Case by Case:
Critical Issues in Superficial Bladder Cancer Management
Case Study 1

- A 22-year-old man with a history of gross total painless hematuria: two times in two months, both after jogging
- No history of UTI, STD, or stones
- He smokes pot and his family history is positive for lung and breast cancer

How would you manage this patient?

UTI, urinary tract infection; STD, sexually transmitted disease.
Case Study 1: Multiple Choice

A. UA (negative); C&S, cytology
B. Ultrasound: bladder and kidneys
C. IVP or CT urogram and cystoscopy
D. Urinary markers
E. Combinations of above, e.g., UA, CT, cytology, and cystoscopy

UA, urinalysis; C&S, culture and sensitivity; IVP, intravenous pyelogram; CT, computed tomography.
Case Study 2

- A 42-year-old asymptomatic woman has a routine UA with 5-10 RBC/hpf
- She smokes 1 pack of cigarettes daily
- Repeat UA x2 yields same results

What would be your next steps for this patient?
Case Study 2: Multiple Choice

(Choose the best response)

A. Urine markers
B. Cytology (negative)
C. Ultrasound
D. Cystoscopy
E. Other
Case Study 2: Rationale

- The mortality of bladder cancer in women, relative to the incidence, is higher than it is in men (26% vs. 19%), so we need to be extra vigilant in our evaluation and treatment.

- Even with a negative cytology, an upper tract imaging study and cystoscopy are indicated. Cytology is commonly negative in patients with low-grade tumors.

Our 42-year-old female patient is found on local cystoscopy to have a solitary 1-cm papillary tumor lateral to the right ureteral orifice.

Renal US is negative.

What is next in the management of this patient?
Case Study 2, Part 2: Multiple Choice

A. Tumor biopsy/fulguration in the office under local anesthesia

B. Resection and bimanual exam under anesthesia

C. A or B plus immediate (within 6 hours) intravesical chemotherapy

D. Resection and retrograde pyelogram

E. Resection followed by BCG

BCG, bacillus Calmette-Guérin.
Case Study 2, Part 2: Rationale

- Safety and efficacy of resection under local anesthesia; an acceptable option (III/C)

- My preference: resection under anesthesia; tumor is completely resected and biopsy adequate for staging (III/C)

- Initial chemotherapy significantly reduces tumor recurrence, even in solitary low-grade tumors (I/A)

- In my opinion, resection followed by BCG should be standard practice. Prefer CT or IVP at a later date rather than a retrograde pyelogram at the time of resection (I/A)

Postoperative Instillation of Chemotherapy*

- A meta-analysis of 7 randomized trials with recurrence information on 1,476 patients
- Decrease of 39% in the odds of recurrence with chemotherapy (OR 0.61, P<.0001)
- Patients with a single tumor (OR 0.61) and those with multiple tumors (OR 0.44) benefited
- However, after 1 instillation 65.2% of patients with multiple tumors had recurrence compared with 35.8% of patients with single tumors, showing that 1 instillation alone is insufficient treatment for patients with multiple tumors

*This is an off-label use of chemotherapy prophylaxis. Please see the full Prescribing Information before using any product mentioned.

OR, odds ratio.

Case Study 2, Part 3

- Biopsy of the tumor in the 42-year-old patient shows low-grade, stage T0 urothelial carcinoma (G1,Ta TCC).
- There is stroma in the specimen that shows no invasion, but muscle is absent. There was nothing palpable on bimanual exam.

What can you tell from this?
Case Study 2, Part 3: Multiple Choice

A. The biopsy is inadequate because no muscle was present and patient should go back to surgery

B. Random biopsies should have been done and were not—another reason to repeat the procedure

C. A 6-week course of mitomycin is indicated

D. Cystoscopy in 3 months is all that is required
Case Study 2, Part 3: Rationale

- The rule is to obtain muscle for adequate staging, but we have higher priority rules—such as “do no harm” and don’t perform a procedure when the risk exceeds the benefit. It can be difficult to safely obtain a good muscle biopsy, especially when the tumor is on the dome or the bladder is thin. With low-grade tumor and lamina propria that is free of disease, I would not put her through another anesthesia to prove what we already know.

