Management of Superficial Bladder Cancer

1. (title slide) Every Urologist is familiar with the management of superficial bladder cancer. However, several new concepts have emerged in the recent past that require us to challenge some long-held practices.

2. The listed topics will be the focus of this presentation.

3. Even the very term, “superficial bladder cancer”, is being challenged, and justifiably so. It suggests reassurance, but many non-muscle-invasive bladder tumors are high grade and inevitably progressive unless treated aggressively. The more applicable term, non-muscle-invasive, accurately characterizes this heterogeneous group of malignancies. The WHO consensus guidelines have failed to gain universal acceptance, but they suggest replacing the old term “transitional cell carcinoma” with “urothelial carcinoma”. The guidelines have also added the category of “Papillary urothelial neoplasm of unknown malignant potential”, or its acronym, PUNLMP.

4. Easily misinterpreted as simply a new term for grade 1 urothelial carcinoma, PUNLMP is a low grade tumor that recurs often enough that most current guidelines (fade in Ta photo) would suggest following them in a manner similar to low grade Ta tumors. However, we believe that with further experience, that urologists will comfortably minimize invasive investigation for these lesions.

5. In contrast, high grade tumors present significant risk unless diagnosed and treated early in their course. These tumors can be stage Ta—non-invasive; T1—invasive of the underlying lamina propria, or carcinoma-in-situ— also non-invasive. The risk of progression for all is high.

6. The next concept challenged is the tradition of considering bladder cancer to be two diseases—superficial or invasive.

7. For example, stage Ta tumors are defined as non-invasive, and are usually low grade and minimal risk. However, if such tumors are high grade, their risk of progression has been to equal that of invasive T1 tumors in some reports.

8. T1 tumors are defined as invading lamina propria, which can sometimes involve the wispy muscularis mucosae fibers. Such findings often create a confusing pathology report easily mistaken for detrusor invasion. We have a low threshold to discuss the findings with the pathologist if there is any doubt of the presence or absence of detrusor, or muscularis propria, invasion.

9. Based on the low risk of progression for low grade tumors, regardless of stage, and the high risk of progression for high grade tumors, regardless of stage, we advocate replacement of the traditional dichotomy of superficial and invasive with high and low grade—much more clinically pertinent.

10. Does a delay in diagnosis of recurrence matter? Clearly it does, several studies have found that a delay in cystectomy more than 90 days after the recognition of muscle invasion risks a significantly lower survival. Moreover, patients who develop muscle invasion while on surveillance protocols
appear to have a worse prognosis than those that present with muscle invasion, challenging the long-held belief that we can prevent progression by careful surveillance alone.

12. This risk is most likely related to the inability of traditional TURBT to adequately stage patients with high grade disease. In the highly select group of patients that proceed to cystectomy for presumed “superficial” disease, 27-62% have muscle invasion at the time of cystectomy, and 8% have metastatic disease.

13. As a result, it has become clear through many studies, including our own experience at Cleveland Clinic, that repeat TUR on patients with high grade disease without demonstrated muscle involvement plays a vital role in management. This is especially crucial if there is no muscle in the specimen, as the Vanderbilt group has shown that almost 2/3 of these patients without muscle in the specimen have muscle invasion if repeat TUR is performed. Tumor persistence on repeat TUR suggests a high likelihood of disease progression, and persistence after intravesical therapy is particularly concerning, as shown on the right.

14. Perioperative chemotherapy—administered within 6 hours of resection—has been declared a new standard of care. Level 1 evidence demonstrates decreased tumor recurrence, and it is suggested that the financial benefits of avoiding future TUR are significant. We have embraced this less enthusiastically based on several concerns. First, it is mandatory that no perforation exists. Second, reports and Cleveland Clinic experience with severe bladder irritation, calcified eschar formation, and rare bladder contracture are of concern. Third, the financial benefits have been overstated. Although reports of the number-needed-to-treat is 8.5, our own calculations are less enthusiastic. Moreover, we treat most small recurrences in the office, so the financial benefits are mitigated. Finally, the level 1 evidence demonstrates no improvement in progression or survival, so we believe this concept merits further exploration prior to declaring a standard of care. For these reasons, we attempt to enroll patients into randomized controlled trials at Cleveland Clinic in order to further our understanding of this common situation.

15. Unlike intravesical chemotherapy, BCG does reduce the likelihood of progression—as long as maintenance therapy is administered.

16. Maintenance therapy has been unjustly criticized because only 16% of patients completed a full course in the Southwest Oncology Group trial. An alternative interpretation—our interpretation—is that maintenance reduced progression despite the inability of most patients to complete a three year trial. We believe this demonstrates that three years is probably not necessary, and that even short term maintenance—3 weekly treatments every 6 months—is vital to reducing progression and mortality.

17. Determining successful treatment with BCG can be challenging. The necessity of automatic biopsy is controversial, and we rely on urinary cytology and UroVysion fluorescence in-situ hybridization or FISH to dictate biopsy. If both are negative and cystoscopy identifies no suspicious findings, biopsy can usually be avoided. In a manner similar to intravesical chemotherapy to reduce the need for repeat TURBT, avoiding biopsy in the operating room offers potential financial benefit.
18. Much exciting work is ongoing in the field of intravesical therapy, including alpha interferon, novel chemotherapeutic agents, and electromotive therapy to enhance response, but the vast work is beyond the scope of this presentation.

19. Based on the risk of progression in patients with high grade T1 tumors or CIS, especially those persisting after an initial course of therapy, we now advise all such patients that cystectomy should be considered. The majority of patients will have at least one course of intravesical therapy, but persistent disease after two courses of therapy responds to further attempts rarely enough that cystectomy is indicated. Although sometimes termed “early cystectomy,” we believe the term coined by Chang and Cookson—timely cystectomy—is more appropriate.

20. Traditional surveillance limited to cystoscopy and conventional urinary cytology has proven inadequate. A number of tumor markers have been developed with mixed success, limited most by specificity. We continue to explore the use of FISH molecular cytology for cancer detection, but as importantly to identify patients at low risk of recurrence in whom aggressive surveillance, including imaging and biopsy, can be limited. As shown here, patients with negative cystoscopy have a markedly different risk of recurrence based on their baseline FISH reading. Using this risk profile allows us to individualize surveillance protocols.

21. Cleveland Clinic is active in evaluating new diagnostic strategies.

22. Fluorescence cystoscopy is performed after administration of Hexvix, which accumulates in malignant tissues. Otherwise subtle—or unperceivable—lesions, both papillary and flat, can be visible using the technology.

23. We also actively explore the role of narrow band imaging to enhance subtle lesions that might be overlooked using traditional white light cystoscopy.

24. This technology is available for both flexible

25. and rigid cystoscopy, including HDTV monitors

26. Finally, even the basic things are important. We have demonstrated that the simple act of allowing men to visualize their cystoscopy findings on the monitor significantly reduces pain scores during the procedure. Balancing disease management with a focus on improving patient experience continues to drive our exploration of this common urologic condition.