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Urol Pract. Author manuscript; available in PMC 2022 March 01.

Published in final edited form as:

Urol Pract. 2021 March ; 8(2): 291–297. doi:10.1097/upj.0000000000000174.

Barriers to single-dose intravesical chemotherapy in non-muscle invasive bladder cancer: what's the problem?

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Abstract

Introduction: The intravesical instillation of mitomycin C immediately following surgery for non-muscle invasive bladder cancer has been shown to be efficacious in reducing cancer recurrence. As a result, the American Urological Association adopted guidelines for non-muscle invasive bladder cancer care to support its use in low to intermediate risk patients. Despite this, urologists' use of this drug following transurethral resection of a bladder tumor (TURBT) has been reported as low as 5% or less. Our study objective was to better understand the barriers urologists experience in using mitomycin C.

Methods: Semi-structured interviews were conducted with 13 practicing urologists at 4 geographically distinct practice locations throughout Indiana between 2017 and 2018. Cognitive task analysis was used to explore factors that influenced their clinician decision-making about Mitomycin C use following TURBT in specific patient cases. Interview transcripts were coded and analyzed using immersion/crystallization to identify emergent themes.

Results: The median age of the urologists interviewed was 44 (IQR 40–48). Eighty-five percent were male. Approximately 30% had completed urologic fellowship training; 62% were in private practice. Three major themes related to the use of mitomycin C emerged: cumbersome workflow processes, urologists' fears of side effects, and issues of identifying patients most likely to benefit.

Conclusion: Workflow, fear, and value are key factors and also represent complexities of translating efficacy into effectiveness for a drug with known benefits to patients. Areas of potential intervention development to improve the use of mitomycin C to reduce recurrence of bladder cancer are suggested. Alternatives such as gemcitabine may also help overcome these barriers.

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Introduction:

The treatment and follow-up care for non-muscle invasive bladder cancer (NMIBC) is particularly challenging due to frequent recurrences, the burden of surveillance for patients who endure repeated invasive procedures, economic costs of lifelong follow-up, and potential for progression into more aggressive muscle-invasive disease. Notwithstanding, the challenges in managing NMIBC, randomized clinical trials supporting the use of intraoperative intravesical chemotherapy following transurethral resection of bladder tumors (TURBT) do exist. [1] Thirteen trials have demonstrated a reduction in recurrence of NIMBC by using intraoperative intravesical chemotherapy, [2–4] that when pooled together demonstrated an absolute risk reduction of 12% in those who received the therapy.[5]

Research to date suggests that utilization of intraoperative intravesical chemotherapy ranges from 3.2% to only 38% of TURBT cases.[6,7] Previous attempts to understand barriers to utilization have been methodologically incomplete.[8–10] Without knowing more about the decisions to use, or not use the treatment, interventions for improvement would be difficult, if not impossible, to craft successfully. Given the knowledge gap, we sought to understand urologists' reasons for use and underuse of single-dose postoperative chemotherapy following TURBT.

Methods:

Sampling and number of planned interviews.

Urologists were identified from the membership directory of the Indiana Urologic Association, Inc. (IUA). Invitations to participate in the study were sent by mail to all active members with detailed contact information on how to respond if interested by either phone and/or email. Due to a lack of response from this method, convenience-sampling methods were then used. We strategically contacted urology practices in 4 distinct geographic regions of the state by contacting a physician at each representative practice.

Data collection and analysis for this exploratory study were based on principles of cognitive task analysis (CTA),[11] interview and qualitative analysis techniques designed to aid experienced practitioners in describing aspects of cognitive work that are often difficult to articulate. CTA techniques ground the interview in lived experiences to increase the accuracy and richness of recall. [12,13] Using this approach, we interviewed 13 urologists at 4 locations representing multiple regions within Indiana. This is a typical number of interviews for exploratory CTA, in which the objective is to identify factors influencing a decision process, providing foundational findings that can be used to frame the problem, inform interventions, and inspire future research [12,13].

The interview approach chosen for this study included face-to-face semi-structured interviews, leveraging two CTA interview techniques. [12] The task diagram was used at the beginning of each interview to obtain an overview of the task and workflow from the interviewee's perspective. [13] The critical decision method was used to obtain specific examples and explore decision making context. CTA methods have been used to study

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decision making across a range of complex work settings, and more recently have been tailored for use in health care research.[14] The interview guide is provided in Appendix 1.

