

Open to Debate

The Motion: Perioperative Chemotherapy in Muscle Invasive Bladder Cancer Improves Survival



For the motion

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Cystectomy is considered the gold standard treatment for localized muscle-invasive bladder cancer, but despite this treatment around 50% of patients with muscle-invasive bladder cancer will die. In contrast, 10–20% of patients with clinically evident metastatic bladder cancer treated with platinum-based chemotherapy will be long-term survivors. These rates are similar to those seen in patients

with metastatic breast and colorectal cancer who are treated with chemotherapy. In breast, lung and colorectal cancer, the value of early chemotherapy in operable localized and locally advanced disease is well established; relative survival is improved by 5 to 30%. This survival benefit established the rationale for the evaluation of early administration of chemotherapy in bladder cancer patients with operable localized and locally advanced disease. Based on the theoretical and observed benefits, the treatment paradigm has shifted toward multimodality therapy rather than surgery alone.

It is currently widely recognized that the use of perioperative chemotherapy and an adequate pelvic lymph node dissection are two important factors influencing long-term survival [1]. The survival benefits of neoadjuvant chemotherapy have been established in two large randomized trials and three meta-analyses (Medical Research Council, Ontario, Cochrane) support the concept that neoadjuvant chemotherapy for patients with muscle-invasive bladder cancer provides a survival benefit of 5 to 5.6% greater than surgery alone [2]. However, a survival benefit still needs to be shown in the adjuvant setting for those patients who have not received neoadjuvant chemotherapy and who have extravesical or node-positive disease following cystectomy. Consequently, enrolment in a clinical trial in this area should be encouraged.

Further advantages of administering chemotherapy prior to surgery include better treatment tolerance, the ability to assess treatment response of the primary tumour to chemotherapy and pathologic down-staging, which provide prognostic significance, as well as immediate treatment of micrometastatic disease. This is of importance as major pathologic response correlates with prolonged sur-

vival. The availability of post-treatment tissue for analysis of molecular prognostic and predictive markers is also a plus. Finally, there is the possibility of bladder preservation in highly selected and well informed patients who achieve a clinical P0 status.

The primary drawbacks claimed against neoadjuvant chemotherapy are the toxicity of chemotherapy in certain patients and the delay in carrying out potentially curative surgery. However, in certain healthcare systems, waiting lists might delay surgery anyway and this provides a window of opportunity to treat the patient with neoadjuvant chemotherapy. Another negative factor is that pathologic stage is not always correctly determined before cystectomy and some low stage, low-risk patients may unnecessarily receive neoadjuvant chemotherapy. Toxicity and proper patient selection for either chemotherapy or other investigational approaches are issues that are now starting to be addressed.

Urologists are sometimes reluctant to pursue neoadjuvant chemotherapy because they fear that it may increase the incidence of perioperative morbidity. However, when neoadjuvant and adjuvant chemotherapy have been compared, neoadjuvant chemotherapy did not increase perioperative morbidity [3]. In the past, studies were conducted with methotrexate, vinblastine, adriamycin and cisplatin (M-VAC) or cisplatin, methotrexate, and vinblastine (CMV) regimen, which are more toxic than those currently used. Retrospective data show that neoadjuvant gemcitabine /cisplatin (GC) is similar to M-VAC in both pathologic response in the bladder and time to cystectomy but is better tolerated. Besides, it may be possible to predict responses to chemotherapy based on the genomic profile of the tumour. Advances in molecular research may help to develop reliable tumour markers that enable the clinician to tailor more accurately the appropriate therapy for

individual patients. Apart from the variable expression of intratumoral determinants of cytotoxic response (P53, P21, vascular endothelial growth factor, ratio matrix metalloproteinases-9/E-cadherin), there is also an emerging understanding of the role of molecular pharmacology in the prediction of response to chemotherapy. Recently ERCC1 and BRCA1 have been correlated with survival in patients with bladder cancer treated with chemotherapy [4,5].