- In patients with multiple tumors or a “field of grass,” a 4-to-6 week course of chemotherapy may be useful, but randomized controlled trials have shown extended courses to not be significantly better than a single postoperative instillation.

Case Study 2, Part 4

- At 3 months, the same patient has 3 new tumors
- Resection shows intermediate grade, stage Ta papillary urothelial carcinoma (Grade 2, Ta TCC), and random biopsies show severe atypia

Which of the following statements are true?
Case Study 2, Part 4: True or False?*

立即术后化疗再次被建议。多柔比星（50mg/25cc），一种插层剂，可以被使用。

如果穿孔发生在切除过程中，顺铂可以被使用，但不能使用多柔比星或丝裂霉素。

3个月后的复发会显著增加进一步复发的风险以及进展。丝裂霉素现在被建议使用。

因进展的风险，BCG维护方案是现在的一个合适的选择。

*这是多柔比星和丝裂霉素的非标签使用。请在使用任何提及的产品前，查看完整的处方信息。

Immediate postoperative chemotherapy is again indicated. Doxorubicin (50mg/25cc), an intercalating agent, can be used (True)

If perforation occurs during resection, thiotepa, but not doxorubicin or mitomycin, can be used (True)

Recurrence at 3 months significantly increases risk for further recurrence as well as progression. Mitomycin is now indicated (False)

Due to the risk of progression, BCG using a maintenance schedule is now an appropriate choice (True)
SWOG BCG Versus Doxorubicin: Time to Treatment Failure

In 9 eligible clinical trials, 1,277 patients were treated with BCG and 1,133 with mitomycin C. Within the overall median follow-up of 26 months, 7.67% of BCG group and 9.44% of mitomycin C group had tumor progression (combined OR = 0.77; 95% CI 0.57 to 1.03; \( P = .081 \)). In BCG maintenance subgroup, the combined results of 5 individual studies showed a statistically significant superiority of BCG over mitomycin C (OR = 0.66; 95% CI 0.47 to 0.94; \( P = .02 \)) (I/A). The results demonstrated statistically significant superiority for BCG compared with mitomycin C for the prevention of tumor progression only if BCG maintenance therapy was provided (I/A).

CI, confidence interval.
Case Study 2, Part 5

- What else might be done to reduce this woman’s risk for tumor recurrence—and possibly progression?
Case Study 2, Part 5: Multiple Choice

- Smoking cessation is most important
- Eliminate environmental carcinogens
- A diet high in fruits and vegetables
- Soy, garlic, and green tea
- High-dose vitamins A, B₆, C, and E
True, evidence shows reduction not only in recurrence, but progression as well (II/B)

Absolutely (III/C)

Yes. Did you know that diets high in fruits and vegetables can reduce DNA adducts in urine associated with smoking? (III/C)

While in vitro and animal data have suggested benefits, epidemiologic studies are contradictory—even suggesting that soy and tea may increase the risk of bladder cancer, therefore we cannot recommend soy or tea at this time (III/C)

While natural healthful foods with their micronutrients and vitamins are thought to be optimal, diets are hard to change. A randomized controlled trial found a high-dose vitamin combination reduced recurrence by 40%. (I/A)


Intake of fruits and vegetables in smokers decreased DNA adducts in smokers (Airoldi L et al. *Carcinogenesis*. 2002;23:861-866.)

286 Ta, T1 patients: Quitting increases recurrence-free ($P<.003$) and progression-free ($P<.001$) survival (*J Urol*. 1999;161:172.)
Kaplan-Meier Estimate of 5-Year Tumor-Free Rate

Case Study 2, Part 6

- True or false? Maintenance mitomycin at monthly intervals followed by quarterly intervals should/should not be used because:
Case Study 2, Part 6: Which of the following is True?

