

Risk Factors for Disconcordance Between Pre and Post Radical Cystectomy Stages

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Purpose: To investigate the correlation between pre and post surgical staging in patients undergoing radical cystectomy (RC), and study the possibility of predicting their disconcordance.

Materials and Methods: We reviewed medical records of 186 patients diagnosed with transitional cell carcinoma of the bladder, who had undergone RC between the years 2007 and 2010. We determined the correlation between pre and post surgical stages and then studied the association between stage disconcordance and age, gender, smoking, history of previous transurethral resection of bladder tumor (TURBT) and intravesical treatments, re-TURBT in high-risk superficial bladder tumors, and the treatment delay between diagnosis and RC. Analysis was performed using Chi-Square and Fisher's Exact tests.

Results: Post surgical up-staging occurred in 86 (46.24%) patients and even more (69.35%) if lymph node involvement was also considered as up-staging. Smokers and those with pre surgical stages of $\leq T1$ and $T2$ with no history of re-TURBT had a significantly increased risk of disconcordance. The risk of up-staging was almost halved by an early re-TURBT in high-risk patients.

Conclusion: Disconcordance between pre and post surgical stages in patients undergoing RC is common. Until better ways of staging are developed, decision making in patients with bladder tumor should be done by extra attention to patients who have risk factors associated with increased risk of up-staging, including smokers and those with nonmuscle-invasive bladder tumors or $T2$ tumors. An early re-TURBT will decrease the up-staging rate.

Keywords: urinary bladder neoplasms, neoplasm staging, cystectomy, smoking

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INTRODUCTION

Bladder cancer is the second most common urologic tumor and the fourth common cancer in men.⁽¹⁾ Upon diagnosis, 75% of newly diagnosed bladder tumors (BT) are nonmuscle-invasive bladder tumors (NMIBT).⁽²⁾ Of those patients with muscle-invasive bladder tumors (MIBT), 57% are primary (have muscle invasion upon diagnosis and have no previous history of BT), while 43% have progressed from a superficial state.^(3,4) One-third of

patients with BT have metastasized at diagnosis.⁽⁴⁾

Defining the exact stage of the BT is essential for planning right treatment and determining the patient's prognosis. This goal is being chased by transurethral resection of bladder tumor (TURBT) and imaging modalities, such as computed tomography (CT) scan, magnetic resonance imaging (MRI), or positron emission tomography (PET)

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scan. Currently, these tumors are being staged according to the TNM staging, which was developed in 1997 and modified in 2002. World Health Organization grading system (1973 and 2004) was used for grading.^(5,6)

Radical cystectomy (RC) is the best treatment option for MIBTs.^(3,4,7) Although improvements in surgical techniques and peri-operative care have resulted in less morbidity and mortality,⁽⁸⁾ unpredictable surprises, such as the 46% to 52% rate of discordance between pre and post surgical stages⁽⁹⁻¹¹⁾ and the 50% rate of local and distant recurrence⁽⁹⁾ might change treatment modalities and prognosis to a great deal.

In order to help physicians and patients with pre-operative decision making, we made a comparison between pre and post surgical stages and tried to see if the discordance between these two situations (stages) could be predicted by any suggested risk factors.

MATERIALS AND METHODS

We reviewed medical records of 186 patients diagnosed with transitional cell carcinoma of the bladder, who had undergone RC and bilateral pelvic lymph node dissection, with curative intent between the years 2007 and 2010.

All specimens were fixed in 10% formalin. Thereafter, standard sections were taken of the bladder and resected lymph nodes, and stained with Hematoxylin and Eosin.

The studied parameters include age, gender, smoking, history of previous TURBT and intravesical treatment, re-TURBT (in high-risk NMIBTs), time interval between diagnosis and RC (treatment delay), and pre and post surgical stages (TNM staging before and after RC). Re-TURBT was performed within 2 to 6 weeks after the first TURBT if it had shown a high-risk NMIBT. High-risk NMIBTs in whom re-TURBT was indicated were defined as those with incomplete TURBT or when a high-grade or T1 tumor was detected.⁽⁴⁾

In this study, the pre and post surgical stages were referred to as clinical stage (eg, cT1) and surgical stage (eg, sT1), respectively. Radical

cystectomy specimens were divided into primary radical cystectomy (PRC) and secondary radical cystectomy (SRC) specimens.

Primary radical cystectomy specimens were those who underwent RC because: 1- Their first TURBT showed a \geq cT2 tumor, or 2- Their first TURBT showed a high-risk NMIBT and underwent an early re-TURBT that showed a high-grade cT1c or a \geq cT2 tumor.