It is plausible that in the immediate future treatment will be customized for each individual on the basis of tumour gene expression. This will allow us to model chemotherapy according to predicted responses and chose more accurately those patients who might clearly benefit from neoadjuvant treatment. This will substantially increase the survival benefits that have already been observed.

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Against the motion

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neobladders and almost 2000 cystectomies have been carried out in Ulm. For the past 15 years he has been editor-in-chief of *Urologe*, the official journal of the Deutsche Gesellschaft für Urologie, which has a circulation close to 10,000 making it one of the most widely distributed urological journals. Dr. Hautmann has trained urologists of renowned institutions, among them the chair persons of Berlin's Charité, the University of Munich and a chair person in the US. He is member and an honorary member of many prestigious urological associations, including the America Urological Association.

In 2005, the Advanced Bladder Cancer (ABC) Meta-Analysis Collaboration group retrospectively eval-

uated all randomized studies on neoadjuvant [1] and adjuvant [2] chemotherapy in patients with invasive bladder cancer. The data on neoadjuvant treatment prompted an enthusiastic editorial comment in the *Lancet* [3]: "Vale and colleagues' meta-analysis provides strong evidence that neoadjuvant platinum containing combination chemotherapy improves survival in patients with locally advanced bladder cancer. Their meta-analysis thus defines a new standard of care and is the end of the beginning for combined modality therapy in locally advanced bladder cancer." To determine the optimal use of chemotherapy in the neoadjuvant and adjuvant setting in patients with advanced urothelial cell carcinoma, a consensus conference by the World Health Organization (WHO) and the Société Internationale d'Urologie (SIU) again critically reviewed the published literature. This article reports of international guidelines for the treatment of those patients [4]. My opponent has been the lead author of this excellent piece of work, which includes key statements on the use of chemotherapy in this setting. The statement on adjuvant chemotherapy is: Available trials provide insufficient evidence to support the routine use of adjuvant chemotherapy in clinical practice (grade B). Two key statements were made on neoadjuvant chemotherapy:

1. Available data suggest that for "average-risk" cancer patients with cT2, the benefit of adding chemotherapy to local therapy is at best modest. Likewise, all available studies suggest a much more substantial benefit for patients with high-risk disease, such as cT3b cancers (grade B).
2. The quality of the surgery is a confounding factor in these studies (grade B).

There has been a recent report by David et al. [5] from the national cancer data base on the limited use of perioperative chemotherapy for stage III bladder cancer during 1998 to 2003. Treatment patterns were analyzed in 7161 patients with stage III bladder transitional cell carcinoma. Perioperative chemotherapy was administered to 11.6% of patients with stage III bladder transitional cell carcinoma, with 10.4% receiving adjuvant chemotherapy and 1.2% receiving neoadjuvant chemotherapy. To assess the effect of adjuvant chemotherapy (Acht; M-VAC or GC) on the rate of cancer-specific survival and overall survival, a US/Canadian study group has evaluated cancer-specific survival after cystectomy following adjuvant chemotherapy for bladder cancer in a matched case-control study [6]. This analysis showed that neither M-VAC nor GC chemotherapy had an

effect on cancer-specific of overall survival after radical cystectomy in high-risk patients. Finally, most urologists worldwide have not been convinced that all operable patients with invasive bladder cancer should receive neoadjuvant chemotherapy. Most papers conclude that cystectomy is the "gold standard" against which to compare new treatments [7].

