Management of Node-Positive Bladder Cancer After Neoadjuvant Chemotherapy and Radical Cystectomy: A Survey of Current UK Practice

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Abstract

There is little evidence on how patients with bladder cancer who have positive lymph nodes after radical cystectomy and neoadjuvant chemotherapy should be managed. An electronic survey was sent to all UK pelvic oncology centers to determine their current practice and rationale for treatment. Opinions were divided between the choice of chemotherapy and timing of administration.

Introduction: Because of the lack of published evidence, this study was done to explore the decisions and rationale of uro-oncology consultants regarding the treatment of patients with muscle-invasive bladder cancer who have positive lymph nodes after radical cystectomy (RC) and neoadjuvant chemotherapy (NAC). **Materials and Methods:** An electronic survey was sent to UK pelvic cancer centers regarding: (1) choice of NAC regimen; (2) indications for reimaging; (3) choice and indication of adjuvant chemotherapy (AC) for patients with nodal disease after NAC and RC; (4) choice and indication of chemotherapy regimen if disease continues to progress in patients with advanced bladder cancer; and (5) guidelines used by those surveyed. **Results:** Consultant uro-oncologists from 77% of UK pelvic cancer centers responded, who treated a median of 13 patients per year with NAC before RC. Three cycles of gemcitabine and cisplatin was the most common NAC regimen, with 93% and 67% respondents giving it for downstaging of cN1- and cN2- and 3-positive patients, respectively. Forty-five percent would not give AC after NAC and RC in patients with positive lymph nodes. The patient's performance status, followed by response to NAC were key factors in dictating the use of AC. In the presence of disease progression, 46% of participants would use a taxane. Fifty-two percent of responders do not follow any guidelines. **Conclusion:** In the United Kingdom, the treatment of patients with nodal disease after NAC and RC is variable. There is little evidence on which to base the management of such patients. The creation of national and international guidelines might help clinicians to optimize care for these patients.

Clinical Genitourinary Cancer, Vol. 13, No. 3, e153-8
Keywords: Lymph node, Muscle invasive bladder cancer, Transitional cell carcinoma

Introduction

Radical cystectomy (RC) is the mainstay of treatment for patients with muscle-invasive bladder cancer. However, despite radical surgery, up to 44% of patients with extravesical disease without lymph node involvement will experience recurrence of disease within 5 years and 37% will develop distant metastases.[1,2] The use of neoadjuvant chemotherapy (NAC) has been shown to downstage primary bladder cancer and reduce the incidence of lymph node-positive metastatic disease at RC.[3] In addition, NAC results in a modest but significant 5% absolute survival advantage at 5 years

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Submitted: Sep 12, 2014; Revised: Nov 12, 2014; Accepted: Nov 13, 2014; Epub: Nov 20, 2014

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1558-7673/$ - see frontmatter
http://dx.doi.org/10.1016/j.clgc.2014.11.006

(hazard ratio [HR], 0.87; 95% CI, 0.78-0.9; $P = .016$).[4] This has led to the recommendation that all patients with mucle-invasive bladder cancer (MIBC; $\geq$ T2 disease) should be treated with platinum-based NAC.[5] Commonly used NAC regimens include 3 to 6 cycles of M-VAC (metothrexate, vinblastine, doxorubicin, and cisplatin) and Gem/Cis (gemcitabine and cisplatin).

Despite NAC, 19.3% of patients are found to have lymph node-positive disease on postoperative pathological analysis.[3] Currently, there are no guidelines on how to manage this group of patients. Clinicians are therefore faced with a dilemma. Further use of platinum-based chemotherapy in the adjuvant setting, after patients have been treated with NAC, is limited because of the development of resistance. Moreover, the only licensed second-line chemotherapy treatment in Europe is vinflunine, a third-generation, semisynthetic vinca alkaloid, that recently failed to gain approval by the National Institute for Healthcare Excellence (NICE) in the United Kingdom. Patient-related factors such as performance status, NAC regimen used, response to previous chemotherapy, and the presence of visceral metastatic disease must be taken into account. In a review, Herr et al reported that because of postoperative complications, poor performance status, impaired renal function, psychological factors, and patient choice, only 50% to 70% of patients after RC in randomized trials received at least 3 cycles of chemotherapy.[6] In additon, the lack of a standardized definition to determine response to adjuvant chemotherapy (AC) confounds the issue. T0 status or radiological downstaging are commonly used to determine NAC response although this might be attributed to an excellent transurethral resection of bladder tumor.