Interview Methods

Task Diagram: The task diagram interview provides a framework to aid the interviewer in eliciting the major steps required to complete a task and highlighting for further examination those that are most cognitively complex [12].

Critical Decision Method: The critical decision method[13] is perhaps the most established CTA method. Data collected using this method are particularly valuable because they include a first-person perspective in the context of challenging real-world scenarios. Each participating urologist was asked to describe a case in which he or she used intravesical chemotherapy, and a case for which he or she did not, with an emphasis on cases that were not straightforward. Critical points about the case were then probed to explore elements such as goals, options, use of cues, and specific contextual elements considered during the case. Each interview was digitally audio-recorded.

Data Collection and Analysis: The Indiana University Institutional Review Board approved the study prior to data collection. Interviews were conducted from August 2017 to May 2018. After each interview, the recordings were transcribed and housed in a password-protected Dedoose software database. (*Version 8.2.14, Los Angeles, CA)* Following each interview, the research team met to review field notes and develop analytic memos to highlight interview findings. After the interviews were transcribed, two researchers independently coded the interview segments and identified provisional themes. A codebook listing each theme and its description was created. (Appendix 2). Codes representing the themes were re-applied to the transcripts to ensure accuracy and consistency.

Results:

Sample description

Demographics of the participants are detailed in Table 1. The median age of those interviewed was 44 years; nearly all were white (92%), most were male (84%), and most (69%) had been in practice for 10 years or less. About a third (30%) had fellowship training beyond residency. The main clinical settings represented were academia (15%), private practices with more than 8 urologists (62%), and hospital-employed urologists (23%).

Emergent themes

Workflow processes—Workflow was identified as a broad theme that was subdivided into categories of ordering, instilling, and draining the drug from the bladder. Of these, instilling the drug was the most straightforward, and no barriers were identified related to this portion of mitomycin C use. Experience with ordering and draining mitomycin C varied by institution and seemed largely related to the volume of cases seen at each site. Table 2 details challenges described by participants across the thematic categories.

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Ordering the drug.: At surgery sites with fewer procedures, ordering mitomycin C was often more problematic. As one participant noted "[I] tried to figure out how to put it in the computer system and couldn't figure it out. I told the nurse to give her 40mg, and then the pharmacist called me to confirm the dose." This example also highlights issues related to ordering the drug category, specific to each site's electronic health record system. One participant stated that when he "logged into the electronic medical record, I could not find the order, so I had to call the pharmacist who had to page the chemotherapy pharmacist." Breakdowns in communication such as these delayed care and increased the time requirements of involved healthcare personnel.

Several participants reported a more streamlined process in which they listed mitomycin C as a note embedded in the operating room schedule. This alerted the pharmacist for the case to prepare the drug before the case began on the same day as the procedure. This strategy allowed the physician to have the drug immediately available in the operating room if everything went according to plan.

There were also tensions about when to order the drug, to avoid wasting it. If ordered too soon and there was a bladder perforation, then the drug would be wasted. Conversely, if it were mixed later during the procedure, then the urologist would likely have to wait to receive the medication from pharmacy. This tension was evidenced by one of the participants stating, "sometimes it takes an hour to get the stuff, so it just depends on...I probably could do a better job of pre-ordering it, but they don't like to mix it if you don't know you're going to use it."

Draining the drug from the bladder.: At some sites, the lack of established protocols for postoperative care and limited chemotherapeutic training of recovery-room nurses led to frustration for physicians. In some cases, the urologist was called back to the recovery room to drain the drug from the bladder after s/he had moved to another patient. Participants at some sites noted a lack of recovery-room nurse training, sometimes resulting in confusion about how to dispose of the medication. One participant stated, "you get a lot of push-back from PACU nurses who do not want to give that medication... so they really encourage us to do it in the operating room, so that can be kind of a delay as well". Another participant stated, "generally phone calls have been an issue", regarding how to drain it or properly dispose of it.

Additional issues unique to delivery of this medication were how it differs from other medications administered in the operating room. For example, the pharmacist mixes mitomycin C on the day of the procedure. The drug expires relatively quickly and cannot be stored for later use. Mixing a potentially hazardous chemotherapeutic agent requires a chemical safety hood, which isn't routinely available in the smaller operating room pharmacies, necessitating mixing the drug at a larger hospital pharmacy and transporting it to the operating room where the surgery is taking place.

