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Comparative Effectiveness of Trimodal Therapy Versus Radical Cystectomy for Localized Muscle-invasive Urothelial Carcinoma of the Bladder

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Abstract

Given the lack of randomized evidence comparing trimodal therapy (TMT) to radical cystectomy (RC) for muscle-invasive urothelial carcinoma of the bladder (UCB), we performed an observational cohort study to examine the comparative effectiveness of these two definitive treatments. Within the National Cancer Data Base (2004–2011),we identified 1257 (9.8%) and 11 586 (90.2%) patients who received TMT and RC, respectively. Inverse probability of treatment weighting (IPTW)–adjusted Kaplan-Meier analysis showed that median overall survival (OS) was similar between the TMT (40 mo, 95% confidence interval [CI] 34–46) and RC groups (43 mo 95% CI 41–45; $p = 0.3$). In IPTW-adjusted Cox regression analysis with a time-varying covariate, TMT was associated with a significant adverse impact on long-term OS (hazard ratio 1.37, 95% CI 1.16–1.59; $p < 0.001$). Interaction terms indicated that the adverse treatment effect of TMT versus RC decreased with age ($p = 0.004$), while there was no significant interaction with gender ($p = 0.6$), Charlson comorbidity index ($p = 0.09$) or cT stage ($p = 0.8$). In conclusion, we found that TMT was generally associated with worse long-term OS compared to RC for muscle-invasive UCB. However, the survival benefit of RC should be weighed against the risks of surgery, especially in older patients. These results are preliminary and emphasize the need for a randomized controlled trial to compare TMT versus RC.

Patient summary: We examined the comparative effectiveness of trimodal therapy versus radical cystectomy for muscle-invasive urothelial carcinoma of the bladder. We found that trimodal therapy was generally associated with worse long-term overall survival, although there may be no difference with radical cystectomy in older individuals.

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Over the last decades, several multimodal bladder-sparing protocols using radiation therapy (RT) have been tested to challenge the well-established dogma of radical cystectomy (RC) as the only effective local treatment option for muscle-invasive urothelial carcinoma of the bladder (UCB). The most-studied conservative approach remains trimodal therapy (TMT), comprising maximal transurethral resection of bladder tumor (TURBT) followed by ≥60 Gy of RT with concurrent radiosensitizing chemotherapy delivered in a split or continuous course [1].

However, existing evidence is inconclusive with regard to the comparative oncological outcomes associated with delivery of TMT versus RC. Indeed, a unique randomized controlled trial failed to meet the original recruitment targets [2], and very few retrospective studies compared TMT to RC, with their own set of limitations [3–5]. Against this backdrop, we hypothesized that these two local treatment options may have a similar effect on overall survival (OS). We used the National Cancer Data Base to assess the comparative effectiveness of TMT versus RC in a large sample of contemporary US patients with muscle-invasive UCB.

From a population of 341 667 men and women diagnosed with bladder cancer between 2004 and 2011(ICD-0-3 codes C67.0–C67.9), we identified 12 843 individuals treated with TMT or RC for localized muscle-invasive UCB (cT2–4N0M0) who were considered in our final study population (Supplementary Fig. 1). The TMT group included those who received TURBT followed by 60–65 Gy of RT delivered to the bladder with concurrent single- or multiple-agent radiosensitizing chemotherapy, as well as those who underwent immediate salvage RC after ≥39 Gy of chemoradiation. Patients who underwent RC with or without perioperative chemotherapy and who did not receive any RT to the bladder before surgery were included in the RC group.

