Treatment of non-muscle-invasive bladder cancer

Author
Michael A O'Donnell, MD, FACS

Section Editor
Seth P Lerner, MD

Deputy Editor
Don S Dizon, MD, FACP

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INTRODUCTION — Worldwide, bladder cancer accounted for 386,000 cases and 150,000 deaths in 2008 [1]. In developed areas of the world, such as North America and western Europe, these bladder cancers are predominantly urothelial. (See "Epidemiology and etiology of urothelial (transitional cell) carcinoma of the bladder", section on 'Epidemiology'.)

Approximately 70 percent of new urothelial (transitional cell) bladder cancer cases are classified as non-muscle-invasive [2]. This category of bladder cancer includes Ta (papillary), T1 (submucosal invasive) tumors (table 1), and Tis (carcinoma in situ, CIS) which account for approximately 70, 20 and 10 percent of non-muscle invasive cancers, respectively. (See "Pathology of bladder neoplasms".)

The initial treatment generally is a complete cystoscopic (transurethral) resection of all visible bladder tumor (TURBT). This is often followed by adjuvant intravesical therapy.

The management of non-muscle invasive bladder cancer is discussed here. The clinical presentation, diagnosis, and staging of bladder cancer, and an overview of the treatment of urothelial bladder cancer are presented separately. (See "Clinical presentation, diagnosis, and staging of bladder cancer" and "Overview of the management of urothelial (transitional cell) bladder cancer".)

PROGNOSTIC FACTORS — An estimated 40 to 80 percent of non-muscle invasive bladder cancers recur within 6 to 12 months if managed with a TURBT without additional therapy, and 10 to 25 percent will develop muscle-invasive, regional, or metastatic disease. Thus, more aggressive therapy is often required even though an initial complete transurethral resection is possible.

The most important prognostic factors are histologic stage and grade. Other factors that have been assessed include the presence of multicentric disease, the frequency of recurrence, the tumor size, and the presence or absence of concomitant CIS.

Stage — Non-muscle invasive bladder cancers are classified into three groups, Ta, Tis (also referred to as carcinoma in situ, CIS), and T1 lesions, based upon their growth pattern and depth of invasion (table 1). (See "Pathology of bladder neoplasms", section on 'Pathologic tumor staging'.)

Ta tumors — Ta tumors are noninvasive papillary lesions that are confined to the urothelium and have not penetrated the basement membrane. These papillary tumors usually present as low-grade lesions that frequently recur multiple times prior to becoming invasive. The natural history of patients with Ta tumors without other evidence of invasive disease or Tis was illustrated by a retrospective series of 363 patients, in which only 6 percent eventually died of bladder cancer [3]. The fraction of patients who eventually progress to a high-grade lesion and require more aggressive treatment ranges from 6 to 28 percent in different series [3,4].

Tis — Tis (also called carcinoma in situ [CIS]) is characterized by severe cellular dysplasia in the absence of discrete tumor formation. Areas of mucosal involvement with Tis are often found in association with invasive disease. The presence of Tis in the mucosa adjacent to a Ta or T1 tumor appears to increase the risk for muscle invasive disease [5-8].

The potential prognostic significance associated with Tis is illustrated by a multicenter series 243

patients who underwent radical cystectomy for carcinoma in situ without more invasive disease [7]. Staging based upon the cystectomy specimen revealed that Tis, T0, or Ta in 48, 8, and 8 percent of cases, respectively. However, T1, T2, T3, and T4 disease was detected in 13, 12, 5, and 6 percent of cases, respectively. Lymphovascular invasion and positive lymph nodes were found in 9 and 6 percent, respectively.

The presence of Tis without invasive urothelial cancer is associated with a high incidence of progression to invasive disease, even after transurethral resection and treatment in intravesical BCG. In a retrospective, single institution series of 155 patients managed with transurethral resection and intravesical bacillus Calmette-Guerin (BCG), the five-year cumulative incidence of progression to cT1 or higher disease was 45 percent (95% CI 37-55) [8].

Diffuse involvement of the mucosa with Tis is associated with particularly aggressive disease. Invasive bladder cancer develops in 60 to 80 percent of such patients [9,10].

T1 lesions — T1 tumors are by definition invasive cancers and are characterized by extension into the underlying lamina propria (also known as the submucosa) but without involvement of the muscularis propria, the true detrusor muscle of the bladder. Virtually all T1 tumors are high-grade, and one-half have associated Tis. Recurrence rates by one, three, and five years are 50, 70 to 80, and 90 percent, respectively, and 20 to 25 percent progress to invasive disease [11,12]. T1 lesions occurring in patients who had a prior tumor resection for Tis or Ta disease have a higher frequency of progression after BCG treatment compared to those with an initial presentation with T1 disease [13].

