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Lesson 14 Volume 40

Management of Patients with Non-Muscle Invasive Bladder Cancer with Variant Histology*

Learning Objective: At the conclusion of this continuing medical education activity, the participant will be able to determine how different variant histologies may affect clinical decision making and outcomes for patients with non-muscle invasive bladder cancer.

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INTRODUCTION

Non-muscle invasive bladder cancer accounts for approximately 80% of new cases of bladder cancer diagnosed each year.[1] Historically, 90% of bladder cancers were categorized as conventional or pure urothelial carcinoma, with the other 10% being pure squamous or adenocarcinomas.[2,3] However, in recent years there has been increasing recognition of other histological patterns that in many cases seem to portend a worse prognosis. For the purposes of this Update, we define variant, or aberrant, histology as any non-pure urothelial carcinoma.

There are more than 30 different histological subtypes of bladder cancer described in the 2016 WHO pathology guidelines (see Appendix).[2–4] This is a rapidly changing landscape for pathologists. In a pathological re-review of more than 1,000 cystectomy specimens from 1980 to 2005, Linder et al found that more than 30% of those previously categorized as conventional urothelial cancer actually harbored one or more variant histologies, calling into question the control arm of many retrospective case series that did not include pathology re-review.[5] We do not yet have molecular tests to identify most of these subtypes, and there may be considerable inter-observer variability in identification of some of them, especially micropapillary tumors. The importance of the percentage of the tumor that harbors variant histology in either a transurethral resection or cystectomy specimen is also controversial. And finally, it is not uncommon today for 2 or more subtypes to be identified in a single specimen (eg micropapillary plus plasmacytoid), and the significance of this remains unclear. **The changing landscape of this variant histology makes it very difficult to rely on retrospective data sets or population-based studies to understand the behavior of this disease unless the study included complete pathological re-review of every case (including in the control arm).**

Many retrospective series have focused on patients undergoing cystectomy, mostly for muscle invasive disease, and have shown that variant histology is associated with a high risk of upstaging and poor outcomes.[6,7] Several more recent and larger series with careful pathology review have questioned whether some variant histologies really have a worse prognosis independent of their association with more advanced pathological stage.[8,9] The role of systemic chemotherapy and efficacy of chemoradiation for muscle invasive cancers with variant histology are also still unanswered questions; however, they are outside the scope of this Update.

As community and academic pathologists are becoming more familiar with these histological subtypes, they are being identified more frequently in transurethral resection specimens in the absence of muscle invasion. At our institution, more than 10% of TUR specimens with only cT1 disease are currently read as having some component of variant histology, and that number has continued to rise. There is considerable controversy about the best way to manage patients with non-muscle invasive cancer with variant histology. In this Update, we will discuss what is known about non-muscle invasive bladder cancer with variant histology and suggest an algorithm for the clinical approach to these patients.

CLASSIFICATION OF VARIANT HISTOLOGY

The WHO updated its guidelines on the pathological diagnosis of cancer of the bladder in 2016.[3] The new classification lists an increased number of recognized variants, with a few significant changes from the prior edition. These can be divided into "pure" non-urothelial cancers, urothelial cancers with divergent differentiation, and other urothelial variants.

Non-urothelial bladder cancer. This group includes patients with pure squamous or adenocarcinoma of the bladder, as well as sarcomas, melanoma, lymphoma and metastatic lesions. Pathological review is particularly critical for patients diagnosed with pure squamous cell or adenocarcinoma, since there is often a component of conventional histology identified, such as urothelial carcinoma in situ, that would re-categorize the patient to urothelial cancer with divergent histology (see below). Pure squamous cell carcinoma is often associated with chronic inflammation such as from an indwelling catheter or *Schistosoma haematobium* infection in places where that is endemic. Pure adenocarcinoma may arise in the urachal remnant or from non-urachal locations in the bladder, or may represent direct extension or metastasis from a colon primary tumor. Pure sarcomas of the bladder are rare in adults and may be associated with prior pelvic radiation therapy.

These non-urothelial cancers are rarely discovered in the absence of muscle invasion. A study of nonbilharzial squamous cell carcinoma using the Surveillance, Epidemiology, and End Results (SEER) database demonstrated that of the 614 cases identified only 22 (3.6%) were stage T1.[10]

Generally, patients with non-urothelial cancers are recommended to undergo partial or radical cystectomy, even in the case of non-muscle invasive disease. If conservative treatment such as TUR alone is considered, for example in a frail patient, repeat resection would be strongly recommended to confirm complete resection. Assisted cystoscopy such as fluorescent "blue light" cystoscopy may help identify occult carcinoma in situ, which would reclassify the patient. In some cases, systemic chemotherapy, radiation or combination therapies may be recommended, for example in patients with lymphoma or metastatic tumors, depending on histology, location and resectability.