A. Maintenance chemotherapy is shown to reduce recurrence over induction chemotherapy

B. Only maintenance chemotherapy can reduce disease progression

C. Repeated chemotherapy in animal models can actually induce bladder cancer

D. Maintenance chemotherapy reduces the formation of resistant cancer cell lines
Case Study 2, Part 6: Responses

A. Maintenance chemotherapy is shown to reduce recurrence over induction chemotherapy (False)

B. Only maintenance chemotherapy can reduce disease progression (False)

C. Repeated chemotherapy in animal models can actually induce bladder cancer (True)

D. Maintenance chemotherapy reduces the formation of resistant cancer cell lines (False)

Case Study 2, Part 7

With a 6-week course of BCG, our 42-year-old woman with G2, Ta TCC and severe atypia remains tumor free for 2 years.

- Cystoscopy remains negative, but voided cytology is suspicious.
- FISH is positive.
- Repeat bladder biopsies are negative, bladder wash cytology is negative.
- Ureteral cytologies are suspicious and FISH is positive from the right ureter. Retrograde pyelograms show no lesions.

What would you do?
Case Study 2, Part 7: Multiple Choice

A. Continue close observation; re-evaluate in 3 months

B. Perform right ureteroscopy with biopsy of any suspicious areas

C. Resect/biopsy distal right ureter and then give maintenance BCG

D. Perform right nephroureterectomy with bladder cuff, open or laparoscopic
Case Study 2, Part 7: Rationale

A. With a negative cytology and retrograde pyelogram, this is reasonable

B. An appropriate next step in the workup

C. While this can be an effective treatment for distal ureteral TCC, in my opinion it should be reserved for confirmed disease, not just positive cytology or FISH

D. Too aggressive. What will you do when the pathologist cannot find any cancer? When the opposite side develops tumor? (Cystectomy series show up to 17% CIS in distal ureters)

Case Study 2, Part 8

- A papillary lesion is seen in the distal right ureter. Biopsy shows low-grade noninvasive TCC. Cytology remains suspicious, FISH positive.

What are your treatment options?
Case Study 2, Part 8: Multiple Choice

A. Right distal ureterectomy with reimplant
B. Right nephroureterectomy with bladder cuff
C. Endoscopic resection
D. Endoscopic resection followed by BCG maintenance
Case Study 2, Part 8: Rationale

A. This is an acceptable option (III/C)

B. While once standard treatment, improved intravesical therapy and endoscopy can lead to similar results with less invasive surgery (III/C)

C. Appropriate, but does not address the risk of recurrence (III/C)

D. Appropriate, if BCG is made to come in contact with the ureter (III/C)*

*This is an off-label use of BCG. Please see the full Prescribing Information before using any product mentioned.
A 63-year-old man presents with high-grade, stage T1 bladder tumor with associated CIS

He received perioperative mitomycin treatment

Because of the high risk of cancer progression, your next step is:
Case Study 3: Multiple Choice

A. Mitomycin 40mg/20cc with overnight dehydration, bicarbonate alkylinization of the urine, and careful, complete bladder emptying before instillation to be done weekly for 6 weeks

B. Repeat TUR. There is more than a 30% risk of residual carcinoma and a significant risk of understaging

C. BCG, to be given weekly for six weeks, beginning two weeks after resection

D. Six-week BCG followed by three-week maintenance at three, six, 12, 18, 24, 30, and 36 months
Case Study 3: Rationale

A. If mitomycin is given, this protocol improves the response. BCG is the treatment of choice for CIS and high-grade TCC (I/A)

B. A common practice in Europe, not in the US. Not adequately studied in the context of immediate chemotherapy instillation, and not demonstrated to improve the response in BCG-treated patients (III/C)

C. Does not address the significant risk of disease progression. BCG is found to reduce progression, but only when maintenance schedules are employed (I/A)

D. Maintenance BCG is the current treatment of choice. Optimal maintenance schedule not defined, but only three-week induction has been confirmed to significantly reduce recurrence and progression compared with six-week induction (I/A)*

*This is an off-label use of 3-week maintenance BCG. Please see the full Prescribing Information before using any product mentioned.

Case Study 4

- A 76-year-old man has a history of grade 2-3, stage Ta TCC 2 years ago. He was treated with a 6-week course of BCG.
- He now presents with 3 small recurrent high-grade, stage Ta urothelial carcinomas.

