Restaging Transurethral Resection for Non-Muscle Invasive Bladder Cancer

Who, Why, When, and How?

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KEYWORDS

• Non-muscle invasive bladder cancer • Transurethral resection • Repeat resection
• Second-look cystoscopy • Restaging • Upstaging • Understaging

KEY POINTS

- Understaging rates of up to 40% for non-muscle invasive bladder cancer have been reported based on radical cystectomy data.
- Absence of muscularis propria MP in the specimen leads to a significantly higher rate of understaging (60%–78%).
- Patients with high-grade (HG) Ta and HG T1 tumors, regardless of presence of muscle, are strongly encouraged to undergo a restaging transurethral resection (TUR).
- Repeat resection should be performed 2 to 6 weeks following initial TUR.
- Deep biopsies in the base and periphery of the old resection site should be performed.

Non-muscle invasive bladder cancer (NMIBC) comprised the vast majority of the estimated 73,510 new cases of bladder cancer diagnosed in the United States in 2012.[1] Approximately 70% to 75% of patients with bladder cancer initially present at a low stage (stage 1), a category that includes carcinoma in situ (Tis – 1–10% alone as primary), tumors confined to the urothelial mucosa (Ta – 70%–80%), and those that invade only the underlying lamina propria (T1 – 20%).[2–4] The prognosis for patients with NMIBC is generally good, with approximately 80% to 90% of patients alive at 5 years.[2] In contrast, muscle-invasive bladder cancer, which represents about 25% of cases, has a significantly lower relative 5-year survival rate of 17% to 66% depending on tumor stage.[2,5] Epidemiologic evidence demonstrates that these trends in incidence and survival for noninvasive and invasive bladder cancer have remained relatively stable since 1993.[2] The most significant risk factor for bladder cancer is cigarette smoking.[6] While the risk may decrease with smoking cessation, former smokers still have a higher risk of bladder cancer than never smokers.[6] Additionally, in patients with NMIBC, current tobacco use and cumulative lifetime exposure are closely associated with recurrence and progression.[7,8] There is no currently accepted genetic or inheritable cause of urothelial carcinoma of the bladder, but studies suggest that polymorphisms in 2 carcinogen-detoxifying genes, GSTM-1 and NAT-2, may be responsible for increased susceptibility to developing bladder cancer in certain patients.[9]

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WHO TO RESTAGE

Understanding the Predictors of Understaging, Recurrence, and Progression

Patients with NMIBC represent a heterogeneous group and demonstrate a broad range of outcomes with respect to recurrence, progression, and survival. Accurate staging and a fundamental understanding of the pathologic findings that predict outcome are therefore of utmost importance in clinical management. Thus, when considering the value of restaging transurethral resection (TUR), the first question that must be addressed is "who?" That is, which patients may benefit from additional resection rather than proceeding to intravesical chemotherapy/surveillance cystoscopy? Importantly, restaging TUR, which assumes a complete initial TUR, is distinguished here from a repeat resection performed when a complete initial TUR cannot be accomplished.[10]

Most (55%–75%) of Ta tumors are low grade (LG), and patients with high-grade (HG) tumors are at much greater risk of recurrence, progression, and death from bladder cancer compared with those with LG disease.[2,11,12] Long term follow-up of Ta LG tumors demonstrates that the overall recurrence rate is 55%, with 6% and 20% experiencing progression of stage and/or grade, respectively.[13] In contrast, 30% to 35% of Ta HG tumors will progress to at least T1 disease.[11,12] Ta HG urothelial cancer is associated with a significant risk of progression and death as manifested by progression-free survival and disease-specific survival rates of 61% and 74%, respectively, according to 1 study.[14] This has important implications when considering the merits of restaging TUR, since adequate tumor stage and grade information clearly guides future management decisions, including administration of intravesical therapy or a recommendation for early cystectomy in patients found to be understaged at initial TUR.

Along with Ta HG bladder cancer, carcinoma in situ (CIS) and T1 cancers are all considered high-risk NMIBC. Clinical stage T1 tumors, those invading beyond the mucosa but confined to the lamina propria at the time of TUR or biopsy, represent approximately 20% of NMIBC and behave more aggressively than Ta tumors. They may also be classified as HG or LG, but in contrast to stage Ta, most T1 tumors are HG and therefore have a high risk of progression.[12,15] Within stage T1 urothelial cancer, studies have shown that deeper invasion into the lamina propria leads to higher progression rates (58%) compared with superficial invasion (36%), and depth of invasion (as measured by muscularis mucosae involvement) is a significant independent predictor of progression.[15–17] While this is likely related in part to increased aggressiveness of more deeply invading tumors, this may also be indicative of the increased likelihood of an incomplete endoscopic resection in patients with tumors invading into the muscularis mucosae. Thus, adequate TUR is critical not only to ensure accurate staging and guide future management options, but also to remove all tumor from the bladder.

It should be emphasized that invasion of the muscularis mucosae is still considered non-muscle invasive disease in contrast to muscularis propria (MP) invasion, which is the hallmark of true muscle invasion (stage T2). Therefore, a TUR specimen with only muscularis mucosae and no MP is still considered inadequate for determination of muscle invasion. **Fig. 1** demonstrates a cT1 tumor with MP present in the specimen and not involved by cancer. **Fig. 2** demonstrates a cT1 tumor with only muscularis mucosae present in the specimen; it is therefore inadequate for the determination of muscle invasion due to lack of MP. The ability to distinguish between the MP and muscularis mucosae is challenging, however, as these images show. MP is a distinct layer of muscle fibers, whereas muscularis mucosae is typically a few smooth muscle cells arranged in fibers dispersed throughout the lamina propria.[18]

Sylvester and colleagues[19] reviewed 7 European Organisation for the Research and Treatment of Cancer (EORTC) trials in NMIBC and found that the probability of progression for T1HG disease ranged from 20% to 48% at 5 years, and the

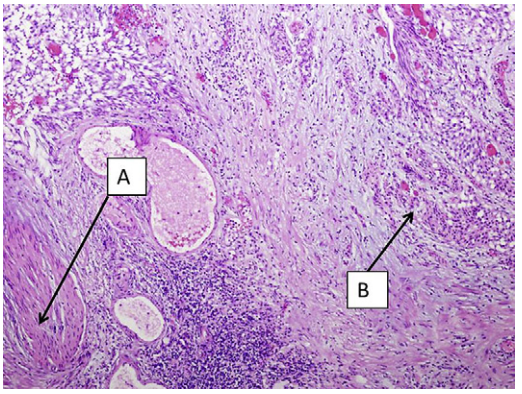

Fig. 1. TUR specimen demonstrating muscularis propria present in the specimen but not involved by urothelial carcinoma. Image shows a thick bundle of muscle fibers (*A*) that are seen in the resected specimen and are separate from the area of tumor (*B*). The tumor is high grade, demonstrating significant cytologic atypia with a desomplastic reaction and lamina propria invasion (stage T1). (*Courtesy of* Lan Gellert MD, PhD, Department of Pathology, Vanderbilt University.)