Because of the risk of progression, T1 tumors are generally treated with intravesical therapy, such as bacillus Calmette-Guerin (BCG), which reduces the recurrence rate by 30 to 40 percent [14,15] and may also reduce progression [16]. (See 'Intravesical BCG' below.)

Grade — In addition to tumor stage (Tis, Ta, or T1), histologic grade influences the rate of recurrence and ultimately survival [17,18]. The importance of histologic grade was illustrated in a retrospective series of 249 patients with Ta or T1 lesions who were treated with local resection, without adjuvant intravesical therapy [17]. Among patients with grade 1, 2 or 3 lesions, invasive cancer developed in 2, 11, and 45 percent, respectively. In another series of 252 patients with non-muscle invasive bladder cancer, multivariate analysis revealed that the grade of the initial tumor was the only significant predictor of subsequent invasive disease [19].

Patients with grade 1 or grade 2 papillary (Ta) lesions who remain free of recurrence for at least five years usually have a good prognosis. In a series of 198 such patients diagnosed between 1991 and 1996, 89 percent remained free of recurrence five years after diagnosis [20]. However, active surveillance is still required because of the risk of recurrence.

In 2004, the World Health Organization revised its 1973 grading system in an attempt to improve interobserver agreement and provide better prognostic information [21]. The new system employs the terms papillary urothelial neoplasm of low malignant potential (PUNLMP), low-grade urothelial carcinoma, and high-grade urothelial carcinoma. Because there remains disagreement among both pathologists and clinicians about the merits of the new classification system, the older system is still commonly used. (See "Pathology of bladder neoplasms".)

Multicentricity and frequency of recurrence — Patients who have multiple papillary tumors at the time of presentation have higher rates of both non-muscle invasive and invasive recurrence [17,18,22], but not necessarily worse survival [23]. As an example, the risk in one series for progression to muscle-invasive disease for multiple and solitary lesions was 14 and 5 percent, respectively [22].

Molecular markers — Molecular markers may provide an additional way to identify non-muscle invasive bladder cancers that are likely to progress to muscle invasive or high-grade disease [24,25]. The earliest studies focused on chromosomal abnormalities, and these provided the basis for identifying specific genetic alterations.

The presence of mutations in fibroblast growth factor receptor 3 (FGFR3) appears to identify a subgroup of patients with a favorable prognosis [21,26,27]. Although some studies have suggested that abnormalities in p53 are associated with a less favorable prognosis [28-30], a prospective evaluation of p53 status based upon immunohistochemistry in 499 patients treated with radical cystectomy for stage pT1N0 or pT2NO urothelial cancer did not observe a difference in either recurrence rate or overall survival [31]. (See "Adjuvant chemotherapy for urothelial (transitional cell) carcinoma of the bladder", section on 'Contemporary trials'.)

Gene expression profiling may offer another approach to identifying those patients who are most likely to progress to muscle-invasive disease and thus would benefit from more aggressive treatment [32]. (See "Overview of gene expression profiling, proteomics, and microRNA profiling in clinical oncology".)

Risk stratification — Multiple studies have analyzed large retrospective series in an attempt to classify patients according to their risk of disease recurrence and progression to invasive disease [33-35].

For a patient to be considered at low risk, all of the following features should be present:

- Initial presentation with a non-muscle invasive Ta tumor
- Greater than one year between tumor recurrences
- Three or fewer lesions, all of which are small (≤3 cm), with a papillary appearance, and on a fine stalk
- No invasion of the lamina propria and no associated CIS (Ta only and not T1 or Tis, (table 1)) and well or moderately differentiated histology (grade 1 to 2)

Conversely, the presence of **any** of the following features is associated with an increased risk of recurrence or progression:

- Multiple papillary recurrences within a short time period (eg, two or more tumor recurrences in a given year) [36]
- More than three lesions, or any one tumor >3 cm in diameter, sessile, or with a thick stalk
- Invasion of the lamina propria (T1 tumor, (table 1)) or poorly differentiated histology (grade 3)
- Incomplete resection due to diffuse bladder involvement and/or unfavorable location
- The presence of diffuse Tis alone, or Tis in association with papillary tumors [37]

A quantitative calculator to more accurately predict the risk of both recurrence and progression has been developed by the European Organization for Research and Treatment of Cancer (EORTC), based upon data from nearly 2600 patients [38,39]. Risk is calculated using a scoring system based on six factors: number of tumors, tumor size, prior recurrence rate (ie, first time occurrence versus recurrence >1 year from prior diagnosis versus recurrent tumor <1 year from prior diagnosis), T category, carcinoma in situ, and grade. The five-year probabilities of recurrence or progression, based on total score, ranged from 30 to 80 percent and 1 to 45 percent, respectively.