Urothelial cancer with divergent differentiation. Urothelial cancers with divergent differentiation are fairly common, being reported in approximately 20% of patients with newly diagnosed NMIBC. Divergent differentiation refers to the presence of some percentage of urothelial carcinoma along with other variant histologies, most commonly squamous differentiation or glandular differentiation.[3] It is important to distinguish divergent differentiation from pure forms of variant histology such as pure squamous cell carcinoma or pure adenocarcinoma as the latter are typically more aggressive.[10,11] In general, urothelial carcinoma with divergent differentiation is treated the same as conventional UC, although there is a suggestion that these subtypes may portend a worse prognosis. Neither

ABBREVIATIONS: AUA=American Urological Association, BCG=bacillus Calmette-Guérin, GU=genitourinary, NMIBC=non-muscle invasive bladder cancer, TUR=transurethral resection, TURBT=transurethral resection of bladder tumor, UC=urothelial carcinoma, WHO=World Health Organization

the AUA nor the European Association of Urology guidelines specifically address management of these patients. However, the AUA Guideline does recommend a restaging TURBT if a bladder-sparing approach is considered.[1]

There are several studies suggesting that patients with squamous differentiation may have a worse prognosis compared to those with conventional UC. Li et al reported on 227 patients with cT1 NMIBC with squamous differentiation and showed a lower 5-year cancer-specific survival rate compared to those with conventional UC (69% vs 91%, p <0.001).[9] However, repeat TUR was done in only about 20%, and lymphovascular invasion was present in 30% compared to 8% of conventional UC patients. In addition, the patients in this study were treated with intravesical chemotherapy rather than intravesical BCG. Lin et al performed a meta-analysis confirming that squamous differentiation was associated with a worse prognosis, although most of the studies included cystectomy patients with muscle invasive bladder cancer.[12] A small study of 47 patients with NMIBC with squamous or glandular differentiation suggested some potential benefit of BCG over surveillance or intravesical chemotherapy.[13] Gofrit et al studied 41 patients with NMIBC with variant histology, including 22 patients with squamous or glandular differentiation.[14] All patients underwent repeat TURBT prior to intravesical therapy with BCG plus maintenance. The 9 patients with glandular differentiation had a 100% cure rate, but the 12 with squamous differentiation had a 40% progression rate at 3 years.

According to the AUA Guideline on the management of NMIBC, patients with divergent differentiation are generally not included in the variant histology group.[1] Most groups suggest treating patients with UC with squamous or glandular differentiation the same as those with conventional UC.

Urothelial variant histology. Although there is a very long list of described variants (see Appendix), most are extremely rare and are managed on a case-by-case basis. The most common variants include micropapillary, plasmacytoid, neuroendocrine and nested variants. **There are still problems in the pathological evaluation of these tumors, with significant under-identification and inter-observer variability even among pathological experts, especially in TUR specimens.[15,16] Sampling and cautery artifact may significantly affect the accuracy of pathology. Although noninvasive variants have been described, variant histology in general should only be identified in invasive tumors (cT1 or above).[3,17]**

The AUA Guideline on the treatment of bladder cancer recommends central pathology review by a dedicated GU pathologist for any patient with suspected variant histology.[1] Luchey et al in 2016 reported significant changes in the interpretation of TUR specimens by dedicated GU pathologists at a comprehensive cancer center compared to those interpreted at community hospitals.[18] Variant histology was identified in 212 of 1,191 patients, and 54% of those were not previously recognized. Shah et al in 2013 had similar findings.[15] In that study, the most frequently reclassified histologies included lymphoepithelial, plasmacytoid, nested variant, micropapillary and small cell.

