Referral and treatment rates of neoadjuvant chemotherapy in muscle-invasive bladder cancer before and after publication of a clinical practice guideline

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Abstract

Introduction: The objective of this study was to compare referral and treatment rates of neoadjuvant chemotherapy for patients with muscle-invasive bladder cancer before and after publication of a clinical practice guideline.

Methods: This was a retrospective comparative cohort study of 236 patients diagnosed with clinical stage ≥ T2 bladder cancer in Alberta, Canada. Patients were divided into 2 groups based on the time of diagnosis relative to the publication of the Alberta Genitourinary Oncology Group Clinical Practice Guideline on Bladder Cancer (CPG), which recommends cisplatin-based neoadjuvant chemotherapy for muscle-invasive disease. The pre-CPG group included patients (n = 129) diagnosed prior to publication of the CPG (November 1, 2002 to October 31, 2004, inclusively). The post-CPG group included patients (n = 107) diagnosed after publication of the CPG (November 1, 2005 to October 31, 2007). There was an accrual blackout period of 6 months before and after the CPG release date. The primary analysis compared the two groups with respect to neoadjuvant chemotherapy referral rates, treatment-offered rates and treatment-administered rates.

Results: Referral to medical oncology regarding neoadjuvant chemotherapy occurred in 2.3% and 23.4% of patients in the pre- and post-CPG groups, respectively ($p < 0.01$). Neoadjuvant chemotherapy was offered to 0.8% and 18.7% of patients in the pre- and post-CPG groups, respectively ($p < 0.01$). Neoadjuvant chemotherapy was administered to 0.8% and 14.0% of patients in the pre- and post-CPG groups, respectively ($p < 0.01$).

Interpretation: Neoadjuvant referral and treatment rates increased after publication of the CPG. However, overall referral and treatment rates remained low, which warrants additional exploration.

Résumé

Introduction : L'objectif de l'étude était de comparer les taux de recommandation et de traitement par chimiothérapie néoadjuvante chez les patients atteints de cancer de la vessie avec envahissement musculaire avant et après la publication d'un guide de pratique clinique.

Méthodologie : Il s'agit ici d'une étude comparative rétrospective de cohorte comptant 236 patients de l'Alberta, au Canada, chez qui on avait diagnostiqué un cancer de la vessie de stade clinique T2 ou pire. Les patients ont été répartis en 2 groupes selon que leur diagnostic avait été posé avant ou après la publication du guide de pratique clinique sur le cancer de la vessie (GPC) de l'Alberta Genitourinary Oncology Group, qui recommande une chimiothérapie néoadjuvante à base de cisplatine pour le traitement des cas de cancer avec envahissement musculaire. Le groupe pré-GPC comprenait des patients (n = 129) chez qui le diagnostic avait été posé avant la publication du GPC (du 1er novembre 2002 au 31 octobre 2004, inclusivement). Le groupe post-GPC incluait des patients (n = 107) chez qui le diagnostic avait été posé après la publication du GPC (du 1er novembre 2005 au 31 octobre 2007). Une période cumulative de censure a été calculée 6 mois avant et après la date de publication du GPC. L'analyse préliminaire a comparé les deux groupes quant aux taux de recommandation de la chimiothérapie néoadjuvante, aux taux d'offre et d'administration du traitement.

Résultats : La chimiothérapie néoadjuvante a été recommandée chez 2,3 et 23,4 % des patients dans les groupes pré-GPC et post-GPC, respectivement ($p < 0,01$). Elle a été offerte à 0,8 % et 18,7 % des patients de ces mêmes groupes ($p < 0,01$), et administrée à 0,8 et 14,0 % des patients des groupes pré-GPC et post-GPC, respectivement ($p < 0,01$).

Interprétation : Les taux de recommandation et de traitement concernant la chimiothérapie néoadjuvante ont augmenté après la publication du GPC, mais sont tout de même demeurés faibles, ce qui nécessite une analyse plus poussée.

