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Original contribution

Neoadjuvant chemotherapy–related histologic changes in radical cystectomy: assessment accuracy and prediction of response ☆

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Summary We evaluated the spectrum of histologic changes associated with neoadjuvant chemotherapy (NAC) and compared them with those resulting from transurethral resection (TUR). Twenty-five patients who received NAC were divided based on both their preoperative clinical/radiographic findings (clinical stage, hydronephrosis, palpable mass) and the cystectomy (RC) findings into NAC respondents (advanced clinical stage and <pT2 + pN0), possible NAC respondents (non–advanced clinical stage and <pT2 + pN0), and NAC nonrespondents (≥pT2and/or ≥pN1). In addition, 14 patients who received TUR alone and had <pT2 + pN0 on RC were included. Presence/absence of the following histologic features was assessed: fibrosis/myofibroblastic reaction, hyalinization in the bladder wall, inflammatory reaction, calcification, foreign-body giant cells, necrosis, sheets of foamy macrophages, and fibrosis/hyalinization/necrosis in the lymph nodes (LNs). Overall, there was a significant histologic overlap between all groups. However, patients who received NAC had a significantly higher likelihood of showing hyalinization and less giant cells and inflammatory reaction than did those who received TUR only. Moreover, the only significantly different histologic features in NAC respondents versus TUR respondents were hyalinization and LN changes, with those 2 features in 25% and 0% of the possible NAC respondents group, respectively. Lastly, there was no significant difference in the possible NAC respondent group in comparison to the TUR-only arm. It appears that TUR and NAC result in overlapping histologic changes. In cases with no/minimal residual disease on RC, it is difficult to attribute the changes to NAC effect only, except if (1) hyalinization of the bladder wall or LN changes are present, or (2) if the preoperative clinical stage was beyond what could be resected by TUR.

1. Introduction

Bladder urothelial carcinoma is the ninth most common cancer worldwide and accounts for 165 000 deaths every year in North America and Europe. Although radical cystectomy remains the cornerstone treatment modality for muscle-

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invasive disease, perioperative chemotherapy was shown to improve overall- and disease-specific survival in several randomized clinical trials [1–3]. Adjuvant chemotherapy and neoadjuvant chemotherapy (NAC) have been increasingly used in major tertiary care centers, and their inclusion in the treatment plan is currently considered the standard of care. In comparison to adjuvant chemotherapy, NAC holds 2 main advantages. First, it can be administered to a higher number of patients, as surgical complications may prevent the delivery of chemotherapy to certain patients in an adjuvant setting. Second, level 1 evidence derived from many large robust studies supports the use of NAC for patients with muscle invasive bladder cancer with a 5-year overall survival benefit of 5% [1–5]. The other side of the medal is the fact that not all patients respond to NAC, which may result in unnecessary delays in surgery in which the curability window may be missed. Therefore, predicting response to NAC at the time of diagnosis has become the center of ongoing research to enrich the patient population who would benefit from this approach. This research effort focuses on correlating the expression of different biomarkers in biopsy specimens with the degree of response to NAC. In that regard, the response to NAC is assessed depending on the histologic findings in radical cystectomy specimens (RCs).

Traditionally, the assessment of response to NAC in nonurothelial cancers such as sarcomas, gastroesophageal, and ovarian carcinomas rests on evaluating the residual viable tumor's size in relation to the macroscopic tumor size, with patients showing no or minimal residual disease being considered good respondents [6–8]. However, the bladder site is unique in that RC is preceded by transurethral resection (TUR) of the tumor, a procedure that not only is associated with histologic changes but may result itself in complete resection of the tumor. In fact, it is well known that up to 18% of muscle-invasive urothelial carcinomas on TUR show no residual disease (pT0) on RC after TUR alone [5]. Therefore, the assessment of histologic response to NAC in bladder cancer cannot be accurately performed without taking these facts into consideration.

The purposes of this study were to evaluate the spectrum of histologic changes associated with NAC and to compare them with those resulting from TUR, in order to determine whether the presence of minimal or no residual disease on RC can be attributed to NAC or TUR effect or both solely based on histologic examination.

2. Materials and methods

Institutional ethics approval was obtained. Thirty-nine patients were included in the study. Of those, 25 patients received NAC and were divided based on both their preoperative clinical or radiographic findings as well as radical cystectomy findings into NAC respondents (n = 14) and NAC nonrespondents (n = 11). The NAC respondents' group was divided into 2 groups: "definitive" NAC respondents included 6 patients with advanced preoperative clinical stage (>cT2, >cN0, hydronephrosis, palpable mass) who had no/minimal residual disease on RC (<pT2 + pN0). Those patients were considered definitive respondents because their RC findings were beyond the resectability of the TUR. The second group was labeled as "possible" NAC respondents and consisted of 8 patients with no/minimal residual disease on RC (<pT2 + pN0) who had nonadvanced preoperative clinical findings (cT2, cN0, no hydronephrosis, no palpable mass) in whom TUR alone could have theoretically accounted for the absence of advanced residual disease on RC. NAC nonrespondents consisted of 11 patients who had advanced pathological findings on RC (≥pT2 and/or ≥pN1), regardless of their preoperative clinical stage. The control arm of the study was a group of 14 patients who did not receive NAC after TUR and who had no/minimal residual disease on RC (<pT2 + pN0). This group was labeled as "TUR respondents." The NAC regimen was cisplatin-based combination chemotherapy in all patients.

All the RCs' hematoxylin and eosin slides were retrieved and reevaluated by one genitourinary pathologist blinded from the precystectomy procedure status (TUR versus TUR + NAC). Presence or absence of the following histologic features was assessed and compared between different groups:

1. Fibroblastic/myofibroblastic reaction: the morphology ranged from hypercellularmyofibroblastic granulation tissue-like reaction, to hypocellular dense collagen-rich scar-like tissue.
2. Hyalinization of the bladder wall: defined as an acellular glassy pink homogeneous material which involved any layer of the bladder wall
3. Severe inflammatory reaction: mild to moderate inflammation was not noted as it is a frequent finding in benign lamina propria.
4. Calcifications
5. Foreign-body giant cells reaction
6. Necrosis: only large geographic areas of necrosis were included. Focal intra-tumoral necrosis was not accounted for.
7. Sheets of foamy macrophages
8. Changes in the lymph nodes: in the form of fibrosis, hyalinization or necrosis

3. Results

Overall, there was a significant histologic overlap between different groups, with rare exceptions (see Figs. 1 and 2).

3.1. TUR alone versus TUR + NAC

Although 36% of patients who received NAC showed hyalinization of the bladder wall, none of those who received TUR only showed this finding ($P = .001$). Also, in comparison to the TUR-only group, a significantly lower proportion of patients receiving NAC showed severe inflammation (12%