

selection and use of adjuvant chemotherapy should be kept in mind. The toxicity profile was, as expected, significant. CRT with gemcitabine resulted in slightly fewer grade 3 and 4 side effects with at least comparable efficacy results, and seems a valuable alternative, certainly for cisplatin-unfit patients for whom CRT is considered.

**Conflicts of interest:** The author has nothing to disclose.

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## Re: Impact of Immune and Stromal Infiltration on Outcomes Following Bladder-sparing Trimodality Therapy for Muscle-invasive Bladder Cancer

Efstathiou J, Mouw K, Gibb E, et al

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### Experts' summary:

Transcriptome-wide gene expression profiling of trans-urethral resection of bladder tumor (TURBT) specimens from a cohort of 136 bladder cancer patients who had been treated with bladder-sparing trimodal therapy (TMT) were compared to that of 223 patients treated with neoadjuvant chemotherapy (NAC) and radical cystectomy (RC). The authors compared disease-specific survival (DSS) and overall survival (OS) by treatment type, stratifying cases by a genomic signature for CD8<sup>+</sup> T-cell infiltration, an IFN- $\gamma$  gene expression signature, and a signature for stromal infiltration (genes expressed in fibroblasts and myofibroblasts). Cases with higher tumor T-cell infiltration and IFN- $\gamma$  signaling scores were associated with better DSS after TMT. This association was not observed in the NAC/RC cases, although patients in this cohort had worse DSS in the presence of a stronger stromal signature [1].

### Experts' comments:

The development of gene expression-based molecular taxonomies for bladder cancer has important therapeutic implications [2], particularly as we recognize that traditional methods of grading and staging only partly inform us of the underlying tumor biology. Although Efstathiou and colleagues have performed an interesting investigation into whether genomic expression patterns can be discerned to select for patients who might benefit from TMT, it is important to bear in mind some key limitations. First, associations observed via gene expression classifiers require validation in multiple independent cohorts, ideally from studies that are prospectively planned [3]. In the present study, 59% of the NAC/RC cohort were classified as stage T3 or greater, compared with only 28% of the TMT cohort,

potentially affecting survival patterns. Second, tumor heterogeneity probably impacts genomic classifications. It is possible, for example, that tumor from one location in the bladder will be classified differently from samples taken from other locations. Patients undergoing TMT may have undergone a more radical TURBT than those in the NAC/RC cohort, potentially affecting consensus classifications. Third, salvage cystectomy was required in 129 of the 475 patients who underwent TMT according to the original report [4], and although we do not know which of these cases ultimately comprised the 136 specimens that were analyzed, survival comparisons certainly need to be considered within this context. As newer and more granular molecular classifications for bladder cancer emerge, it is becoming more apparent that we are only just beginning to understand how genomic subtyping will fit into clinical practice, and efforts in establishing consensus and external validation of these classifiers will become increasingly important.

**Conflicts of interest:** Colin P.N. Dinney has performed consulting for Merck, the National Cancer Institute, FKD Therapies Oy, and Janssen, and research for Merck, National Cancer Institute, and The University of Eastern Finland, Faculty of Health Sciences. The remaining authors have nothing to disclose.

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## Re: Evaluation of Cancer Specific Mortality with Surgery versus Radiation as Primary Therapy for Localized High Grade Prostate Cancer in Men Younger than 60 Years

Huang H, Muscatelli S, Naslund M, Badiyan SN, Kaiser A, Siddiqui MM

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### Experts' summary:

In this retrospective study, the authors focused on men younger than 60 yr with high-risk, localized prostate cancer (PC) from the Surveillance, Epidemiology and End Results (SEER) database who underwent upfront radical prostatectomy (RP) or radiation therapy (RT; either external beam [EBRT] or EBRT + brachytherapy [BT]) from 2004 to 2012. The population consisted of 2228 men, of whom 65.5% underwent RP as their initial treatment.

For median follow-up of 44 mo, multivariate analysis revealed that RP was associated with better PC-specific mortality (hazard ratio [HR] 0.37, 95% confidence interval [CI] 0.19–0.74;  $p = 0.005$ ) and overall mortality (HR 0.41, 95% CI 0.24–0.70;  $p = 0.001$ ) compared with initial RT treatment.

### Experts' comments:

Whereas active surveillance is recommended or at most single-modality treatments for low-risk and even some intermediate-risk PCs, for high- and very high-risk PCs there is more of a tendency to recommend aggressive multimodal treatments [1].

Using SEER data to analyze outcomes for young patients with high-risk localized PC, the authors try and answer an age-old question as to what constitutes the “best treatment” in this population with long life expectancy who experience high PC-specific mortality (>50% in this study) and side effects of therapy.

Unsurprisingly, there needs to be a nuanced approach in interpreting these results because of many inherent pitfalls with the population-based data, some of which were accounted for by the authors. First, SEER consists of observational data and was never designed for treatment comparisons per se. Treatment groups are obviously not randomized, and in this case multivariate analysis was performed in an attempt to minimize the influence of selection and other biases. However, there are no data on comorbidities, one of the most important factors that could influence treatment decisions.

In the group of RP patients, 18.2% received adjuvant RT and this is the only information provided on outcome after primary treatment, with no data on pathologic status, whether lymph

node dissection was performed and, if so, to what extent, or the timing of androgen deprivation therapy (ADT).

There are even potential latent confounders within SEER data such as surgical experience, and this earlier timeframe does include the “learning curve” for many robotic surgeons. In addition, radiation delivery has evolved over time, and recent data for combined EBRT + BT demonstrated a significant advantage over EBRT for Gleason 9–10 patients in a study by Kishan and colleagues [3]. Moreover, guidelines recommend long-term ADT for high-risk patients (level of evidence 1b, grade of recommendation A)[1], meaning that all patients in the RT cohort should have received ADT for appropriate comparison with the RP cohort, and this is not precisely known for this study.

Furthermore, the study had median follow-up of <5 yr (44 mo), which is too short in the natural treated history of PC, even for high-risk disease. The survival curves reveal mortality comparable with results from other observational studies for the first 4 yr[2,4]. The differences in estimated mortality at 5 and 7 yr are probably because of the small number of patients at risk after 3 yr of follow-up and the usual biases inherent to SEER. It is even challenging to guess whether the curves would become wider or even narrower with this type of data.

In summary, these results are suggestive at best that RP could be the preferred treatment for younger men. One thing known is that RP is the single most effective modality, since radiation therapy includes ADT for high-risk disease. Randomized clinical trials are being conducted in high-risk disease and perhaps subset analyses for younger males will be provided.

**Conflicts of interest:** The authors have nothing to disclose.

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