and 42%, respectively. The CR rate appeared significantly better in patients treated with the continuous than split schedule with a HR of 0.513, (95% CI of 0.430–0.611), and an absolute benefit of more than 11% (Fig. 2b). No significant differences were observed in 5-year OS, BIS and infiltrating LF rates. Of relevance, SC rates were 19% (268/1416) vs. 25% (287/1144) in the continuous and split regimen, respectively (HR = 1.435, 95% CI = 1.188–1.732), with an absolute benefit of 6% (Fig. 2b).
selected Table ONCH-1907; Choudhury first shipley shipley shipley tester Efstathiou Arias Lin Lagrange Retz George Tirindelli-Danesi Tirindelli-Danesi Tunio Gogna Ott Hara Hashine Given Eapen Gogna Tunio Perdonà Tirindelli-Danesi Tirindelli-Danesi Gamal George Peyromaure Housset Mitin Mokarim Retz Sabaa Lagrange Fellin Zapatero Lin Arias Elstathiou Chen Miyazaka Khaufman Hagan Tester Shipley Shipley Shipley


3.1. Subgroup analysis

A subgroup analysis was attempted, testing the effects of the two treatment regimens on outcomes according to prognostic and treatment variables. As expected, CR and 5-year OS rates were in general significantly better in patients with T2 than >T2 tumour stage (79% vs. 62%, p < 0.0001 and 61% vs. 47%, p = 0.0001, respectively, Fig. 3a). In this latter group, the 5-year OS rate appeared significantly better in patients treated with the continuous rather than the split treatment course (HR = 0.641, 95%CI = 0.424–0.969) with an absolute benefit of 11% (Fig. 3b).

CR rates resulted better also in patients without rather than with hydronephrosis (77% vs. 38%, p = 0.0001), while the difference in OS rates between these two groups resulted not significant (Fig. 4).

Fig. 5 shows CR (panel a) and OS (panel b) rates as a function of the EQD2. While there seem to be no influence of total dose on 5-year OS rates, CR rates appear to increase when increasing the EQD2.

Data on the effect of different drug regimes are too sparse to be correctly evaluated. The addition of other drugs to CP or the use of different drugs does not seem to give a benefit for 5-year OS and CR (data not shown). Because of the
limited number of patients receiving drugs other than CP, we analyzed only those patients receiving CP and CP-containing regimes. In both these groups, while no significant difference in survival could be detected between the two radiation schedules, significantly higher CR and lower SC rates were observed by continuous compared to split course regime (HR = 0.411, 95%CI = 0.305–0.554 and HR = 1.487, 95%CI = 1.161–1.903, respectively (Fig. 6).

From the limited, currently available data, the use of NACT did not appear to produce any significant benefit in terms of rate of OS and CR (Fig. 7a). However, while no difference in OS was detected between the two radiation schedules in the absence of NACT, significantly better CR and OS HRs were observed in the continuous compared to the split regime when NACT was added to CRT (Fig. 7b).

Multivariate analysis testing the significance of treatment type (continuous vs. split), NACT and CP-based treatment for the various endpoints, confirmed the continuous course as an independent prognostic variable only for CR rate.
4. Discussion

Bladder preservation strategies are perceived by many urologists to result in inferior survival in comparison to radical cystectomy (RC) and, therefore, RC is considered as the “gold standard” in the treatment of MIBC. Nevertheless, many patients may be not candidates for radical surgery due to advanced age and/or multiple co-morbidities and need a safe and effective treatment that can be an alternative to radical cystectomy. Furthermore, organ preservation and quality of life in bladder cancer, as with other sites (breast, larynx, anus, prostate, etc.), are increasingly being requested by patients, providing the complete eradication of cancer cells remains the primary goal of the treatment. Appropriate randomized trials would give definitive answers on the possibility of choosing the most beneficial treatment for patients with MIBC. In the meanwhile, a systematic review of radical cystectomy vs. organ-sparing TMT trials, reporting a temporary evaluation of the benefit of these two most important treatment modalities, has been just completed by our group and will be separately reported (paper submitted).

The present overview shows that an average 56% of patients with MIBC who underwent TMT survived at 5 years, with approximately 80% of them living with their own
bladder. These seem to be excellent results in consideration that, with the exception of the RTOG 8903 [19] and BC 2001 trials [35], they are not obtained by well conducted randomized studies, but are results emerging from prospective and retrospective studies conducted by individual institutions reporting the results of the routine therapeutic activity without any patient selection.