In view of the lack of evidence on which to base the management of patients with positive postoperative nodal disease despite previous NAC, and to gain an insight of the current practices and mangement of this group of patients in the United Kingdom, we carried out a survey of uro-oncologists. Our specific objectives were to assess: (1) the regimen of NAC used; (2) the use of radiological imaging in cases of positive nodal disease after NAC and RC; (3) current practices on the use of AC in this setting; and (4) factors influencing decisions about the regimen of AC.

Materials and Methods

Survey Tool Development

A 13-question survey was developed in 3 iterative phases to ensure robustness and feasibility. Specifically, the tool sought to demonstrate:

- Content validity: the survey should capture all relevant aspects of the treatment of patients with positive nodal disease after NAC and RC.
- Face validity: the survey should be perceived as relevant and comprehensive by expert oncologists.
- Feasibility: the survey should be feasible to complete in that the questions/items ought to be understood easily and uniformly by the intended respondents, and the tool should not take too long to complete.

Aiming to achieve these properties, in phase 1, the literature on the treatment of patients with positive nodal disease after NAC and RC was reviewed and key themes were extracted (NV, BWL). The main themes were the choice of NAC regimen, indications for reimaging, the choice and indication of initial AC choice, the indication of subsequent chemotherapy regimen if patients' disease progresses, and guidelines used by participants.

In phase 2, the themes that were extracted in phase 1 were discussed within the research team and a long-list of relevant questions was formulated for potential inclusion in the survey. To ensure adequate domain coverage and feasibility, 3 experts blinded to phase 1 contributed to phase 2: 3 Consultant Urologists (TL, JA, GB), and 2 Consultant Oncologists (HP, SH). The selected questions mirrored the themes that were extracted in phase 1.

Finally, in phase 3, the draft survey tool was piloted with a group of clinicians (including JSAG) with expertise in survey development and validation to ensure feasibility (adequate question comprehension and reasonable length of time taken to complete survey). A few amendments were carried out as a result of this phase, resulting in the final version of the tool for data collection (a copy of the final tool used is available from the corresponding author upon request). The final survey incorporated multiple choice questions (n = 6), and open-ended questions (n = 7), for which participants freely recorded their views.

Participants

Participants were recruited between March and July 2013. Recruitment was purposive to ensure representation of oncologists who treat patients with advanced bladder cancer in UK pelvic cancer centers. Contact details for consultant oncologists from each UK pelvic cancer center were obtained from the Web sites of each cancer network.

Data Collection

Potential participants were sent an electronic invitation to fill out an electronic survey. The survey was administered electronically via freely available software (*http://www.surveymonkey.com*). Before administration, the survey was piloted on the software among members of the research team to ensure complete and accurate data capture and no technical problems.

Statistical Analyses

Qualitative answers were grouped into emerging themes (thematic analysis carried out by NV and BWL). Descriptive statistics are reported for each element of the evaluation (mean, minimum, maximum; or percentage, standard deviation, or 95% confidence intervals). All statistical analyses were performed using SPSS version 20.0 (SPSS Inc, Chicago, IL).

Ethics

The study protocol was reviewed by the lead of Whipps Cross R&D Department. No patients or patient data were involved in the study and it was judged to be an audit to improve current practice, and therefore ethical approval was not required. All potential participants were sent full information on the study and participation was opt-in in nature. When participants responded to the survey invitation, consent was assumed.

Results

A total of 29 Consultant Oncologists and 1 Consultant Urologist, representing more than three-quarters (20/26) of UK pelvic