Let us now look at three factors influencing what might have gone wrong: quality of surgery, study populations and the chemotherapy applied. In regard to surgery, radical cystectomy quality and pelvic lymph node dissection (PLND) extent have a major impact on invasive bladder cancer survival. Who performs the surgery and where and how well it is done matter. The mortality from cystectomy is higher at low versus high volume hospitals (3.1% vs. 0.7%). Experienced surgeons who frequently perform cystectomy achieve better survival and fewer complications than surgeons who perform an occasional cystectomy. Even more compelling evidence of the importance of surgical quality was provided by an analysis of INT-0080 in the US involving multiple institutions and surgeons. Negative surgical margins and 10 or more lymph nodes removed were associated with better overall survival independent of patient age, pathological stage, nodal status and whether chemotherapy was given [8,9]. These surgical factors also predicted pelvic relapse, which is a death knell in most patients. Of the patients, 15% had local recurrence and all eventually died of the disease. Local recurrence developed in 68% of cases with positive surgical margins compared with 6% with negative margins, while high versus low volume urologists had a positive margin rate of 4% versus 14%. This cooperative group trial showed that the quality of cystectomy and PLND directly impact the chances of survival and they are both surgeon dependent. Not all of these aspects have been considered in the studies of the two meta-analyses [1,2]. In the Southwest Oncology Group (SWOG) study, the lymph node status was unknown in almost 50% of patients, the positive margin rate remained unclear and 268 patients came from 109 institutions and were operated on by 106 surgeons [8-10]. The quality of surgery is further challenged when one compares a 20% survival advantage in our recent surgery only series [11] against the control arm of the neoadjuvant ABC study (68% vs. 45%) [1]. A potential excuse for all of these meta-analyses is that the patients were recruited beginning almost 3 decades ago.

Let us consider study populations. In the EORTC, the SWOG and Nordic studies, most patients were young (median age 63-65 years), with an excellent performance status and good creatinine clearance.

It is thus questionable as to whether or not these results can be generalized to most of the usually elderly patients presenting with bladder cancer. In regard to the chemotherapy regimen applied, from the neoadjuvant meta-analysis it appears that 20 patients need to be given chemotherapy to obtain a survival gain of one patient at 5 years. In addition, the meta-analysis provides no data on the price to pay by all treated patients in terms of toxicity and quality of life. Almost all studies included in the meta-analyses are flawed when one considers the three aspects discussed above.

In conclusion, there is insufficient proof that the routine use of adjuvant chemotherapy is effective. It is also clear that there is no indication to treat a stage II tumour perioperatively with chemotherapy. Such treatment should be reserved for study patients, since we are currently unable to prove that perioperative chemotherapy in muscle-invasive bladder cancer improves survival.

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Rebuttal 1

J. Bellmunt

A meta-analysis has provided strong evidence that neoadjuvant platinum containing combination chemotherapy improves survival in patients with locally advanced bladder cancer. The most important point of discussion is how relevant a 5–6.5% benefit might be. By itself it might seem insufficient regardless of statistical significance. However, in other oncological settings, such as breast cancer (i.e. use of chemotherapy in node negative breast cancer), for most clinicians an increase in overall survival of 6–10% makes therapy worthwhile [1]. Additionally, even though doctors and nurses might be less likely to accept radical treatment for minimal benefits, most patients are willing to accept intensive chemotherapy for small benefits [2].

I agree that in 2008, the evidence is still insufficient to support the clinical use of adjuvant chemotherapy and that there is an urgent need for further studies.

Regarding neoadjuvant chemotherapy, Dr Hautmann raises the point of whether the benefit seen in the meta-analysis is worthwhile. It is good to know that with further follow-up (beyond 7 years), the benefits observed in the EORTC neoadjuvant study are still increasing with even greater gains observed in survival (R. Hall, personal communication). Another point raised is that all available studies suggest a much more substantial benefit for patients with high-risk disease, such as cT3b cancers. However, the fact is that in the study reported by Grossman et al [3], improvement in median survival was seen even in patients with T2 tumours receiving chemotherapy in the stratified analysis.

The heterogeneity of patients with bladder cancer and the unreliable nature of retrospective analysis should make us more keen to keep on researching this area. It is obvious that the quality of the surgery is central, and oncologists cannot adequately test new strategies without a good surgeon. To extrapolate and generalize the results coming from clin-

ical studies to the 'global' population of patients is always risky. However, applying strict eligibility criteria is the only way we have to change paradigms and establish new standards when performing clinical trials. A new wave of trials called "Expanded Access Programs" is now being designed to establish the use of new drugs in a more realistic patient population.