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Introduction

Radical cystectomy and bilateral pelvic lymphadenectomy is the standard treatment for muscle-invasive bladder cancer and high-risk, non-muscle-invasive bladder cancer resistant to intravesical therapy.[1] Recent level I evidence has shown a substantial survival benefit conferred by neoadjuvant chemotherapy administered before radical cystectomy and pelvic lymphadenectomy.[2,3] In a meta-analysis of individual patient data from randomized controlled trials involving 3005 bladder cancer patients, cisplatin-based combination chemotherapy rendered a 14% decrease in risk of death, 9% absolute improvement in bladder cancer-specific survival, and 5% absolute improvement in overall survival at 5

years.[2] Unfortunately, uptake rates for neoadjuvant chemotherapy are low. A review of 7000 patients treated for stage III bladder cancer in the United States between 1998 and 2003 showed that only 1.2% of patients received neoadjuvant chemotherapy.[4] Clearly, strategies to increase rates of neoadjuvant chemotherapy for bladder cancer are needed. One potential strategy to improve uptake is implementation of a Clinical Practice Guideline (CPG) recommending multidisciplinary care. The Alberta Genitourinary Oncology Group published a CPG recommending 3 to 4 cycles of cisplatin-based combination neoadjuvant chemotherapy for this indication in April 2005.[5] The primary objective of this study was to compare referral rates and treatment rates of neoadjuvant chemotherapy for patients with muscle-invasive bladder cancer before and after publication of the CPG. A secondary objective was to compare the pT0 and tumour downstaging rates in patients who received radical cystectomy alone against those who received cispatin and gemcitabine (CG) neoadjuvant chemotherapy and radical cystectomy.

Methods

Patients

Patients were eligible for the study if they were over 18 and had received a diagnostic transurethral resection of a bladder tumour (TURBT) and/or radical cystectomy between November 1, 2002 and October 31, 2007. Patients were excluded if their full hospital records were unavailable or incomplete with respect to essential data points. A total of 13 patients were excluded due to incomplete records – 6 from the pre-CPG cohort and 7 from the post-CPG cohort. Most radical cystectomy procedures in the province of Alberta, Canada are performed in the two major metropolitan centres, Calgary and Edmonton. A total of 67 patients were identified in the Calgary Health Region from radical cystectomy histopathological records and 169 patients were identified from the Alberta Urology Institute Radical Cystectomy database in the Capital Health Region of Edmonton.[6] All 236 patients had their corresponding paper and electronic hospital charts reviewed. This study was approved by the University of Calgary Conjoint Health Research Ethics Board and by the University of Alberta Health Ethics Research Board.

Design

This was a retrospective comparative cohort study. Two time-equivalent cohorts were defined with respect to their temporal relation to the Alberta Genitourinary Oncology Group's CPG on neoadjuvant chemotherapy in bladder cancer, which was released in April 2005.[5] The Alberta Genitourinary Tumour Group developed the CPG with the goal of outlining management decisions for bladder cancer. Members of the group included nurses, urologists, medical oncologists and radiation oncologists. These individuals reviewed the medical literature and available guidelines from other health jurisdictions. The members' consensus guideline was circulated to all members of the wider tumour group (including all urologists and oncologists in Alberta) for their review and comments. These were taken into consideration for the development of the final guidelines.[5]

The first cohort of 129 patients (pre-CPG) was diagnosed prior to publication of the CPG (November 1, 2002 to October 31, 2004 inclusive). The second cohort of 107 patients (post-CPG) was diagnosed after publication of the CPG (1 November 2005 to 31 October 2007). A blackout period of 6 months before the CPG for the pre-CPG cohort and 6 months after the CPG for the post-CPG cohort allowed for variability in actual dissemination of the CPG around its release date.

Demographic, clinical, and pathologic characteristics

Demographic, clinical, and pathologic characteristics were abstracted from the patient medical records. Demographic characteristics included sex and age. Clinical characteristics included clinical stage, date of radical cystectomy, surgeon, and date and type of neoadjuvant chemotherapy, if applicable. Pathologic characteristics, including TNM stage, were recorded according to the American Joint Cancer Committee/Union Internationale Contre le Cancer TNM protocol.[7]

Outcome measures

The primary outcomes were differences between the pre- and post-CPG groups with regard to referral rates to medical oncology for consultation regarding neoadjuvant chemotherapy treatment-offered rates for neoadjuvant chemotherapy, and treatment-administered rates for neoadjuvant chemotherapy. Secondary outcomes were differences between patients treated with radical cystectomy alone and those treated with neoadjuvant chemotherapy plus radical cystectomy with regard to pT0 and pathologic tumour downstaging.

