Occult distant micrometastasis at the time of radical cystectomy leads predominantly to distant failures in patients with locally advanced muscle-invasive transitional cell carcinoma of the bladder. Cisplatin-based combination chemotherapy enhances survival in patients with metastatic urothelial cancer. Studies evaluating adjuvant chemotherapy have been limited by inadequate statistical power. However, randomized clinical trials have demonstrated a survival benefit for neoadjuvant cisplatin-based combination chemotherapy, which should be considered a standard of care. In addition, neoadjuvant therapy may assist in the rapid development of novel systemic therapy regimens, since pathologic complete remission appears to be a powerful prognostic factor for long-term outcomes. Patients who are either unfit for or refuse radical cystectomy may benefit from neoadjuvant chemotherapy with or without radiation to enable bladder preservation.

The use of chemotherapy as adjuvant or neoadjuvant treatment of localized, invasive transitional cell carcinoma (TCC) of the uroepithelium remains controversial, with no clear consensus in the literature. Survival of patients with invasive bladder TCC treated with cystectomy alone is overestimated in large series due to the inclusion of patients with recurrent but superficial TCC. The long-term survival rate with invasive cancer is less than 50%, and primarily dependent upon clinical stage.[1,2] Patients with invasive bladder TCC treated with trimodality bladder-preservation therapy instead of cystectomy appear to have comparable survival,[3,4] although the two approaches have never been compared in randomized trials.

The poor survival after local treatment for TCC, usually due to distant recurrence, has provided impetus for studies of systemic treatment before or after local treatment. Multiple randomized studies have been attempted, some with clear results, but many with either an ambiguous outcome or failure due to lack of accrual. Drs. Sonpavde and Lerner have comprehensively reviewed the clinical trials that have been carried out, particularly for neoadjuvant chemotherapy.

Chemotherapy in TCC
Using metastatic disease as a springboard for the evaluation of different chemotherapy regimens, experts in TCC have concluded that the current standard of care is GC (gemcitabine [Gemzar]/cisplatin) or MVAC (methotrexate/vinblastine/doxorubicin [Adriamycin]/cisplatin).[5,6] For the many patients with metastatic TCC and suboptimal renal function or other medical comorbidities, no clear treatment paradigm exists. Since carboplatin is inferior to cisplatin in the treatment of TCC, taxane-based regimens such as gemcitabine/paclitaxel might be the most appropriate alternatives in nephron-challenged individuals.[7-9]

The majority of adjuvant or neoadjuvant chemotherapy trials have utilized cisplatin-based regimens as well. As Drs. Sonpavde and Lerner point out, the adjuvant trials have been small and inconclusive, or have failed to accrue sufficient patients. The ongoing European Organisation for Research and Treatment of Cancer (EORTC) study offers some hope that we may yet benefit from a large, definitive trial of adjuvant chemotherapy in TCC, but the hope is fading due to difficulty with accrual.

Clinical Trials in Neoadjuvant Chemotherapy for TCC
Four large published investigations of neoadjuvant chemotherapy in TCC have been considered at length individually, and as core components of numerous meta-analyses: the EORTC/Medical Research Council (MRC) trial, the Southwest Oncology Group (SWOG) trial, and the Nordic Cystectomy I and II trials.[10-13] Although improvements in pathologic complete remission were observed, it is important to note that not one of these trials demonstrated a statistically significant survival benefit to neoadjuvant chemotherapy.

The largest trial was the EORTC/MRC study, which initially demonstrated a trend toward improvement in survival with CMV chemotherapy (cisplatin/methotrexate/vinblastine) compared to no chemotherapy among 976 patients. In a 2002 update, the investigators reported a statistically significant benefit of 5.5% after longer follow-up, though the findings have not been published. Meta-analyses combining data from these and other smaller studies suggest a small but statistically significant benefit to neoadjuvant chemotherapy. Proponents of neoadjuvant treatment such as Drs.
Sonpavde and Lerner point to the meta-analyses as proof of benefit, but the clinical significance of the small statistical finding remains dubious. In patients treated with bladder-preservation therapy, a Radiation Therapy Oncology Group (RTOG) randomized trial demonstrated that there was no benefit to neoadjuvant CMV chemotherapy.[14]

The World Health Organization and the Societe Internationale d'Urologie convened a panel of international experts to critically review the published literature and formulate consensus recommendations in the management of patients with locally advanced and metastatic TCC.[6] With regard to neoadjuvant chemotherapy, the panel concluded that overall survival for the whole group was not affected. Certain subsets did exhibit improved survival. Notably, patients treated with cisplatin-based combination chemotherapy had a 5% improvement in survival compared with untreated patients—from 45% to 50%. The numbers were similar to the EORTC/MRC data, since that trial constituted most of the patients in the meta-analysis. The panel further concluded that patients with clinical stage T2 tumors had at best a modest benefit, whereas patients with more advanced-stage disease potentially had a more substantial benefit.

A major benefit to adjuvant chemotherapy over neoadjuvant chemotherapy is the ability to stratify patients based on pathologic stage, or based on tumor biomarkers.[15] In particular, patients with T2 tumors may suffer toxicity from chemotherapy without benefit, and should probably not be treated with chemotherapy. Initial cystectomy would allow definitive separation of T2 from more advanced-stage disease. Furthermore, as rationally targeted drugs are tested in TCC and hopefully are proven to add therapeutic value, the need for sophisticated tissue-based analysis prior to individually tailored systemic therapy will increase. Another consideration is that most urologic surgeons prefer immediate cystectomy, and subsequently refer patients for consideration of medical therapy.

**Conclusions**

Left with uncertainty from clinical trials in both contexts, we have to factor in practical considerations and quality of life as well. In practice, both urologists and medical oncologists at many academic centers and in the community have concluded that adjuvant chemotherapy can be applied more rationally than neoadjuvant chemotherapy. Our need to enroll patients on clinical trials to establish evidence-based best clinical practice remains. However, the reality is that most patients with invasive TCC will have definitive local therapy first, and then be considered for adjuvant therapy based on stage and other prognostic or predictive factors.

—M. Dror Michaelson, MD, PhD

**Disclosures:** The author has no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

**References:**


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