Secondary radical cystectomy specimens were those with a NMIBT that had multiple recurrences or progression after several sessions of TURBTs and intravesical treatments.

In our centers, the patients who had a high-grade cT1c tumor in their re-TURBT specimen were offered the chance to choose surgery. Radical cystectomy in these patients and those who had a MIBT in their re-TURBT specimen was considered as PRC. The RC after an early re-TURBT was not considered a SRC because these patients had not received any intravesical treatments between these two TURBTs and the presence of tumor in the re-TURBT specimen (2 to 6 weeks after the first resection) was not considered recurrence or progression.

We determined the correlation between pre and post surgical stages and then studied the association between stage discordance and aforementioned risk factors. Analysis was performed using Chi-Square test and Fisher's Exact test. A confidence interval (CI) of 95% was considered significant.

RESULTS

The median age of our patients was 65 years (range, 40 to 73 years). Of 186 patients who underwent RC, 7.53% were women and 92.47% were men. Clinical data are summarized in Table 1.

Forty-eight (25.81%) patients underwent RC upon diagnosis or after a re-TURBT (PRC) while SRC was performed in 138 (74.19%) patients. The median time interval between diagnosis of MIBT and surgery was 4 weeks (range, 0 to 72 weeks).

Before RC, 26 patients had a cT1 tumor (RC was SRC in all of them). Twenty-four patients

Table 1. Clinical characteristics of patients undergoing radical cystectomy

| Clinical characteristics | Number | Percentage |
|--------------------------|--------|------------|
| Age, y | | |
| 40 to 50 | 23 | 12.37 |
| 51 to 60 | 61 | 32.79 |
| 61 to 70 | 91 | 48.92 |
| ≥ 71 | 11 | 5.92 |
| Gender | | |
| Male | 172 | 92.47 |
| Female | 14 | 7.53 |
| Smoking | | |
| - | 66 | 35.48 |
| + | 120 | 64.52 |
| Radical Cystectomy | | |
| PRC | 48 | 25.81 |
| SRC | 138 | 74.19 |
| Delay Interval, d | | |
| < 90 | 132 | 70.97 |
| > 90 | 54 | 29.03 |

PRC indicates primary radical cystectomy; and SRC, secondary radical cystectomy.

underwent PRC because the re-TURBT of their high-risk NMIBT showed either a cT2 (23 patients) or a high-grade cT1c tumor (1 patient). Seventy-two patients had cT2 tumors before RC (either primary or secondary), 48 had cT3, and 16 patients had cT4a stages before RC. Pre surgical stages (cT), post surgical stages (sT), and the up-staging rate have been shown in Table 2.

While concordance was seen only in 47.31% of patients, post surgical up-staging occurred in 46.24% of patients and down-staging in 6.45%. Since only 19 patients were diagnosed to have enlarged lymph nodes before surgery and this number increased to 43 after RC, we could say that 129 (69.35%) patients were upstaged if lymph node involvement was also considered as up-staging.

Fourteen (16.27%) patients who upstaged were cT1 or less before the surgery. The re-TURBT

group composed of only 9.3% of the upstaged patients. Forty-nine (56.97%) upstaged patients were cT2 (49) and 15 (17.4%) were cT3 before the surgery.

Table 3 demonstrates the relationship between pre surgical parameters with post surgical stage. It shows that smoking and pre surgical stage are important predicting factors for stage discordance. Smokers and patients with pT2 had the highest rate of up-staging while non-smoker pT3 and re-TURBT patients had the lowest risk.

Since smoking showed to be an important factor and in order to study its impact on up-staging further, we divided the smokers into two groups; those who underwent surgery within 90 days and those who underwent RC after 90 days, and studied the up-staging rate in these groups. Of 25 patients, 20 (80%) of the smokers who experienced surgery after 90 days were upstaged while this percent was 50.53% (48 patients out of 95) in smokers on whom surgery was performed before 90 days ($P = .008$).

Neither age nor gender showed any significant association with stage discordance ($P = .988$ and $P = .941$). Previous intravesical treatments (SRC) or longer time interval to surgery also had no influence on stage discordance ($P = .688$ and $P = .510$).