Statistical analysis

Chi-square tests were used to assess differences between groups for the primary and secondary outcomes analyses. All statistical tests were two-sided ($p \leq 0.05$).

Results

Table 1 shows the demographic and clinical characteristics of the pre- and post-CPG groups. There were no statistically

Table 1. Demographic and clinical characteristics of patient cohorts

	Pre-CPG N = 129 (%)	Post-CPG N = 107 (%)	*p* value
Age >60 years	93 (72.1)	80 (74.8)	0.64
Male sex	103 (79.8)	82 (76.6)	0.55

CPG = clinical practice guideline.

Table 2. Referral patterns for neoadjuvant gemcitabine and cisplatin chemotherapy

	Pre-CPG n/N (%)	Post-CPG n/N (%)	*p* value
Referred to medical oncology	3/129 (2.3)	25/107 (23.4)	<0.0001
Chemotherapy offered	1/129 (0.8)	20/107 (18.7)	<0.0001
Chemotherapy offered among those referred	1/3 (33.3)	20/25 (80.0)	0.078
Chemotherapy administered	1/129 (0.8)	15/107 (14.0)	<0.0001
Chemotherapy administered among those offered	1/3 (33.3)	15/20 (75.0)	0.567

CPG = clinical practice guideline.

significant differences between the 2 groups, which obviated the need for multivariate analyses.

Table 2 shows the results of the primary outcome analyses. Referral to medical oncology for consultation regarding neoadjuvant chemotherapy occurred in 2.3% and 23.4% of patients in the pre- and post-CPG groups, respectively ($p < 0.01$). Neoadjuvant chemotherapy was offered to 0.8% and 18.7% of patients in the pre- and post-CPG groups, respectively ($p < 0.01$). Neoadjuvant chemotherapy was administered to 0.8% and 14.0% of patient in the Pre- and Post-CPG groups, respectively ($p < 0.01$).

Table 3 shows the results of the secondary outcome analyses. Complete pathologic response occurred in 7.7% of patients treated with radical cystectomy alone and 31.3% of patients treated with neoadjuvant chemotherapy plus radical cystectomy ($p = 0.002$). Pathologic tumour downstaging (i.e., pT < cT) occurred in 25.9% of patients treated with radical cystectomy alone and 56.3% of patients treated with neoadjuvant chemotherapy plus radical cystectomy ($p = 0.009$).

Discussion

Recent level I evidence demonstrated a survival benefit conferred by neoadjuvant chemotherapy administered before radical cystectomy and pelvic lymphadenectomy for patients with muscle-invasive bladder cancer.[2,3] Unfortunately, uptake rates for neoadjuvant chemotherapy have been low, requiring additional strategies designed to increase the rates of neoadjuvant chemotherapy for bladder cancer. In the current study, we compared referral rates and treatment rates of neoadjuvant chemotherapy for patients with muscle-invasive bladder cancer before and after publication of a CPG recommending cisplatin-based combination chemotherapy. We also compared patients who received radical cystectomy alone with those who received neoadjuvant chemotherapy plus radical cystectomy with regard to pT0 and tumour downstaging rates. Two main findings emerged. First, referral rates, treatment-offered rates and treatment-administered rates for neoadjuvant chemotherapy increased after publication of the CPG. Second, pT0 and tumour downstaging rates were higher in patients treated with neoadjuvant chemotherapy plus radical cystectomy compared with those treated with radical cystectomy alone.

The main finding of the current study was that neoadjuvant chemotherapy referral and treatment rates increased after publication of the CPG. The absolute increase in referral, treatment-offered and treatment-administered rates were 21.1%, 17.9%, and 13.2%, respectively. Unfortunately, it is difficult to compare these findings with existing data since no previous studies have examined this topic. Nonetheless, the improvement in referral rate from 2.3% before the CPG release to 23.4% after the CPG release displayed a promising trend toward a future goal of complete adoption of the CPG in clinical practice. Moreover, the overall absolute treatment-administered rate after publication of the CPG was 14%, which compares favourably with previously published neoadjuvant chemotherapy utilization rates.[4] It is important to note, however, that a large proportion of patients in our study were not referred for consultation regarding neoadjuvant chemotherapy and, as a result, did not receive it. The reasons for the modest overall referral and treatment rates observed in our study are unknown. Possible explanations include a urologic surgeon's decision to forgo referral to medical oncology on the basis of a patient's request to proceed immediately with surgery, a patient's health status which precluded chemotherapy and/or owing to disease-related factors (e.g., evidence of locally advanced disease). Another possible explanation may be that the urologic surgeon had an informal telephone consultation with a medical oncologist that was not documented as a formal consultation and, as a result, was not coded as a referral for study purposes. Nonetheless, in aggregate, these data suggest that a CPG may increase referral and treatment rates for neoadjuvant chemotherapy in the setting of muscle-invasive bladder cancer, which requires further refinement of CPG implementation and/or ancillary strategies.