The best treatment for this patient is:
**Case Study 4: Multiple Choice**

A. Resection followed by immediate intravesical chemotherapy

B. “A” followed by a repeat 6-week course of BCG

C. “A” plus 3 weekly BCG instillations at 2 weeks and at 3, 6, 12, 18, 24, 30, and 36 months as tolerated

D. BCG plus interferon for 6 weeks
A. Yes, appropriate to prevent early recurrence and minimize tumor burden (I/A)

B. Not supported by clinical data. Second exposure results in accelerated immune response; continued administration results in immunosuppression (III/C)

C. The schedule is arbitrary, but 3-week maintenance is currently the best available treatment (I/A)

D. 60% of patients who fail BCG will respond to combination BCG plus interferon, and when interferon is added, the immunosuppression that occurs with a second 6-week course does not occur. Not shown to be superior to 3-week maintenance alone. (III/C)

**Figure 1:**

- **Percent Tumor Recurrence**
  - **N=385, 3q 3-6mo.**
  - M, TaT1, 3wk maintenance BCG
  - M, CIS, 3wk maintenance BCG
  - I, CIS, 6wk induction BCG
  - I, TaT1, 6wk induction BCG

- **Time in months**
  - 0 1 2 3 4 5 6 7 8 9

- **Global recurrence**
  - **N=126, 6q 6mo.**

- **Completion of Therapy**
- **Apparent Increase in Rate of Recurrence**
- **One Year After Completion of Maintenance**

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Case Study 4, Part 2

- Our 76-year-old patient reports that he had a sensation of chills, temperature of 101º F, and severe dysuria and frequency lasting 5 days following his second of a planned 3 weekly BCG instillations.

- He is now OK and his urine shows many WBC, 5-10 RBC/hpf, no bacteria, and negative nitrite.

What does this indicate in this patient?
Case Study 4, Part 2: Multiple Choice

A. He is developing a reaction to BCG and should not receive any more BCG

B. He has hematuria and BCG is contraindicated at this time

C. The third weekly instillation of BCG can now be given

D. The dose of BCG should be reduced to one third to 1/10th and he should be given a prescription for antibiotics to take in the event of a recurrence of his fever or severe irritative symptoms
Case Study 4: Rationale

A. At increased risk of having a severe reaction, but symptoms do not preclude further BCG treatment. Patients with febrile response to BCG have a lower risk of recurrence than those who have no fever (II/B)

B. Gross hematuria is a relative contraindication to BCG, and BCG should not be given if catheterization is traumatic and causes urethral bleeding. Microscopic hematuria is not a contraindication (II/B)

C. Patient is highly sensitized to intravesical BCG. It would be better to hold the third treatment as done in the SWOG protocol (III/C)

D. O’Donnell’s dose-reduction schedule has not been studied prospectively. Hold BCG and start the next scheduled BCG at one third dose, or reduce to 1/10th or less in this patient. I would also give him a prescription for antibiotics (III/C)*

* This is an off-label use of dose reduction of BCG. Please see the full Prescribing Information before using any product mentioned.

Case Study 5

- A 64-year-old man is receiving BCG for CIS. Biopsy showed 4 of 6 biopsies positive, and he has dysuria.
- Symptoms are slightly improved following a 6-week induction of BCG, but at 3 months his cytology remains positive.
- Repeat biopsy shows 1 of 6 biopsies positive for CIS

The best treatment for this patient is:
**Case Study 5: Multiple Choice**

A. He has failed BCG and should undergo cystectomy

B. He should get a second 6-week course of BCG

C. He should get 3 additional weekly BCG instillations

D. He should get a second 6-week course of BCG plus interferon alfa 2b
Case Study 5: Rationale

A. This treats CIS of the bladder, prostatic urethra, and distal ureters, but will be overtreatment for most patients (III/C)

B. This is the most frequent error in BCG therapy in my opinion. Repeated 6-week courses suppress the immune response and controlled trials have failed to show superiority of induction alone (III/C)

C. Yes; 64% patients so treated will have complete response (I/A)

D. Adding interferon prevents the suppression that would otherwise occur, and this is a satisfactory response. It has not been evaluated in prospective randomized trials like “C” above, and is expensive, so “C” is the preferred treatment (III/C)*

* This is an off-label use of BCG/interferon and BCG 3-week dosage. Please see the full Prescribing Information before using any product mentioned.