DISCUSSION

Transurethral resection of bladder tumor can not comment on stages more than pT2 unless the bladder perforation occurs. Computed tomography scan and MRI have limited sensitivity in identifying extra bladder tumors, especially pT3a and pelvic lymph nodes less than 8 mm. These imaging modalities also

Table 2. Pre and post surgical stages in patients undergoing radical cystectomy

| Pre Surgical stage | Post surgical stage | | | | | Up-staging (n/%) Row percentage |
|---|---------------------|-----|-----|-----|-----|------------------------------------|
| | ≤ pT1 | pT2 | pT3 | pT4 | pN+ | |
| cT1 or less (n = 26) | 12 | 9 | 3 | 2 | | 14/26 = 53.84% |
| cT1c or cT2 after re-TURBT (n = 24) | 4 | 12 | 8 | - | | 8/24 = 33.33% |
| cT2 (initially) (after progression or at first presentation) (n = 72) | 4 | 19 | 40 | 9 | | 49/72 = 68.05% |
| cT3 (n = 48) | - | 2 | 31 | 15 | | 15/48 = 31.25% |
| cT4 (n = 16) | - | - | 2 | 14 | | |
| cN+ (n = 19) | - | - | - | - | 43 | |

Table 3. Association of pre surgical (clinical or pathological) findings with post surgical stage

| Presurgical parameters | Down-staging | Same stage | Up-staging | P |
|----------------------------|----------------|-----------------|-----------------|------|
| Mean age, y | 60 | 59 | 60.69 | .988 |
| Gender | | | | |
| Male | 11/172 = 6.39% | 82/172 = 47.67% | 79/172 = 45.93% | .941 |
| Female | 1/14 = 7.14% | 6/14 = 42.86% | 7/14 = 50% | |
| Smoking | | | | |
| + | 9/120 = 7.5% | 43/120 = 35.83% | 68/120 = 53.13% | .000 |
| - | 3/66 = 4.54% | 45/66 = 68.18% | 18/66 = 27.27% | |
| Stage | | | | |
| cT1 or less | - | 12/26 = 46.15% | 14/26 = 53.84% | |
| cT1c or cT2 after re-TURBT | 4/24 = 16.66% | 12/24 = 50% | 8/24 = 33.33% | .000 |
| cT2 | 4/72 = 5.55% | 19/72 = 26.38% | 49/72 = 68.05% | |
| cT3 | 2/48 = 4.1% | 31/48 = 64.58% | 15/48 = 31.25% | |
| RC | | | | |
| PRC | 4/48 = 8.33% | 24/48 = 50% | 20/48 = 41.67% | .688 |
| SRC | 8/138 = 5.80% | 64/138 = 46.38% | 66/138 = 47.83% | |
| Delay Interval, d | | | | |
| ≤ 90 | 7/132 = 5.30% | 65/132 = 49.24% | 60/132 = 45.45% | .510 |
| > 90 | 5/54 = 9.26% | 23/54 = 42.59% | 26/54 = 48.19% | |

TURBT indicates transurethral resection of bladder tumor; PRC, primary radical cystectomy; and SRC secondary radical cystectomy.

lack specificity, not being able to distinguish inflammatory lymph node enlargement from malignant ones. The accuracy of CT scan for diagnosing extra bladder tumors is about 55% to 92%.^(4,12) This accuracy is somewhat better for MRI and ranges from 73% to 96%. Magnetic resonance imaging also seems more accurate for determining lymph node involvement.^(3,4) There are ongoing and promising researches on PET scan and immunohistochemical markers, such as p53, hoping to improve pre surgical staging.^(9,13) Until better imaging modalities or biomarkers are developed, it seems reasonable to identify the risk factors associated with post surgical up-staging in order to help physicians and patients in pre-operative decision making.

Kunze and colleagues demonstrated the association of smoking (cigarettes or pipes) and risk of bladder cancer in agreement with many other studies.⁽¹⁴⁻¹⁶⁾ Smoking continues to be the most important risk factor for the development of bladder cancer, and this risk has increased over time.⁽¹⁷⁾ The very common habit of smoking in Syria, very high rate of water pipe smoking, might be the cause of high prevalence of bladder cancer in this country. Our study showed that one of the pre-operative parameters contributing to a significant increased risk of up-staging is smoking. On the other hand, we also showed that

smokers who waited a longer time for surgery (> 90 days) had a higher risk of up-staging. Furthermore, the fact that time interval to surgery, on its own, showed no effect on the risk of up-staging, not only shows the importance of smoking regarding up-staging, but also suggests its dose-response relation.

Nonmuscle-invasive bladder tumors can be treated with TURBT and appropriate intravesical treatments, but this treatment is absolutely insufficient if there is an error in stage determination. Our study showed that there is a 53.84% rate of up-staging in NMIBTs and a very modest concordance rate (46.15%) was seen (Table 3). On the other hand, patients with cT2 had the highest rate of up-staging (68.05%). Since these upstaged patients (with sT3 or higher stages postoperatively) might need further treatment, adjuvant chemotherapy, this high rate of up-staging strongly shows the need for pre-operative patient counseling and discussing the possibility of needing such adjuvant treatments.