A second relevant finding of the current study was that pT0 and tumour downstaging rates were higher in patients treated with neoadjuvant chemotherapy plus radical cystectomy compared with those treated with radical cystectomy alone. Complete pathologic response occurred in 31.3% and

Table 3. Pathologic stage and tumour downstaging (all patients were ≥cT2)

pT stage	Radical cystectomy alone N = 220 (%)	Neoadjuvant CT + radical cystectomy N = 16 (%)	*p* value
T0	17 (7.7)	5 (31.3)	0.002*
Ta	2 (0.9)	0 (0.0)	
Tis	20 (9.1)	2 (12.5)	
T1	18 (8.2)	2 (12.5)	
T2	52 (23.6)	2 (12.5)	
T3	79 (35.9)	4 (25.0)	
T4	32 (14.5)	1 (6.3)	
Tumour downstaged	57 (25.9)	9 (56.3)	0.009

*Comparing pT stage T0 between groups (7.7% vs. 31.3%).

7.7% of patients treated with combined therapy and radical cystectomy alone, respectively. Similarly, tumour downstaging occurred in 56.3% and 25.9% of patients treated with combined therapy and radical cystectomy alone, respectively. These findings are consistent with the findings of Dash and colleagues who reported a pT0 rate of 26% with 4 cycles of neoadjuvant CG therapy and a pT0 rate of 28% with neoadjuvant methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) therapy.[8] In addition, Grossman and colleagues reported that a higher proportion of patients who received combined therapy (MVAC plus radical cystectomy) had no residual disease compared with those who received radical cystectomy alone (38% vs. 15%, $p < 0.01$).[9] Given that available evidence suggests that: MVAC and CG have comparable pT0 rates, pT0 and tumour downstaging are independent predictors of overall survival, [9,10,11] and as CG has a more favourable toxicity profile than MVAC,[12,13] CG may be considered an appropriate therapeutic regimen in the neoadjuvant setting.

Our study had several limitations that need to be considered when interpreting the findings. First, it was a retrospective observational analysis and, as a result, it did not provide evidence of a causal relationship between implementation of the CPG and improved neoadjuvant chemotherapy referral and treatment rates. Second, the information about patients' consultation with the urologic surgeon was not available and thus the clinical decision-making process used to determine whether or not to refer a patient to medical oncology for consultation regarding neoadjuvant chemotherapy could not be assessed. Third, the information regarding the CPG dissemination to the treating urologic surgeons was not available and therefore we could not examine the extent to which they were aware of the CPG. Fourth, diagnostic TURBT data was not available for all patients treated in 1 of the 2 centres (Edmonton). As a result, a small proportion of patients in the study may have had high-risk, non-muscle-invasive disease and thus would not necessarily be expected to be referred to medical oncology for assessment regarding neoadjuvant chemotherapy. Importantly, however, it was not a common practice to offer early radical cystectomy to patients with high-risk, non-muscle-invasive disease during the study time period.

Conclusion

Our study compared referral and treatment rates of neoadjuvant chemotherapy for patients with muscle-invasive bladder cancer before and after publication of a CPG recommending cisplatin-based combination chemotherapy. We found that referral and treatment rates increased after publication of the CPG; however, overall rates were low. We also found that pT0 and tumour downstaging rates were higher in patients treated with neoadjuvant chemotherapy plus radical cystectomy compared with those treated with radical cystectomy alone. Future research examining factors that contribute to CPG-induced changes in referral and treatment rates are warranted. Such research may include an analysis of practitioners' understanding of the CPG, how effectively it was initially disseminated, practitioners' understanding of the evidence, and how it has influenced and shaped their clinical practice. Additional research is also required to identify and evaluate strategies for dissemination of best clinical evidence, whether that is through a CPG or other educational tools and media.

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