Patients with the lowest risk disease are usually managed by TURBT alone, often with a single dose of immediate post-operative chemotherapy as recommended by guidelines from both the American Urological Association (AUA) and the European Association of Urology (EAU) [40,41]. Further courses of intravesical therapy are generally recommended for patients with intermediate to high-risk non-muscle invasive bladder tumors in an effort to decrease the risk of recurrence and need for cystectomy. Careful surveillance following treatment is recommended for both low- and high-risk patients. (See 'Intravesical therapy' below and 'Posttreatment management' below.)

INITIAL MANAGEMENT — The initial management of patients with non-muscle invasive bladder cancer includes accurate staging and resection of known areas of disease involvement. Incorporation of information about the depth of invasion, histologic grade, and the presence or absence of multicentric disease are important factors in determining whether management should consist of TURBT alone, TURBT plus intravesical therapy, or cystectomy.

Transurethral resection — The initial treatment of non-muscle invasive bladder tumors is a complete TURBT, which is usually carried out at the time of diagnosis. Many patients can be successively managed with a localized resection, and more aggressive surgical resection should be deferred whenever possible. (See 'Indications for cystectomy' below.)

TURBT in patients suspected of high-grade or T1 disease should include biopsies of apparently uninvolved areas of the bladder mucosa and prostatic urethra to rule out occult involvement with Tis. An examination under anesthesia (EUA) should also be performed, since the presence of a palpable mass suggests muscle invasive disease.

Although clinical staging with TURBT and EUA generally dictates management, it has limitations.

- Approximately 30 percent of T1 tumors will be understaged by TURBT [42,43]. Thus, a repeat TURBT is generally recommended to decrease the likelihood of understaging in patients whose tumors involve the lamina propria, even if the initial resection was thought to be complete [40,41,44-48]. In a retrospective series of 150 cases, residual bladder tumors were found in 76 percent of patients subjected to a restaging procedure, while muscle-invasive disease was found in 49 percent of patients who did not have detrusor muscle present in the initial resection [46].

- Up to 30 percent of non-muscle invasive bladder tumors are multifocal at presentation, probably because genetic abnormalities over the entire urothelial surface (the "field cancerization" effect) predispose to multifocal carcinogenesis. This hypothesis is supported by the observation that multifocal non-muscle invasive bladder tumors appear to be monoclonal [49], and the genetic changes in tumors are also present in adjacent morphologically normal bladder mucosa. The majority of patients with non-muscle invasive bladder cancer will develop new tumors over time, and 15 to 30 percent of these will be invasive. (See "Chemoprevention of bladder cancer", section on 'Rationale'.)

Despite complete TURBT, up to 80 percent of patients with high-risk tumors will recur within 12 months. Because of these high recurrence rates, adjuvant intravesical therapy is widely used in this population. For these patients, a restaging TURBT should be considered. (See 'Intravesical therapy' below.)

Restaging TURBT — Patients with high-risk non-muscle invasive bladder cancer who are candidates for intravesical BCG should undergo a repeat cystoscopy with biopsies of previous areas of involvement prior to therapy. This approach is important both to detect previously undiagnosed disease and to reduce the tumor burden prior to BCG immunotherapy [45,50,51].

The importance of this approach was illustrated by a retrospective single-institution series of 347 patients [45]. Of the 132 patients who did not have a repeat endoscopy, 57 percent had residual or recurrent disease at the first cystoscopy following BCG therapy, and 34 percent later had progression to invasive disease. In contrast, only 29 percent of the 215 patients who had a restaging TURBT had residual or recurrent disease following BCG treatment, and only 7 percent ultimately had progression. A similar beneficial improvement in recurrence for re-resected patients was also obtained in a prospective randomized trial involving stage T1 cancer patients in which the chemotherapeutic drug mitomycin C was used [52].

Fluorescence endoscopy — Fluorescence endoscopy after intravesical instillation of a porphyrin such as hexaminolevulinate or 5-aminolevulinic acid (ALA) may be more effective than white light endoscopic resection for the detection of multifocal tumors, thereby improving outcomes of TURBT [53-60].

Randomized clinical trials have yielded conflicting results, with at least three trials demonstrating that fluorescence endoscopy prolongs recurrence-free survival [54,55,61], while two trials failed to detect an advantage [62,63]. The range of results is illustrated by the following examples:

- In the largest positive trial, 814 patients suspected of having bladder cancer at increased risk of

recurrence were randomly assigned to cystoscopy with or without intravesical hexaminolevulinate one hour prior to the procedure. In the group assigned to fluorescence cystoscopy, patients first were examined with white light and then underwent reexamination with blue light before and after TURBT [61].