Even though we might agree that cystectomy is still the gold standard, long-term outcome in disseminated and advanced bladder cancer should not leave us indifferent to the potential role of chemotherapy in the perioperative setting. It is true that 20 patients need to be treated to obtain a single survival gain, but this is what we see in other tumours types where chemotherapy is routinely applied. Decisions not to provide chemotherapy due to small benefits should be taken at a policy level, since it may be difficult for the clinician to set a limit for the individual patient.

In conclusion, patients with cancer are much more likely to opt for radical treatment with minimal

chance of benefit than people who do not have cancer. It would be easy to conclude that this is an irrational decision resulting from the tremendous stress imposed on these patients by their disease. However, we should focus on identifying those patients who might benefit from this additional treatment.

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Rebuttal 2

R.E. Hautmann

It is important to preface this rebuttal with the reality of the disease: high grade invasive bladder cancer is a lethal disease and any short cuts/mistakes in the treatment can be lethal to the patient. Dr. Bellmunt and I agree that available trials provide insufficient evidence to support the routine use of adjuvant chemotherapy in clinical practice. Results of larger collaborative international adjuvant chemotherapy trials will be needed before the true value of adjuvant chemotherapy can be assessed. The remainder of this rebuttal focuses on neoadjuvant treatment. The MRC trial showed in a subset of patients a 5% absolute improvement in survival at 5 years [1]. This subset analysis must always be viewed in the context of the overall results, which were not positive. The validity can be questioned of pooling studies of neoadjuvant single-agent cisplatin therapy conducted in the 1980s with trials of combined chemotherapy conducted in the 1990s, as well as the relevance of the results to current practice in view of the various improvements made in the field (surgical techniques, postoperative care, newer agents etc.). There is no information for patients with poor performance status or patients with poor creatinine. Were the patient populations representative of the elderly patients with bladder cancer that are most commonly seen? It is thus questionable as to

whether or not these results can be generalized to most of the usually elderly patients presenting with bladder cancer.

Dr. Bellmunt, like almost all authors that favour chemotherapy, uses a 5-year cancer specific survival rate of around 50% for localized muscle invasive bladder cancer. This is in accordance with the 45% of the monotherapy arm of the MRC study. However, contemporary surgery-only series from high volume centres report an almost 70% cancer specific survival rate at 5 years [2]. Currently it is clear that chemotherapy cannot rescue a bad operation!

Dr. Bellmunt accepts that chemotherapy can cause a delay of potentially curative surgery in "certain patients". "Certain patients" comprise a minimum of 40% of all patients subjected to neoadjuvant chemotherapy (non-responders). A recent systematic review of the literature on delay in the surgical treatment of bladder cancer and survival concluded that there is a window of opportunity of less than 12 weeks from diagnosis of invasive disease to cystectomy. Of the 13 papers analyzed, eight found a significant association between delay and cystectomy; in two papers, the delay was an independent variable and in the other six papers, the delay was associated with a higher pathological stage [3]. Even if chemotherapy and completion of a high-quality cystectomy are associated with improved survival, an unintended consequence of this treatment paradigm is that some patients refuse surgery, especially if they have no evidence of

tumour in the bladder after chemotherapy. The outcome of such patients is widely believed to be dismal. For example, of 39 patients who did not undergo cystectomy in the US intergroup trial, only 11% survived [4].

Dr. Bellmunt points out that individual or multiple molecular markers may identify tumours that are more likely to respond to chemotherapy and to select patients for bladder preservation. I agree! However, to date analyses of putative tumour markers have been retrospective and none has been validated prospectively in clinical trials.

Conflicts of interest: The authors have nothing to disclose.

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