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**Re: Bladder Preservation with Twice-a-day Radiation plus Fluorouracil/Cisplatin or Once Daily Radiation plus Gemcitabine for Muscle-invasive Bladder Cancer: NRG/RTOG 0712—A Randomized Phase II Trial**

Coen JJ, Zhang P, Saylor PJ, et al

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**Experts' summary:**

This multicenter randomized phase 2 study compared chemoradiation (CRT) with fluorouracil/cisplatin and twice daily radiation (the RTOG “standard”, arm 1) versus gemcitabine and once daily radiation (arm 2) in fit patients with nonmetastatic advanced bladder cancer. After 40-Gy CRT (induction phase), biopsy-proven complete responders went on to 64 Gy while nonresponders underwent surgery. All patients were offered adjuvant chemotherapy. Two groups of 33 patients had median follow-up of 5.1 yr. Complete responses after induction were found in 88% in arm 1 and 78% in arm 2. Adjuvant chemotherapy was given in 18 patients in arm 1 and 17 in arm 2. Grade 3 and 4 toxicity was not significantly different: 64% in arm 1, although more in the adjuvant chemotherapy phase, versus 55% in arm 2, with more toxicity in the CRT phase. After 3 yr, freedom from distant metastasis was 78% for arm 1 versus 84% for arm 2, with corresponding metastasis-free survival rates of 67% and 72%. In conclusion, both regimens achieved a high response rate. Patients receiving gemcitabine with once daily radiation experienced less toxicity, as expected, and efficacy was at least as good as in the arm with fluorouracil/cisplatin and twice daily radiation.

**Experts' comments:**

Since the outcomes from radical cystectomy have not improved over several decades, treatment strategies other than radical cystectomy are gaining in popularity for nonmetastatic invasive bladder cancer with the aim of less invasive procedures and/or better outcomes with regard to survival and quality of life. Some improvement seems possible with extended node dissection, although only in a subset of patients [1]. Neoadjuvant chemotherapy appears to improve overall survival by 5–8% in trials, but the advantage in real life seems very limited [2].

Bladder preservation with CRT is one such strategy. The 2018 European Association of Urology guideline on metastatic and muscle-invasive bladder cancer mentions CRT or multimodal treatment as the only realistic form of bladder preservation, and the recommendation is to consider CRT in highly selected, well-informed, and compliant patients, since long-term survival is comparable to the results after radical cystectomy. It is also a good

option when patients are unfit for cystectomy. Some selection is indeed necessary. The tumor should not be too large and ideally resected radically. Furthermore, carcinoma in situ and hydronephrosis are relative contraindications. However, multiple studies show good local control and long-term bladder function, low rates of salvage cystectomy, and high survival rates after CRT [3]. Whether long-term survival is similar to that after cystectomy remains unknown [4].

Even after patient selection, cisplatin-based chemotherapy can be an issue. The average age of patients with invasive bladder cancer is the mid-seventies. Many have a smoking history, and performance status and renal function are often impaired. No comparative radiosensitizer data exist, and CRT is currently administered with cisplatin, 5-fluorouracil/mitomycin C, carbogen-nicotinamide, and gemcitabine. These authors are to be complemented for succeeding in a randomized controlled trial that compares not only two chemotherapy regimens but also once and twice daily radiotherapy. Toxicity data for the two chemotherapy regimens show that grade 3 and 4 toxicity was somewhat higher in arm 1 (21/33 patients, 64%), although it was seen more in the adjuvant chemotherapy phase. In arm 2, grade 3 and 4 toxicity was seen in 18/33 patients (55%) and observed more often in the CRT phase. So even in this healthy patients cohort (61/66 patients had a performance status of 0) CRT has a significant risk of side effects, predominantly caused by chemotherapy, and this did not differ between the two arms. The efficacy results in both arms exceeded the goal set for the trial, which was 3-yr freedom from distant metastasis of >75%, with 78% in arm 1 and 84% in arm 2 achieving this result, and corresponding metastasis-free survival at 3 yr of 67% and 72%. It must be realized that the selected patients were above average: 44/66 were younger than 70 yr and all were fit for radical surgery and radiation. Moreover, nonresponders went on to cystectomy, although this was only performed for three patients in arm 1 and five in arm 2. What also increased the results, although it is not standard therapy, was the use of adjuvant chemotherapy after consolidation CRT or cystectomy, which was done for 18 patients in arm 1 and 17 patients in arm 2.

An interesting issue is the contribution of the initial tumor resection. In this trial a “maximally safe transurethral tumor resection” is mentioned. It seems obvious that better initial tumor resection should lead to better CRT results, but this remains to be proven.

My conclusion is that CRT is gaining interest. This trial confirms good efficacy results, although the positive patient

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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