Micropapillary. The most common variant histology type is micropapillary urothelial carcinoma, occurring in about 10% of cystectomy series. Micropapillary variant histology is only present when identified in the invasive component of bladder tumors, and these tumors are associated with upstaging at cystectomy and with extravesical and nodal extension.[3,17] The role of systemic chemotherapy is controversial. There is considerable variability between experienced pathologists in diagnosing this cancer, and there may be poor concordance between the TUR specimen and subsequent cystectomy without any intervening treatment.[19,20] Of 95 patients diagnosed with micropapillary disease on TURBT, only 10 had micropapillary disease identified on subsequent cystectomy, and an additional 59 (11%) of 527 patients diagnosed with pure urothelial cancer on TURBT had micropapillary disease on final pathology.[20] Cautery and retraction artifact can especially mimic micropapillary disease. In one study 10 "classic" micropapillary specimens and 20 less typical ones with retraction artifact and variable size nests that were also diagnosed as micropapillary were distributed to 14 experienced GU pathologists.[16] Although 93% of the pathologists agreed on the 10 classic cases, there was wide variation on the second group, with individual pathologists diagnosing between 0 and 11 specimens as being micropapillary.

Many studies have confirmed that micropapillary tumors have a high rate of upstaging at cystectomy.[21,22] However, a multi-institutional collaboration with pathology re-review did not find that histology was an independent predictor of outcome.[8] Many of these patients did not have the micropapillary histology identified on a TUR specimen prior to cystectomy.

Micropapillary is the most studied variant histology in the non-muscle invasive setting. The group at MD Anderson Cancer Center retrospectively evaluated 72 patients with NMIBC micropapillary tumors and compared those treated with BCG to those undergoing initial cystectomy.[23] The 5-year cancer-specific survival for those with up-front cystectomy was 100% compared to 60% for those who had initial BCG. In the latter group, almost 40% developed metastases prior to cystectomy. Of note, routine repeat TUR was not commonly performed. Patients who only had focal micropapillary histology (<25%) had a similar recurrence rate to those with more extensive micropapillary histology, but had a lower progression rate (30.8% vs 69.2%) and lower node-positive rate at cystectomy (23% vs 54%), although the latter was not statistically significant.[23] Based on this study, their group strongly recommends initial cystectomy for all patients with micropapillary histology, even those with cT1 disease.[24]

In contrast to that series, Spaliviero et al found the opposite result in their study of 21 patients with T1 micropapillary tumors undergoing treatment with intravesical BCG after restaging TURBT at Memorial Sloan Kettering Cancer Center.[25] They found no statistically significant difference in 5-year cancer-specific survival between patients with T1 micropapillary disease who were treated with BCG vs initial radical cystectomy (75% vs 83%, p=0.8). Recurrence was seen in 38% of patients treated with BCG, with progression in only 10%. Most patients had more than 25% involvement with micropapillary tumor on the TURBT, and they did not find that the extent of variant histology was predictive of outcome. Other, smaller studies have also demonstrated recurrence rates that are similar to the study by Spaliviero et al.[17,26] While it is clear that non-muscle invasive micropapillary urothelial carcinoma is inherently aggressive, the optimal management of this disease remains controversial.

Plasmacytoid. **In the new WHO classification, signet ring tumors have been grouped with plasmacytoid carcinoma.[3]** These tumors may contain intracellular mucin (hence the signet ring

or plasma cell-like appearance) but should not contain extracellular mucin. Plasmacytoid urothelial carcinoma is associated with mutations in the gene *CDH1*, which lead to a loss of E-cadherin.[27,28] It is thought that loss of E-cadherin may promote the invasiveness of this tumor.[27,29,30] These tumors are notoriously aggressive and usually present as advanced disease, often with dispersion of individual cells in the detrusor muscle and perivesical tissue (fig. 1). Carcinomatosis is particularly common with this tumor type after cystectomy.[29] A recent cystectomy series from Memorial Sloan Kettering Cancer Center confirmed the high risk of upstaging but did not find that histology was an independent predictor of worse outcome on multivariable analysis.[30]

Nested variant. Nested variant can occur as small or large nested variants. Both tend to have bland appearing cells that mimic low grade cancer but are invasive. **These variants should be suspected when a patient is diagnosed as having low grade cancer with invasion into the lamina propria or muscularis propria.** Typically, the nested variant has been described as appearing with cells containing bland cytoplasm and arranged in small nests or tubules.[3] However, more recent observations have also described a large nested variant, which may appear benign given the presence of larger nests of cells with bland cytoplasm that may resemble benign urothelial proliferations such as von Brunn nests or inverted urothelial papilloma.[31] Unlike the benign urothelial proliferations, the large nested variant has been observed to invade the muscularis propria and thus is thought to have highly aggressive behavior. There are no large series of patients with non-muscle invasive nested variants to guide treatment approach.