The overall discordance rate in our study was shown to be 52.69% (46.24% up-staging and 6.45% down-staging). The high rate of up-staging found in NMIBTs, cT2 tumors, or in all stages, in our study, is consistent with other studies.^(9-11,18-21) Summary of findings of other researchers are shown in Table 4.

Table 4. Results of other studies regarding up-staging of bladder tumor after radical cystectomy.

| First Author | Number of Patients | Clinical stage | Up-staging rate, % |
|-------------------------|--------------------|----------------|--------------------|
| Chang ⁽¹¹⁾ | 169 | all | 46 |
| Cheng ⁽¹²⁾ | 105 | all | 52.3 |
| Dutta ⁽¹⁹⁾ | 78 | ≤ cT1 | 37 |
| Ficarra ⁽²²⁾ | 156 | ≤ cT1 | 42.9 |
| | | cT2 | 74.3 |

Although some authors have denied the usefulness of re-TURBT unless smooth muscle is absent in the initial TURBT specimen;⁽²²⁾ our study showed that the probability of up-staging could be halved by a re-TURBT in high-risk NMIBTs, reaching a 33.33% of up-staging instead of 68.05% and 53.84% for cT2 and cT1 groups, respectively. These findings are also compatible with other studies demonstrating that 24% to 49% of patients with NMIBT will change to the diagnosis of a cT2 tumor with a re-TURBT.^(4,23-25) Furthermore, Dalbagni and coworkers also showed that of the patients who were diagnosed to have a cT1 or less BT by a re-TURBT, only 13.3% upstaged to a sT2 or higher tumor after PRC.⁽²³⁾

As we mentioned before, high-risk NMIBTs (who need re-TURBT) are defined as those with incomplete resection (no muscle in the specimen) or when a high-grade or cT1 tumor is detected.⁽⁴⁾ It should also be mentioned that although the importance of T1 subclassifications (T1a, T1b, and T1c) is not clear and not universally accepted,⁽²⁶⁾ it is the policy of our centers to offer RC to those patients with high-grade cT1c tumors in their TURBT specimens, after discussing the risks and benefits. We had only 1 patient who fell into this category.

McLaughlin and colleagues showed that patients undergoing PRC had a higher risk of up-staging compared to those with a history of intravesical treatments and TURBTs.⁽⁹⁾ This was not the same in our study and neither of the groups showed to have an increased risk of up-staging. The difference between our results and McLaughlin's results might be due to the difference between patients included in the PRC and SRC groups. In our study, some of the patients included in the PRC group were those who underwent RC after an early re-TURBT, which showed a high-

grade cT1c or a cT2 tumor, and we described that up-staging significantly decreased in re-TURBT patients; therefore, the overall risk of up-staging in PRC patients might be decreased due to this selection bias. On the other hand, after extracting the patients with cT2 out of the NMIBTs by re-TURBT, we have ended up with two kinds of NMIBTs: 1) those with a high-grade cT1c tumor who underwent a PRC; and 2) those with a NMIBT who were unresponsive to TURBT and intravesical treatments, and experienced recurrence or progression, and therefore underwent SRP. It would be logical that these patients with their high tendency towards recurrence or progression have more risk of up-staging than SRC patients described in McLaughlin's study.

The delay between diagnosis and surgery was mostly due to the patient's reluctance, seeking different opinions, completing pre-operation laboratory tests, consultations, imaging studies, or receiving neoadjuvant treatment. Although several authors have considered surgical delay more than 3 months to be associated with the worst staging outcome,⁽²⁷⁻³⁰⁾ but this matter is not certain because these studies are not randomized controlled studies and there is a vast variation among published studies, including inconsistent studied cohorts, diverse durations and types of delays, variable treatments, dissimilar investigated end points, and use of different statistical methods.⁽³¹⁾ Furthermore, some studies have shown that surgical delay had no influence on outcome.⁽³²⁾ Our study also showed that this delay caused no significant increase in up-staging ($P = .51$).

One limitation of our study is that it was a retrospective study with patients being referred to us by different urologists, different TURBT techniques, and pathologic examination of the biopsy specimens being done by different pathologists.

CONCLUSION

Since discordance between pre and post surgical stages in patients undergoing RC is a common problem, until better ways of staging are developed, decision making in patients with

bladder tumor should be done by caution, and extra attention should be paid to those who have risk factors associated with increased risk of discordance, including smokers and those with NMIBTs or cT2 tumors. An early re-TURBT will decrease this discordance.

CONFLICT OF INTEREST

None declared.

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