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European Association of Urology

Platinum Priority – Editorial

Referring to the article published on pp. 712–718 of this issue

Improving the Outcome for Invasive Bladder Cancer: The Debate Regarding Pelvic Lymphadenectomy Moves From If to How

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The prognosis from invasive bladder cancer (BCa) has changed little over the last 30 yr [1]. Disease-specific survival remains around 50%, and it appears BCa is at risk of falling behind other solid malignancies. During the last 15 yr, for example, stage for stage improvements in the survival from breast cancer have averaged 1% per annum and are now around 30% better [2]. Improvements in the outcome of invasive BCa will probably occur from a better understanding of the disease, from a more rational approach to its detection and treatment, and from multimodal therapy. The latter needs to be developed through well-constructed clinical trials and requires the collaboration seen during the development of intravesical therapies. The likelihood of a specific (molecular) therapy to dramatically improve survival in BCa is small, given that the disease is characterized by numerous genetic and epigenetic alterations and the lack of familial syndromes [3].

We need to learn more about BCa. The etiology and biology of invasive BCa are only partly understood. We know smoking and occupational carcinogens are risk factors for the disease, but why do some patients develop indolent tumors while others with similar exposures present with high-grade or metastatic cancers? We suspect the disease phenotype reflects specific carcinogens (in isolation or combination), patient factors (genotype), and the sequential order of exposures and molecular alterations. With regard to biology, we recognize that invasive tumors are similar to high-grade non–muscle-invasive cancers and distinct from low-grade tumors [3]. But do all invasive cancers arise from carcinoma in situ, and therefore, could they all be detected at an earlier stage? Given that much of the economic burden of BCa is spent monitoring low-risk, low-grade cancers, it would be appealing to switch this resource to screening patients at high risk of invasive disease. Observations in other cancers suggest this change alone could make more of an impact on survival than any other [4].

We should try to treat the disease more rationally. One facet of this is the realization that some patients have microscopic metastatic foci within regional nodes and that long-term survival can be achieved with their excision. This concept has been slow to reach urology, compared with other cancers, and is well demonstrated within this issue of *European Urology* [5]. May et al report data from >2500 patients who underwent radical cystectomy at one of eight German institutions. This series spans 20 yr and includes 477 patients with lymph node metastases that met the study's inclusion criteria. Nearly 40% of this cohort survived 5 yr, with respect to their cancer, and as previously observed [1], this proportion did not increase over 20 yr of recruitment. When pT2 disease was considered, long-term survival reached 50%. These data appear optimistic but incomplete. The context of disease-specific survival (ie, overall survival), for example, is not reported. If one assumes competing mortality of 25% at 5 yr [6], then 20–30% of patients with metastatic disease are alive 5 yr postcystectomy. One would hope that improvements in the management of pulmonary and ischemic heart disease have reduced competing mortality in the last 20 years, so perhaps overall survival is improving. Furthermore, were surviving patients disease free at 5 yr or merely living through cycles of palliative chemotherapy?

To explore the role of lymphadenectomy, the authors developed and compared statistical models to evaluate the number of excised nodes (as a surrogate for the extent of lymphadenectomy), the number of involved nodes, and the

DOI of original article: 10.1016/j.eururo.2011.01.030

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 doi:10.1016/j.eururo.2011.02.007

lymph node density (ie, the proportion of excised nodes involved with cancer). These analyses revealed that the number of excised nodes was almost as important as the nodal density and that in node-positive disease, the nodal density performed better than the TNM classification. These findings suggest conclusions that require evaluation.

First, is lymphadenectomy now a standard component of radical cystectomy? Most experts within this field believe the answer to this question is undoubtedly *yes*. The presented data add further weight to this conclusion, but one should always caution observations made outside of controlled environments. For example, evidence in prostate cancer suggests that metastatic disease arises from primary tumors rather than from metastases [7]. Perhaps the surviving patients had indolent metastases and removal of the primary cancer was sufficient. Although a randomized controlled trial is required to disprove this latter explanation, the weight of the evidence is sufficient and the risks of the procedure are minimal enough to believe in lymphadenectomy.

Second, should we all practice an extended pelvic lymphadenectomy? The data presented support this conclusion by detailing that a higher nodal yield was associated with a better patient outcome. But nodal yield is not just a marker of lymphadenectomy extent. It varies with lymph node package size, pathology interest, and surgical endeavor [8,9]. These data, however, sit nicely within the field (reviewed within Table 4 of May et al. [5]) and complement nodal mapping studies [10]. Given these observations, it is probably now time to define the new gold standard of lymphadenectomy as one that reaches the level of the ureteric crossing of the common iliac vessels. This approach would excise 90% of potential nodal landing sites from the bladder [10].

Third, is it time to review the TNM nodal staging classification? Although the data presented by May et al. [5] suggest that nodal density was more important than node size (ie, N1 or N2), one must remember these were only node-positive cases. So can we extrapolate the outcomes seen to all cases? In addition, to move to this classification would require a standard technique in all procedures. As admirable as this is, it is probably unrealistic to expect.

Fourth, can we use nodal density to refine and stratify patient care? As shown, nodal density appears to predict death from BCa. Therefore, one should be able to target aggressive adjuvant treatment to the patients at highest risk. Appealing as this seems, the presented data do not support such a hypothesis. Only one-third of patients in this series received adjuvant chemotherapy, and its use was not associated with outcome, whether in all patients or when stratified for nodal density. But could patient selection be responsible for this? A weakness of this work is that potential confounding bias cannot be explored due to its multicenter and retrospective nature.

Although this report contains potential bias due to its retrospective nature, multi-institutional setting, and duration of data collection, the findings are a testament to the fact that some patients with metastatic BCa can be cured with surgery. For this, the authors are to be congratulated for the collaborative nature of this work.

Conflicts of interest: The author has nothing to disclose.

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