Neuroendocrine variant. Neuroendocrine tumors may have a varied appearance and may be mixed with conventional UC or other histological types. Both small cell and large cell variants have been described. Immunohistochemistry using conventional neuroendocrine markers is diagnostic for these tumors and should be performed when in doubt. The neuroendocrine component has a very high likelihood of occult metastases, and past experience with initial cystectomy followed by adjuvant chemotherapy had only a 30% success rate.[32] Lynch et al reported a retrospective series showing markedly improved outcomes with neoadjuvant chemotherapy followed by cystectomy, and that has now become the standard of care for muscle invasive bladder cancer with neuroendocrine differentiation.[1,33] Radiation to the bladder following induction cisplatin with etoposide is also effective.[34,35] At Stanford University, we use neoadjuvant chemotherapy with cystectomy or radiation even with non-muscle invasive neuroendocrine tumors as they tend to be very responsive to systemic therapy. **Because of the high incidence of distant metastases, intravesical therapy is not recommended for neuroendocrine tumors.**

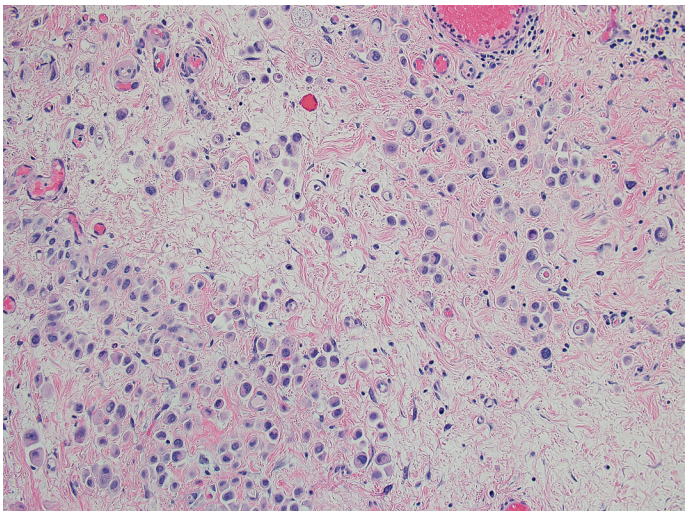

Figure 1. Plasmacytoid bladder tumor shows single cell spread in lamina propria. Reduced from ×20.

Sarcomatoid variant. Sarcomatoid variant is identified by the presence of spindle cell morphology, usually associated with conventional UC.[36] These are highly aggressive tumors, and early cystectomy is recommended.[37] Again, there are few data about alternative management of non-muscle invasive cancers with sarcomatoid variant.

Other variants. The other variants are extremely rare, and most series report on just a few cases collected over many years.[20] All seem to have increased upstaging and worse prognosis compared to conventional UC. Their individual responsiveness to BCG, chemotherapy and cystectomy or radiation is unknown.

CLINICAL APPROACH FOR NMIBC WITH VARIANT HISTOLOGY

The AUA Guideline on the treatment of bladder cancer recommends central pathology review by a dedicated GU pathologist for any patient with suspected variant histology.[1] This is particularly important in patients with NMIBC.

Repeat TURBT is strongly recommended before making further decisions about management. Current pathology standards recommend against diagnosing these tumors on noninvasive biopsies.[3] However, if variant histology is suspected on a specimen that is noninvasive (cTa), repeat TURBT should be performed. **Deep loop resection of the prior tumor bed is recommended rather than simple cold cup biopsy.**

There is a high likelihood of identifying muscle invasion on repeat TURBT for cT1 tumors with variant histology. In the series from Gofrit et al, 59% of 100 patients with variant histology who underwent repeat TURBT were found to have muscle invasive tumor.[14] Neoadjuvant chemotherapy seems logical prior to cystectomy for patients with muscle invasive variant histologies because of the very high likelihood of upstaging and the difficulty of administering chemotherapy postoperatively. However, there is considerable controversy about this, and a thorough multidisciplinary discussion should take place prior to deciding about treatment for each patient.