To account for selection bias, differences observed in baseline characteristics between the TMT and RC groups were controlled for with inverse probability of treatment weighting (IPTW)–adjusted analyses [6]. Balance in covariates between treatment groups was evaluated using the standardized differences approach and Kernel density plots. IPTW-adjusted Kaplan-Meier curves were calculated to compare OS between TMT and RC. The proportional hazards assumption was tested using the Grambsch-Therneau approach. An unbiased bootstrapping method was subsequently used to test for difference in median OS between treatment groups. In addition, an IPTW-adjusted Cox regression model with a time-varying covariate including treatment as a main effect and an interaction term between treatment and time variables was fitted [7]. From the latter model, we tested for equal survival curves using a χ^2 test with two degrees of freedom that both the main treatment effect and the interaction between treatment and time equaled zero [7]. In addition, a 3-mo conditional landmark IPTW-adjusted survival analysis was performed to assess the impact of immortal time bias on our findings. Finally, we conducted exploratory analyses to determine the heterogeneity of the treatment effect according to age (continuous), gender (female vs male), Charlson comorbidity index (CCI; ≥1 vs 0) and cT stage (≥cT3 vs cT2) by testing interaction terms within the IPTW-adjusted Cox model.

All statistical analyses were performed using Stata v.14.0 (StataCorp, College Station, TX, USA). Two-sided statistical significance was defined as $p < 0.05$. An institutional review board waiver was obtained before the study was conducted.

Overall, 1257 (9.8%) and 11 586 (90.2%) patients with clinically localized muscle-invasive UCB underwent TMT and RC, respectively (Supplementary Fig. 1). Unweighted and weighted baseline characteristics of eligible patients, stratified according to treatment group, are reported in Table 1. Results of multivariable logistic regression analysis predicting receipt of TMT versus RC are reported in Supplementary Table 1. Following IPTW adjustment, all standardized differences were <10% (Supplementary Fig. 2). The distribution of propensity scores demonstrated adequate balance between the treatment groups(Supplementary Fig. 3A,B), indicating that the treatment groups were subsequently comparable.

The median follow-up was 44 mo (interquartile range 27–63) in patients alive at last follow-up, while 6627 (51.6%) deaths from any cause occurred over the study period. The proportional hazards assumption was rejected ($p < 0.001$). IPTW-adjusted Kaplan-Meier curves (Fig. 1A) showed that median OS was similar between TMT (40 mo, 95% confidence interval [CI] 34–46) and RC (43 mo, 95% CI 41–45; $p = 0.3$). In IPTW-adjusted Cox regression analysis with a time-varying covariate, TMT was associated with a significant adverse effect on OS after 25 mo of follow-up (hazard ratio [HR] 1.37, 95% CI 1.16–1.59; $p < 0.001$), whereas there was no significant difference before 25 mo of follow-up (HR 0.93, 95% CI 0.83–1.04; $p = 0.2$). The 3-mo conditional IPTW-adjusted analysis showed little impact of immortal time bias on the short-term (HR 0.99, 95% CI 0.89–1.12; $p = 0.9$) and long-term (HR 1.37, 95% CI 1.16–1.58; $p < 0.001$) treatment effects (Fig. 1B).

Interaction terms indicated that the adverse treatment effect of TMT versus RC decreased significantly with age (HR 0.99, 95% CI 0.98–0.99; $p = 0.003$), while no significant interaction was observed with gender (HR 0.93, 95% CI 0.74–1.18; $p = 0.6$), CCI (HR 0.84, 95% CI 0.69–1.03; $p = 0.1$), or cT stage (HR 0.97, 95% CI 0.77–1.22; $p = 0.8$).

Corroborating data from prospective series separately evaluating the oncological outcomes of TMT [8] and RC [9] for muscle-invasive UCB, our study revealed no significant difference in median OS between the treatment groups. Moreover, TMT and RC demonstrated similar OS before 2 yr of follow-up. However, after 2 yr, individuals treated with TMT were 1.40-fold more likely to die following presentation with localized muscle-invasive UCB. These findings suggest that the potential long-term benefit of RC may be attenuated by the immediate risk of postoperative mortality. Finally, with regard to patient selection, we observed that the benefit of RC was less pronounced in older patients who may not live long enough to benefit from such treatment, whereas no significant interaction was found with gender, CCI, and cT stage. That said, these results

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