During the fifth BCG instillation, catheterization is difficult in this 64-year-old man. Treatment is given, but that night you are called because the patient has a fever of 102.5°F. He is otherwise well.

What are your treatment options?
Case Study 5, Part 2: Multiple Choice

A. Fever with BCG is a good sign, associated with a reduced incidence of tumor recurrence. There is no cause for concern

B. Isoniazid 300 mg and a fluoroquinolone should be started immediately

C. Isoniazid 300 mg and rifampin 600 mg should be given immediately

D. Hospitalization is recommended, with IV fluid hydration and antibiotics to cover gram-negative organisms and mycobacteria
A. This is a bit cavalier because a septic reaction may be brewing

B. Yes, these prescriptions can be given ahead of time to expedite delivery

C. These are effective mycobacterial antibiotics, but unlike fluoroquinolones, take up to a week to kill the organism

D. This is a good, safe, and conservative approach and should be done if the patient is not otherwise well, does not have home support, or does not respond promptly to treatment
Case Study 5, Part 3

- Our 64-year-old patient becomes hypotensive and requires fluids and pressors. Results from liver function tests are elevated

What are your next steps for this patient?
Case Study 5, Part 3: Multiple Choice

A. In addition to his gram-negative coverage, including a fluoroquinolone, isoniazid and rifampin are required

B. “A” is correct, but prednisone 40 mg daily should also be added

C. Refer the patient to an infectious disease specialist

D. Add cycloserine 250 mg b.i.d. to “A” above
Case Study 5, Part 3: Rationale

A. Yes (III/C)

B. Yes. Clinical experience (case after case after case) and controlled animal trials confirm that prednisone (but not prednisone alone!) significantly improves survival (II/B)

C. This depends on local resources and talent. You, as treating urologist, need to be sure he gets what he needs (B, above). Not all infectious disease specialists know the appropriate treatment (III/C)

D. While Lamm initially recommended this treatment based on in vitro and limited clinical experience, new data show BCG to be relatively resistant to cycloserine. It is still used as a last resort (III/C)

An 80-year-old man with previous external beam radiation therapy for prostate cancer presents with a solitary 1.5-cm, high-grade, stage T2 urothelial carcinoma on the trigone.

He has COPD and is considered to be a poor candidate for cystectomy.

Re-resection of the lesion and random biopsies show residual high-grade, stage T1 disease but no CIS.

What are your treatment options?
**Case Study 6: Multiple Choice**

A. Cystectomy is required if the patient is to survive

B. Radiation therapy

C. Intravesical chemotherapy

D. Systemic chemotherapy

E. Intravesical BCG, using a 3-week maintenance program
Case Study 6: Rationale

- True for some patients. Few are too sick for an operation when the alternative is death (III/C)
- History of previous radiation would make this a poor choice (III/C)
- Intravesical chemotherapy does not reduce progression (III/C)
- Systemic chemotherapy alone is relatively ineffective for primary bladder cancer (III/C)
- Of 151 patients with T0 or T1 TCC following muscle invasion, 99 were treated with TUR and/or intravesical therapy and salvage cystectomy if needed. Survival was 65% for 52 patients undergoing immediate cystectomy and 82% for 99 patients treated conservatively. (III/C)

Case Study 7

- A 63-year-old man with T2 TCC 6 years after BCG treatment of high-grade, T1 TCC and CIS requests a nerve-sparing cystectomy and orthotopic neobladder

- He has tumor at the bladder neck but no CIS

Which surgery is the best option?
Case Study 7: Which of the following is False?