Urologists' fears of pharmacologic side effects—Several participants expressed a noticeable reluctance to use mitomycin C following a TURBT. Considering use of the drug appeared to create some anxiety, as evidenced by one participant when asked, "Did this

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patient have any trouble [side effects of mitomycin]?" The urologist responded, "no, neither one of them did....Thank God." This statement hints that the participant did not feel confident that mitomycin C could be used reliably without significant side effects from the treatment. Participants expressed an uncertain "trust" of the drug, and concern about potential side effects. One stated, "There was no perforation or anything, but he had a horrible reaction... like chemical cystitis with a lot of pelvic pain." A similar experience led another participant to state, "It made me feel like the treatment was worse than the disease. The net result of the participants' experience was to question whether the benefits of using mitomycin C outweighed the risks, with many favoring the more conservative approach not to use the drug.

Nearly all participants had known about an individual patient or a small number of patients who had experienced significant side effects from the drug, including cystitis, dysuria, or pelvic pain. The low frequency of adverse events had a disproportionately large effect on participants' understanding of the risks involved in using the drug. As noted by one participant, "[One patient]… ended up losing his kidney, and he's had to have two procedures now.... and the whole thing was a nightmare. …if it had only been the one time, then okay, but then my partner... told me about that other perforation with the fat necrosis thing, and so now I'm kind of like, oh yeah, like badness." The fear of side effects seemed to outweigh the evidence-based potential benefit of reduced recurrence of bladder cancer.

Identifying patients most likely to benefit—As the participants recalled specific cases during the interviews, it was clear that there was general agreement about which patients would benefit most from its use. For example, most indicated that patients with "small papillary tumors", "recurrent tumors", and "no perforation of [the] bladder" were most likely to benefit. Similarly, most reported that they would not use the medication for "large sessile tumors", for "larger resection beds in the bladder", or when there was increased risk of perforation due to a deep resection of the bladder during the surgery. There were a few exceptions in which participants described misconceptions and uncertainty about when the drug is most likely to be effective. For example, one participant believed that mitomycin C would be most effective in high-grade but not low-grade tumors. Additionally, two participants used the drug only after multiple recurrences of bladder cancer within a period of 6–12 months.

Three of the 13 participants mentioned clinical details that they believed were relevant to a decision about mitomycin C, but that the research team believed were not relevant according to available medical knowledge and evidence about when to use the medication. [15] Table 3 is a "knowledge table" of participants' appropriate and inappropriate responses about when to use, or not use, the drug.

Discussion

This study focused on understanding urologists' perspectives grounded in guided interviews about actual patients. We identified a number of complexities involved in deciding about, and using, mitomycin C in an intraoperative setting. There were influential workflow processes such as proper order entry to avoid delay in care, timely mixing of the medication

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in the pharmacy, proper postoperative nursing knowledge about disposal of the drug, and individual characteristics that influenced willingness to give the medication based on experiences and fear of side effects.

Our findings expand on others' work that acknowledges that some physicians *never* offer this recommended medication to their patients. One study reported 67% of urologists never used intraoperative intravesical chemotherapy, but reasons for this approach have never been detailed.[10] Our study indicates that the workflow associated with administering mitomycin C is often too complex and time-consuming to justify using the drug. Furthermore, fear of side effects—some based on experience of the participants or their colleagues—presented as an insurmountable barrier for some, despite the low frequency of adverse effects among the population. The recent randomized SWOG S0337 trial data suggests that perhaps gemcitabine in this setting may temper some of these fears of chemical cystitis seen with mitomycin C.[16] In this trial, the risk of grade 3 toxicities was low with gemcitabine (2.4%) and also low with saline (3.4%). In addition, no grade 4 or 5 toxicities were noted. This may result in higher utilization of gemcitabine in the immediate postoperative setting, but this would overcome only one of the barriers found in our study. While cost was not specifically addressed in this study, one may also assume the cheaper cost of gemcitabine compared to mitomycin C would also allow for increased utilization. This would address possible concerns of mixing the medication early before the surgery begins only to have to waste the drug if a bladder perforation occurred during the procedure.