Bladder cancer constitutes a heterogeneous population of patients with a variety of factors that may influence the outcomes (age, gender, co-morbidities, T-stage, hydronephrosis, completeness of TURBT, etc.). The comparison of outcomes not within but only across studies raises concern about absence of prognostic balance between the two treatment schedules. Furthermore, the intention-to-treat report, specified only in few papers, may represent another confounding variable.

For the aim of this study, the trials were simply grouped into two major treatment approaches, i.e. continuous and split treatment course. Although at univariate analysis the continuous treatment showed better outcomes than split regime, multivariate analysis confirmed the continuous schedule as a significant variable only for CR rate. Of relevance, SC rate is unfortunately not reported in all the investigated studies and, owing to the presence of other confounding factors, a higher number of patients is needed to reach the significance at a multivariate analysis. The higher CR and lower SC rates observed at the univariate analysis by continuous treatment, may be due to the fact that patients undergone split course regimen received, by protocol, an early assessment for SC, potentially leading to some unnecessary SC avoidable by a later outcome evaluation. On the other hand, the continuous treatment course allows a sufficient time to exclude SC in patients who either reached CR after the full CRT course or developed distant disease progression during the treatment/follow-up. In this context, although the therapeutic schedule was not shown to significantly influence the 5-year OS rates, continuous treatment seems to offer some advantage for patient quality of life in terms of bladder sparing.

The worst results were observed in patients with stage >T2 or obstructive uropathy. In these cases, however, continuous seems to be more effective than split treatment, with significantly higher CR rates in both with/without hydronephrosis subgroups, and significantly better OS rates in patients with later tumour stages. In these latter, SC does not seem to be sufficient to compensate for the lower CR rate observed after the split course.

As expected, higher CR rates were observed by increasing total RT dose. Owing to the early evaluation after the induction CRT course, when RT dose was only partially delivered, CR rates resulted to be lower in the split than continuous regimen where the evaluation was done after full RT course. Instead no effect of total dose, in general, was observed on 5-year OS rates, possibly because SC was able to compensate for the lower CR rate achieved by the induction CRT course of the split treatment.

Although other drugs in combination or not with CP have shown to be very effective [21,23,32,34,36,38], no conclusion could be made whether their addition to CP or their use in place of CP is better than using CP alone, since CP alone was used in most trials. However, using CP either alone or in combination with other drugs, higher CR and lower SC rates were observed with the continuous rather than the split regime.

Data on the benefit of using NACT are sparse. Although some trials showed improved outcomes with NACT in patients treated by radical cystectomy or RT alone, a recent report from Cochrane Database [42] concluded that there was insufficient information to obtain a definitive answer to the question of whether NACT improves survival in patients with MIBC. The RTOG 8903 randomized trial [18] concluded that two cycles of NACT with the methotrexate, cisplatin, and vinblastine (MCV) regimen was not shown to have an impact on outcomes with respect to CRT alone in patients with MIBC, although the number of patients was too small to detect small significant differences. The results of this overview on more than 900 patients confirm the lack of benefit of the addition.
of NACT to CRT. However, by NACT addition, CR, OS and SC rates were significantly improved in the continuous with respect to the split treatment. Appropriate randomized trials should be addressed to test this suggestion.

5. Conclusion

We are aware that heterogeneity of patient population, large variations in the combined treatments, unbalanced prognostic factors and non-standardized reporting of results among the trials may all introduce some biases especially in some subgroup analyses. For this reasons, the results emerging from the current review cannot be taken as definitive evidence of the benefit of the continuous over split treatment course. Furthermore, not enough trials have been conducted to reliably compare late specific toxicity events between the two treatment schedules. BST by TMT exhibit good results no matter how it is done (split or continuous). However, in the absence of randomized trials or trials with specific objectives, the results of this overview seem to indicate that, compared to the split, the continuous regimen may offer some

![Graph showing CR and 5-year OS rates in patients receiving neoadjuvant chemotherapy (NADCT+) or not (NADCT−).](image)

![Forest plot of HRs and 95% CIs of CR, cystectomy and 5-year OS rates comparing continuous vs. split treatment course in patients receiving or not receiving NACT.](image)
advantage, essentially in terms of higher CR and likely lower SC rates. The most important benefit of the continuous treatment schedule might be achieved in late stage tumours, with or without hydronephrosis, using total radiation doses higher than 60 Gy in combination with CP-based regimes and preceded by 2 or 3 NACT cycles. Appropriate randomized trials should be addressed to confirm the results of the present review.

Conflict of interest statement

None.

Reviewers

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