- Kock pouch has the lowest reoperation rate
- Indiana pouch should be considered
- Studer pouch can be done if the urethral margin is clear
- Regardless of diversion, a thorough node dissection is suggested
Case Study 7: Rationale

A. Reoperation rates for Kock pouches are high, not low (III/C)

B. The Indiana pouch should be discussed (III/C)

C. Incidence of urethral recurrence is much lower with the Studer pouch and this is an appropriate option. It also has the advantage that, should urethrectomy or neobladder cystectomy be required, the tubularized ilium can be brought to the skin as a standard loop (III/C)

D. Survival is increased with a thorough node dissection (II/B)

Case Study 8

- A 61-year-old male patient is diagnosed with TaG2 transitional cell carcinoma [one 1.8 cm papillary lesion] 2 years ago
- He was initially treated with TURBT and had a recurrence one year later [3 papillary lesions G2 none larger than 2 cm]
- He received a 6-week course of BCG and has had negative cystoscopies and cytologies for the past year
- He finds that cystoscopy aggravates his LUTS symptoms and desires a significant change or elimination in his cystoscopy schedule

Evidence-based options include:
Case Study 8: Multiple Choice

- Elimination of cystoscopy and follow up with cytology only
- Follow up with a protein-based urine marker every three months with yearly cystoscopy if the marker is negative
- Extension of follow-up based on classic schedule of negative exams over the first year of treatment
- Elimination of cystoscopy and follow up with a genomic-based marker
- Combination of urine protein marker and genomic marker with the elimination of cystoscopy
Case Study 8: Rationale

A. Cytology alone would be a poor choice because it misses a large proportion of lower grade and moderate grade tumors, although its sensitivity and specificity for high grade lesions and CIS is very high (III-C).

B. While protein-based urine markers have the ability to increase tumor detection beyond classic cytology, they can be affected by inflammation and hematuria (false positives, poorer specificity). There is no prospective data to suggest that altering cystoscopy interval based on marker status is a safe alternative (III-C).

C. The general schedule of gradually extended follow-up is based on authority opinion, not research, yet has proven a reasonable approach to follow-up especially for patients treated after the appearance of moderate grade/lesions (III-C).

Case Study 8: Rationale (cont’d)

Genomic-based assays (FISH, and microsatellite analysis) provide the benefit of potentially greater specificity predictive ability. While a reasonable adjunct to follow-up, the data is sparse with regard to altering the follow-up schedule in such patients (III-C).

Combination of markers may be of hypothetical and research interest but have little supporting clinical data (III-C).

Case Study 8, Part 2

- The patient agrees to the standard cystoscopy schedule now set for every six months over the next year
- After a totally negative evaluation, his next work-up demonstrates a negative cystoscopy, negative cytology, but a positive FISH

What is the next most appropriate step?
Case Study 8, Part 2: Multiple Choice

- Reassurance and continue cystoscopy on a six-month basis at this time
- Repeat cystoscopy with random cold cup biopsies and bilateral retrograde pyelograms
- Shorten cystoscopy interval to 3 months
- Corroborate findings with protein based marker
- Repeat FISH analysis
Case Study 8, Part 2: Rationale

1. Current data suggests that 25% of “false positive” findings actually anticipate distinct future recurrences. Lengthening the cystoscopy interval would be inappropriate (III-C)

2. Within the context of the available clinical data, aggressive re-biopsy of all areas would not be warranted (III-C)

3. The current data suggesting the anticipatory nature of this genomic-based test would suggest shortening the cystoscopy interval (III-C)

4. There is no data that the addition of other markers would detract from or strengthen the validity of this positive finding (III-C)

5. This may be a reasonable first response although variability for this test (FISH) is fairly low (III-C)

Conclusions

- Low-risk (solitary Ta, G1) patients are best treated with a single instillation of chemotherapy post TUR (I/A)
- Continue chemotherapy for 4-6 weeks for multiple tumors (III/C)
- Intermediate risk patients can be treated with chemotherapy (immediate, plus weekly) or BCG (III/C)
- High-risk (G3, T1, or CIS) patients are best treated with BCG (I/A)
- BCG provides superior protection from tumor recurrence and unlike chemotherapy, with maintenance, BCG reduces the risk of progression (I/A)
Conclusions (cont’d)

- Optimal induction? “6+3” increased CR in CIS from 69% to 84%, $P<.01$ (II/B)
- Optimal maintenance? 3 weekly Q6-12 months appears best to date (II/B)
- Dose reduction reduces toxicity; excess BCG is immunosuppressive; double/triple antibiotics and even steroids may be required (III/C)
- Beware of occult invasive, prostatic, or upper tract TCC and consider cystectomy for BCG failure patients (III/C)