Underutilization of immediate intravesical chemotherapy following TURBT: results from NSQIP

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Introduction: *A single perioperative dose of intravesical chemotherapy (IVC) following transurethral resection of bladder tumors (TURBT) for non-muscle invasive bladder cancer has demonstrated a reduction in tumor recurrence. In this study, we investigate the contemporary (2010) utilization of IVC following TURBT using a prospective national database.*

Materials and methods: *Using the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database, we identified patients with bladder cancer using ICD-9 codes. From this group, patients undergoing TURBT based on Current Procedural Terminology (CPT) codes were analyzed. We then identified those patients who underwent TURBT and also received intravesical therapy. Operative time, length of hospital stay, and perioperative complications were evaluated.*

Results: *From January 1 to December 31, 2010, 1273 patients at participating ACS-NSQIP sites underwent TURBT for bladder cancer. There were 417 (33%) small, 486 (38%) medium, and 370 (29%) large tumors treated. In total, 33 (2.6%) patients received IVC. When comparing patients who received perioperative IVC to those who did not, there was no difference in median operative times (27 mins versus 28 mins, p = 0.899). There was one urinary tract infection in the IVC group.*

Conclusions: *IVC remains greatly underutilized despite current data documenting its efficacy in reducing tumor recurrence for TaT1 bladder cancer. Instillation of IVC following TURBT does not increase morbidity. Our findings support the continued need to explore ways of improving rates of perioperative IVC administration following TURBT.*

Key Words: intravesical chemotherapy, bladder cancer, transurethral resection, NSQIP

Introduction

In the United States, approximately 74690 new cases of bladder cancer will be diagnosed in 2014.[1] Of these, 70% will initially be staged as non-muscle invasive.[2] Non-muscle invasive bladder cancer (NMIBC) has a high rate of recurrence varying from 30%-80%, as well as a risk of progression to muscle invasion.[3] To reduce the risk of recurrence, administration of postoperative intravesical chemotherapy (IVC) has been advocated. IVC is thought to reduce recurrence by preventing re-implantation of circulating tumor cells after resection and by targeting any microscopic residual tumor that may be missed by resection.

The 2012 recommendations by the European Association of Urology for the initial diagnosis of bladder cancer include transurethral resection of bladder tumors (TURBT) and perioperative instillation of IVC in apparent low risk (Ta, low grade) bladder cancer if there are no contraindications.[4] The American Urological Association (AUA) guidelines maintain that in the initial diagnosis of bladder cancer, a single dose of IVC following TURBT is a therapeutic option and is fully recommended following TURBT for low grade, Ta bladder lesions.[5]

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Despite data supporting IVC administration within 24 hours of TURBT, estimates of use range from 0.33% to 3.2%.[6,7] Although it is accepted that a gap may be present between the establishment of evidence based practices and their implementation,[8] a decade has passed since the publication of initial guidelines supporting the use of perioperative IVC. Using the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) data files from 2010, we sought to determine contemporary utilization of IVC following TURBT for bladder cancer.

Materials and methods

The ACS-NSQIP is a national prospective outcomes-based database designed to measure surgical quality of care by collecting 30 day perioperative complication data from participating U.S. hospitals. We queried the NSQIP participant user files from January 1 to December 31, 2010 for patients with a diagnosis of bladder cancer, identified by International Classification of Diseases (ICD-9) codes 188 through 188.9. From this group, patients undergoing TURBT with Current Procedural Terminology (CPT) code 52234 for small, 52235 for medium, and 52240 for large tumors, were identified. This group was then reviewed for the CPT code 51720 for administration of IVC. We analyzed operative time and perioperative complications including urinary tract infections, bleeding requiring transfusion, and sepsis or septic shock.

Statistical analysis was performed using SPSS version 21 (IBM Corporation, Armonk, NY, USA). For continuous variables, a Mann-Whitney U test was performed and medians are reported. Pearson's chi-squared test was used to analyze categorical variables. Statistical significance was defined as $p < 0.05$.

Results

Using the 2010 NSQIP data files, 1273 patients were identified as having undergone TURBT for small (n = 417, 33%), medium (n = 486, 38%) or large (n = 370, 29%) bladder tumors. The median patient age was 74 years and 75% (n = 951) were male. Preoperative platelet count < 150,000 was present in 130 patients, of which one received IVC. The majority of cases were performed under general anesthesia (83%, n = 1062) and as an outpatient (83%, n = 1054).

Of the 1273 patients undergoing TURBT, 2.6% (n = 33) received perioperative IVC. IVC administration was not associated with the size of tumor resected (p = 0.49). In a comparison of patients receiving IVC and those not, there was no difference in median operative time (27 mins versus 28 mins, p = 0.899). Five patients were excluded in the calculation of operative time because of incomplete data.