INTRAVESICAL THERAPY FOR CONFIRMED cT1 TUMORS WITH VARIANT HISTOLOGY

Neuroendocrine and sarcomatoid tumors have a particularly poor prognosis, and intravesical therapy is not recommended for those patients. The other subtypes of variant histology might be considered for intravesical therapy if they are confirmed to be free of muscle invasion on repeat resection. **Cases with large (>3 cm) or multifocal tumors, those that have already recurred after prior BCG and tumors that demonstrate lymphovascular invasion or deep lamina propria invasion on either initial or repeat TUR should all be strongly considered for initial cystectomy instead of intravesical therapy.**

There are few studies of the results of using BCG in patients with other histological subtypes. Gofrit et al studied 41 patients

with NMIBC with variant histology, all of whom underwent repeat TURBT prior to intravesical therapy with BCG plus maintenance.[14] Of these patients 22 had squamous or glandular differentiation. Outcomes of the entire group were worse than a comparison group of 141 patients with conventional urothelial cancer (although the pathological details of the comparison group were not included in the publication). As a whole, the patients with variant histology did somewhat worse than the conventional urothelial patients. In an unpublished series from our institution of 59 selected patients with cT1 aberrant histology, including 32 with aggressive variants, outcomes with repeat TURBT and intravesical BCG were equal to or better than a comparison group with conventional urothelial cancer.

Although cystectomy is likely to be curative in the majority of patients with cT1 bladder cancer with variant histology, it may be overtreatment for patients who present with a small, completely resected variant who have no tumor or only cTa or carcinoma in situ conventional urothelial cancer on repeat TURBT. The risks and quality of life impact of cystectomy are not trivial, and a large number of such patients are elderly or may have a high likelihood of serious complications or death with a radical cystectomy. Those risks must be balanced with the potential benefit of surgery for these patients.

We factor in the variant histology type, the extensiveness of variant histology, the presence of other adverse pathological features, and the patient's prior bladder cancer history, age and comorbidities in determining who may be managed with a trial of intravesical BCG. A suggested algorithm for approaching the patient with non-muscle invasive bladder cancer with variant histology is illustrated in figure 2.

SUMMARY

Most variant histologies appear to be more aggressive than pure urothelial carcinomas. Most of our current literature has focused on patients undergoing radical cystectomy, and the data on treatment of variant histology with intravesical therapy are very limited. As variant histology becomes more frequently described in pathology reports, it is important for us to continue to evaluate the data regarding the optimal treatment for this heterogeneous subset of bladder cancer. Given the available data, as well as our personal experience, we suggest the following approach for managing patients with non-muscle invasive bladder cancer with variant histology:

1. Central pathological review by a dedicated GU pathologist for any suspected variant histology or incongruent histology reports such as low grade T1 disease. May also consider review for patients diagnosed with pure squamous or adenocarcinoma of the bladder since reclassification as urothelial carcinoma with divergent differentiation may change treatment recommendations.
2. Consideration of up-front radical cystectomy for aggressive variants such as plasmacytoid and sarcomatoid variants, and neoadjuvant chemotherapy followed by surgery or radiation for neuroendocrine or small cell tumors. One should also strongly consider radical cystectomy for patients with variant histology and high risk features such as persistent invasive variant histology on re-resection, deep lamina propria invasion, recurrence after prior BCG or lymphovascular invasion.
3. Consideration of treatment with restaging TURBT followed by intravesical BCG in patients with no tumor or only carcinoma in situ or conventional urothelial cTa on repeat TURBT.

FUTURE DIRECTIONS

As with other cancers, better understanding of the molecular and genetic makeup of bladder cancers with histological variants will improve accuracy of diagnosis and may help predict