This study is limited by its small sample size. The reproducibility and generalizability of our findings are, therefore, uncertain. The sampling was initially aimed to be purposeful, but due to low response rates to mailed invitations, convenience sampling was used instead. The effect, if any, of sampling on outcomes is unknown. However, the urologists sampled covered a wide geographic area within the state of Indiana and were trained in a variety of residency programs across the country. Over 50% of participants did received their medical school degrees from Indiana University. Despite the limited geographic sampling due to funding constraints, the diverse residency training background of participants may reduce this potential limitation. It is also worth noting that the study lacks the input of additional stakeholders, such as nurses, pharmacists, and patients, who were involved in the care.

These limitations notwithstanding, the findings establish a model upon which to build in creating interventions to improve adoption and effectiveness. Additionally, this is the first qualitative exploratory study to provide first-person perspective, context, and insight, which a survey or large administrative dataset is unable to provide.

In summary, moving from efficacy to effectiveness requires understanding the context and environment in which the drug is going to be used. To date, investigators have seemingly not paid enough attention to the complexities we have uncovered in this study and may explain why the drug, despite its efficacy, has not been effectively used. Future directions of research will be to develop, test, and refine interventions targeting the workflow process that would assist with efficient ordering, instilling, efficient drainage of the drug, appropriate apprehension of the side-effect profile, and appropriate patient selection.

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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Key of Abbreviations:

TURBT	Transurethral resection of bladder tumor
IUA	Indiana Urologic Association

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Table 1.

Self-reported study participant characteristics of the 13 participating urologists

Characteristic	N
Median Age (IQR)	44 (40–48)
Race/Ethnicity N (%)	
• Caucasian	12 (92.3)
• African-American	1 (7.7)
• Asian	1 (7.7)
Gender N (%)	
• Male	11 (84.6)
• Female	2 (15.4)
Years in urology practice N (%)	
• 1–5	5 (38.5)
• 6–10	4 (30.8)
• 11–15	1 (7.7)
• 16–20	2 (15.4)
• >20	1 (7.7)
Fellowship training N (%)	
• Urologie Oncology	2 (15.4)
• Minimally-invasive/robotic	2 (15.4)
• None	9 (69.2)
Type of Urology practice N (%)	
• Academic	2 (15)
• Private practice (>8 urologists)	8 (62)
• Hospital employed	3 (23)
Hours/week in clinical practice N (%)	
• <25	0
• 26–45	4 (30.8)
• 46–60	6 (46.2)
• >61	3 (23.1)
Approximate # of TURBTs * per 3 month period N (%)	
• 1	0
• 2–5	0
• 6–10	6 (46.2)
• 11–15	3 (23.1)
• >15	4 (30.8)
Location most commonly performing TURBTs	
• Hospital only	9 (69.2)

Characteristic	N
• Ambulatory surgery center only	0
• Both	4 (30.8)

*TURBT = transurethral resection of bladder tumor

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Table 2.

Barriers and Facilitators to Workflow for postoperative chemotherapy*

	Ordered before OR	Ordered in OR	Location Barriers	Who does it	Disposal
Ordering it	• Tells scheduler to put on OR schedule • Should be part of preop checklist • No delay in getting medication when mixed at first of case • May not use it and thus waste it	• Generally a delay of 15–60min • Variation in how its ordered resulting in various wait times ⇒ -Verbal ⇒ -Enter into EMR (unscrub) ⇒ -Written order	• Different computer systems across hospital makes ordering confusing	• Physician orders it in some fashion at all sites	
Instilling it			• Some PACU nurses are comfortable instilling medication • Pharmacy won't mix it until we know we need it	• Physician almost universally instills it • At times when delayed, physician have to go back to PACU to instill it • Usually being done in OR, but can be done in PACU—Most don't like given in PACU	
Draining it				• Recovery room nurses almost always drain it • Nurses follow protocol that was developed	• Nurses dispose of it in chemo bins and pharmacy takes care of it (seems not an issue)

*Green: Facilitator; *Gray: Barrier

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Table 3.

Correct and Incorrect Physician responses identifying patients thought most likely to benefit from postoperative chemotherapy.

Correct non-use mitomycin C:	Correct use mitomycin C:	Incorrect use of mitomycin C
• Invasive • High Grade • Perforation • Clearly sessile tumor • Sessile high grade • Large papillary tumor • Large surface area • Extensive resection into the muscle • Extensive resection into the fat • Bulky tumor • Patient bleeding • Loss of integrity of bladder wall	• Has had recurrence >1yr • Any low-grade tumor • Multi-focal low grade	• High grade tumors • Multiple quickly recurring tumors