The most common complication in the TURBT only group was a urinary tract infection (Clavien[9] grade I) in 42 (3.4%) patients. Additionally, in the TURBT only group, there were 25 (2%) incidences of bleeding requiring transfusion (Clavien grade II) and 6 (0.5%) patients developed sepsis or septic shock (Clavien grade IV). In the TURBT and IVC group, one patient had a urinary tract infection. There were no other reported complications in the group receiving IVC.

Discussion

Instillation of intravesical agents for the treatment of bladder cancer was first described in the 1960s. Since that time its use has been widely studied and several randomized control trials have been published documenting the effectiveness of intravesical treatment following TURBT in reducing bladder cancer recurrence. The data supporting the use of perioperative IVC is compelling. In 2004, Sylvester et al[10] published a meta-analysis of seven randomized control trials (RCTs) including 1476 patients comparing TURBT alone to TURBT and an immediate single dose of IVC in patients with primary or recurrent TaT1 bladder cancer with a median follow up of 3.4 years. TURBT with perioperative IVC demonstrated a reduction in tumor recurrence for both single (OR 0.61, $p < 0.0005$) and multiple tumors (OR 0.44, $p = 0.06$). There was an overall reduction by 39% in the risk of recurrence and a comparatively low number needed to treat of 8.5. A more recent meta-analysis by Abern et al[11] including 18 RCTs showed a 13% absolute risk reduction with a NNT of 7.2 patients. Both meta-analyses included trials using various chemotherapeutic agents, including mitomycin C, epirubicin, thiotepa, pirarubicin, and gemcitabine.

When making recommendations regarding the administration of immediate IVC following TURBT, the AUA's Bladder Cancer Clinical Guideline Panel analyzed two randomized control trials[12,13] and determined that patients receiving a single immediate postoperative dose of mitomycin C had a 17% reduction in tumor recurrence. Table 1 is a review of the available RCTs using perioperative mitomycin C in the treatment arm. The AUA guidelines justify use of IVC as an option, as opposed to standard, citing cost issues, uncertain pathology at time of resection, and side effects.[6]

The particular agent (mitomycin C, thiotepa, epirubicin, doxorubicin, or valrubicin) used for the

TABLE 1. **Review of randomized control trials using mitomycin C**

Study	Year	Arm 1	Arm 2	Follow up	Recurrence/patients		p value
					TUR only (or placebo)	TUR + chemo	
Tolley et al[12]	1996	TURBT alone	TURBT + 40 mg mitomycin C within 24 hrs	7 years (median)	128/157 (82%)	62/149 (42%)	p < 0.001
Solsona et al[13]	1999	TURBT alone	TURBT + 30 mg mitomycin C within 6 hrs	94 months (median)	35/64 (55%)	23/57 (40%)	p = 0.115*
Barghi et al[19]	2006	TURBT + placebo	TURBT + immediate 30 mg mitomycin C	15.7 months (mean)	1/21 (5%)	8/22 (36%)	p = 0.007
El-Ghobashy et al[20]	2007	TURBT alone	TURBT + 30 mg mitomycin C within 6 hrs	44 months (median)	17/32 (53%)	12/31 (39%)	NS*
De Nunzio et al[21]	2011	TURBT alone	TURBT + 40 mg mitomycin C within 24 hrs	90 months (median)	46/105 (44%)	10/97 (10%)	p = 0.001

*both studies showed statistically significant reduction in early (< 2 years) tumor recurrence in the IVC arm.
NS = not significant

33 patients identified in this study is not known, but mitomycin C is the most commonly used in the United States.[6] Contraindications to administration include known hypersensitivity, active urinary tract infection, significant bleeding, and evidence of or suspicion of bladder perforation. It is not possible to know from this dataset if patients had a bladder perforation precluding administration of IVC. A relative contraindication to intravesical mitomycin C is thrombocytopenia as systemic absorption may cause myelosuppression. One patient who did receive IVC had a preoperative platelet count of < 150,000 prior to receiving IVC, but this did not result in additional complications.

No added morbidity was observed for patients receiving IVC, although patient selection could account for low perioperative complications in this group. The most commonly documented toxicities of IVC are transient, local bladder symptoms such as dysuria, frequency, and gross hematuria.[10] Although the NSQIP database does not capture this particular side effect, in only one case a postoperative complication (a urinary tract infection) was reported. In addition, instillation of IVC did not increase operative time.