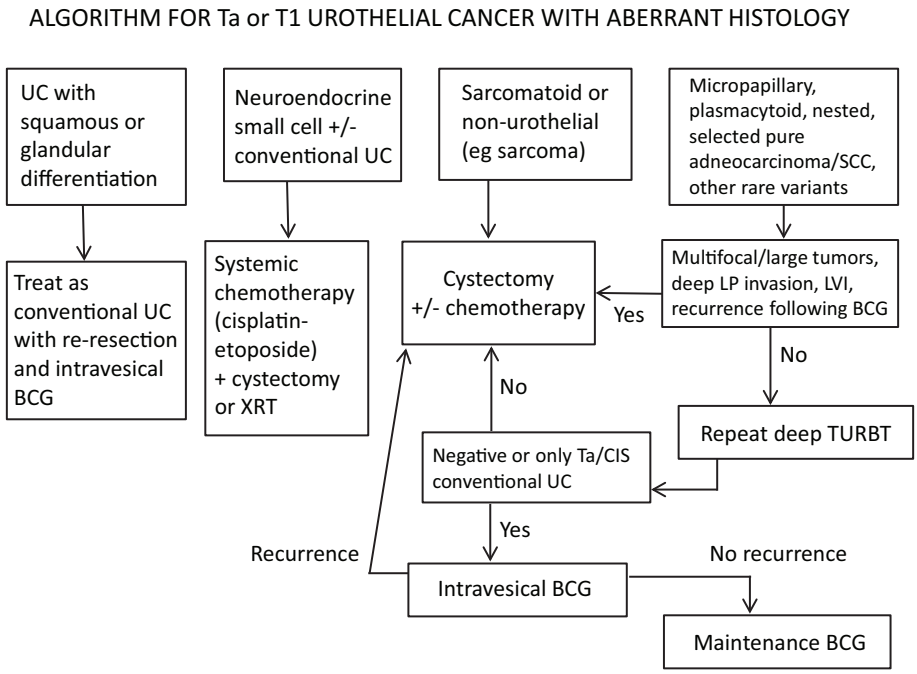

Figure 2. Suggested algorithm for management of non-muscle invasive tumors with variant histology. *CIS*, carcinoma in situ. *LP*, lamina propria. *LVI*, lymphovascular invasion. *SCC*, squamous cell carcinoma. *XRT*, radiation therapy.

response to therapy. Future studies should include, whenever possible, pathological re-review of both the variant and the control group to help sort out the real impact of these variants on prognosis.

DID YOU KNOW?

- Data regarding the management of patients with non-muscle invasive bladder cancer with variant histology remain limited.
- Pathological evaluation of non-muscle invasive bladder cancer variant histology is challenging. Therefore, the AUA recommends central pathology review by a dedicated genitourinary pathologist when the presence of variant histology is suspected.
- Primary treatment with systemic chemotherapy should be considered for patients with non-muscle invasive bladder cancer with small cell neuroendocrine variant histology.
- Primary treatment with radical cystectomy should be considered for patients with non-muscle invasive bladder cancer with aggressive variant histology, such as sarcomatoid or plasmacytoid.
- Cases without aggressive variant histology or small cell neuroendocrine variant histology should be managed as high risk non-muscle invasive bladder cancer.

Appendix. Classification of bladder tumors

Urothelial:	Conventional urothelial
	Micropapillary
	Plasmacytoid/signet ring/diffuse
	Nested, large nested
	Sarcomatoid
	Neuroendocrine (small cell, large cell)
	Lymphoepithelioma-like
	Giant cell
	Poorly differentiated
	Lipid-rich
	Microcystic
	Clear cell
Non-urothelial:	Squamous cell
	Glandular (enteric, mucinous, villous, urachal)
	Melanoma
	Sarcoma
	Lymphoma
	Metastatic tumor

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Study Questions Volume 40 Lesson 14

1. A risk factor for pure squamous cell carcinoma of the bladder is
   a. clean intermittent catheterization
   b. recurrent urinary tract infections
   c. bilharzial urinary tract infection
   d. metformin exposure

2. Neoadjuvant chemotherapy is indicated for which of the following NMIBC variant histologies?
   a. sarcomatoid
   b. plasmacytoid
   c. small cell (neuroendocrine)
   d. urothelial cancer with extensive squamous differentiation

3. A 68-year-old man with gross hematuria is found to have a 2 cm bladder tumor on cystoscopy. He undergoes TURBT and his pathology, read by a dedicated genitourinary pathologist at an academic referral center, shows high grade T1 urothelial carcinoma of the bladder with 20% micropapillary variant. The next step is
   a. restaging TURBT
   b. intravesical BCG induction and maintenance
   c. neoadjuvant chemotherapy followed by radical cystectomy
   d. radical cystectomy

4. A 70-year-old man with a bladder tumor undergoes TURBT at his local community hospital. The pathology report stages his bladder tumor as high grade T1 urothelial carcinoma with 30% plasmacytoid variant histology. The next step is
   a. pathology re-review by a dedicated GU pathologist
   b. restaging TURBT
   c. intravesical BCG induction and maintenance
   d. radical cystectomy

5. An 89-year-old man undergoes TURBT and is found to have high grade T1 urothelial carcinoma with 2% micropapillary variant histology. He undergoes a restaging TURBT and the pathology is negative for residual disease. The next step is
   a. observation
   b. induction BCG followed by maintenance therapy
   c. neoadjuvant chemotherapy followed by radical cystectomy
   d. radical cystectomy