It is difficult to predict the number of cases for which IVC would ideally be administered. In clinical practice, the urologist does not know the pathologic grade or depth of invasion at the time of resection and must give IVC in cases that are clinically Ta or T1 where no contraindications exist. In a study of over 1900 patients undergoing TURBT, clinical data such as disease status, tumor number and type, and clinical stage was collected. It was determined that 36% of patients met ideal criteria for IVC as they had one or two completely resected clinical stage TaT1 papillary tumors at the time of resection.[15] However, of 1273 TURBT cases identified in the NSQIP data files, only 33 (2.6%) were documented as receiving IVC. This falls short of estimates regarding predicted optimal use of IVC. Other studies have also recognized the low utilization of perioperative IVC. In 2011, Chamie et al[7] published their analysis of Surveillance, Epidemiology, and End Results (SEER) data from 1992-2002, approximately one decade before our NSQIP cohort, in which 2847 patients with NMIBC and 3.2% received IVC within 3 days of TURBT. Using claims data from 1997-2004, Madeb et al[6] identified 14,677 patients with newly diagnosed bladder cancer undergoing bladder tumor biopsy or resection. In this cohort, only 0.33% received IVC within 24 hours of resection. This study also provided a cost analysis, estimating that perioperative IVC could decrease medical expenses by $15-$25 million per year in the United States. Concurrent IVC administration remains low with no upward trend a decade after these initial cross-sectional snapshots, indicating a generalized lack of progress implementing this treatment strategy.

Recent data from the Urological Surgery Quality Collaborative project identified reasons for patients not receiving IVC.[15] Modifiable factors reported were educational and logistical barriers. Educationally modifiable reasons for patients not receiving IVC included the surgeon not being convinced of the benefit in administering IVC following TURBT. Logistical barriers included medication not being available or not ordered preoperatively and insufficient resources in the post-anesthesia care unit (PACU). We suspect that a major potential barrier to implementation is time as well as a lack of resources. Surgeons may be unable or unwilling to endure the delay at end of case to wait for mitomycin preparation, and then instillation. Even though it can be administered in the PACU, there may not be appropriately trained ancillary staff available. Additionally, the dwell time required may be disruptive to workflow patterns if not anticipated. At our institution, we have implemented protocols to guarantee ease of access, including contacting pharmacy preoperatively to prepare the agent and having auxiliary staff both in the operating room and PACU with appropriate training in handling the cytotoxic agent. Disseminating the data from this study is an opportunity to correct the educational barrier. Just as Soloway and Arianayagam[16] argued in favor of IVC following TURBT, we agree that these barriers need to be overcome to deliver this effective treatment and ensure evidence based care is provided to patients.

Physician non-adherence to guidelines is not restricted to urology and has been explored in other fields, where findings may be instructive. Lugtenberg and colleagues have explored barriers to physician adherence to guidelines among general practitioners in the Netherlands. For example, in the implementation of guidelines for treatment of urinary tract infections, barriers included lack of agreement with the guidelines, unavailable testing materials, and inaccessibility of some drugs.[17] In other arenas, a questionnaire study elucidated reasons for lack of adherence to guidelines, which included physicians not agreeing with the guideline or feeling it was not applicable. Also insufficient knowledge of the guidelines, ambiguous guidelines, and workflow constraints were cited as reasons for guideline non-compliance.[18] These factors must be considered in order to form appropriate strategies and improve physician adherence to IVC guidelines, whether it be integrating electronic medical record based clinical pathways, providing accessible clinical decision making tools, linking reimbursement to guideline adherence, or revising guideline language.

The use of administrative databases, such as NSQIP, has several benefits and potential limitations.[14] NSQIP provides a large cohort of patients from multiple centers, offering a broad representation of practice patterns and care being delivered across variable demographics. However details regarding specific tumor characteristics, prior TURBT procedures, and oncologic outcomes are not available with the NSQIP database. Furthermore, the timing of IVC administration following TURBT is not provided. Since the inclusion of patients in the IVC group relied on billing codes, it is possible that IVC administration is underreported as IVC may have been administered and not billed. Given these limitations, NSQIP is useful for generating clinical hypotheses, rather than drawing firm conclusions.

Even with established evidence on the benefits and safety of IVC, only 2.6% of patients undergoing TURBT received IVC in this study. Data has shown a significant reduction in the risk of bladder tumor recurrence with a single dose of IVC following TURBT without a significant added risk in morbidity.[10,11] The current AUA guidelines recommend immediate postoperative IVC in patients with small volume and low grade, Ta disease and as an option in patients presenting with an abnormal urothelial tumor. It is conceivable that urologists find this guideline verbiage impractical and not applicable, since IVC is administered before pathologic confirmation of grade and stage is available. We suggest that the use of IVC be given a full recommendation for the management of patients undergoing TURBT for the initial diagnosis of bladder cancer for suspected TaT1 disease in the absence of a contraindication to IVC administration. A stronger guideline may help to increase the rate of IVC administration following TURBT, thereby reducing bladder cancer recurrence, preventing additional procedures, and ultimately improving quality of care.

Conclusion

Intravesical chemotherapy remains greatly underutilized despite current data documenting its efficacy in reducing tumor recurrence for TaT1 bladder cancer. Instillation of IVC following TURBT does not increase morbidity. Our findings support the continued need to explore ways of improving rates of perioperative IVC administration following TURBT. □

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