Among the patients examined with fluorescence cystoscopy, 47 of 286 patients (16 percent) with at least one Ta or T1 lesion had one or more additional lesions detected at reexamination with blue light. Furthermore, at the nine month follow-up, there was a statistically significant decrease in the recurrence rate in those who initially were managed with fluorescence endoscopy (128 of 271 [47 percent] versus 157 of 280 [56 percent] in the white light group). The results of this trial were the basis for the Food and Drug Administration approval of hexaminolevulinate.

- In a multicenter trial, 301 patients with suspected non-muscle invasive bladder cancer were randomly assigned to TURBT using either fluorescence endoscopy with aminolevulinic acid or white light [55]. All patients with non-muscle-invasive tumor underwent repeat endoscopy with white light six weeks later. At that time, significantly fewer patients whose initial procedure used ALA had residual tumor (5 versus 25 percent with white light). On subsequent follow-up, the relapse-free survival was significantly higher in patients who had been evaluated with fluorescence endoscopy (88 versus 73, 84 versus 64, 79 versus 54, and 71 versus 45 percent at two, four, six, and eight years, respectively).

- In contrast, in another trial, 300 patients were randomly assigned to cystoscopy with or without 5-aminolevulinic acid; both observers and pathologists were blinded to study assignment [62]. There was no significant difference in the number of tumors (1.7 with fluorescence versus 1.8 with white light). At 12 months, there was no difference between groups based upon recurrence-free or progression-free survival rates.

The improved early detection and treatment of tumors needs to be balanced by a slightly higher false-positive rate (mainly due to inflammation and scarring), the requirement for a special lens system, the need to instill the photosensitizer one hour prior to cystoscopy, and the need for rigid rather than flexible cystoscopy, as well as the higher cost.

Indications for cystectomy — Cystectomy is indicated in patients for whom the initial staging indicates muscle-invasive (T2) disease (table 1). Cystectomy is also indicated for patients with symptoms related to the bladder pathology (eg, urinary frequency, hemorrhage) that cannot be adequately managed medically. (See "Radical cystectomy and bladder-sparing treatments for urothelial (transitional cell) bladder cancer".)

In addition, radical cystectomy may be indicated for earlier stage disease in high-risk patients to prevent progression to T2 disease, which is associated with a poorer prognosis.

The potential importance of cystectomy prior to the development of T2 disease was illustrated by a cohort of 402 consecutive patients who underwent cystectomy for bladder cancer at a single-institution [64]. The cohort was divided into three groups based upon the indication for cystectomy: patients with high-risk disease (clinical stage Tis or T1), those who presented with Tis or T1 disease but had then progressed to clinical T2 involvement while being treated conservatively (the "early" T2 group), and those who presented with T2 disease de novo.

There was no survival benefit when cystectomy was deferred as part of a strategy to conserve the bladder until T2 disease developed (the "early" T2 group), compared to those presenting with de novo T2 involvement. The three-year disease-specific survival was significantly better for patients having cystectomy for clinical stage Tis or T1 disease, and there was no difference in outcome between those who developed T2 disease while under close observation and those who presented with T2 disease (76 versus 63 and 64 percent, respectively).

Non-muscle invasive disease — Cystectomy should be considered in patients with multiple

tumors or frequent recurrences, particularly if tumors recur within a short period of time despite treatment with intravesical BCG. In addition, non-muscle invasive tumors of the prostatic urethra are frequently managed by cystectomy, particularly if a complete resection cannot be accomplished.

T1 tumors — Management with TURBT alone is generally inadequate, with recurrence rates at one, three, and five years of approximately 50, 80, and 90 percent, respectively. Treatment with intravesical BCG after TURBT results in 70 percent five-year survival for T1 tumors [11]. This is similar to the results achieved with immediate radical cystectomy. However, cystectomy is appropriate for patients who relapse with recurrent T1 tumors within 6 to 12 months after combined treatment with TURBT and intravesical BCG.

INTRAVESICAL THERAPY — Intravesical therapy permits high local concentrations of a therapeutic agent within the bladder, potentially destroying viable tumor cells that remain following TURBT and preventing tumor implantation. The decision to proceed with intravesical therapy depends upon various risk factors and the likelihood of whether or not the patient will have a recurrence. (See 'Risk stratification' above.)

Intravesical therapy is generally used in the adjuvant setting, to prevent further recurrence. Less commonly, intravesical therapy may be given for residual disease that remains in the bladder following TURBT. This situation is relatively infrequent, except in cases with diffuse CIS. Indeed, BCG is considered the treatment of choice for patients with CIS. In a meta-analysis of 700 patients with CIS, 68 percent achieved a complete response with BCG versus 51 percent with chemotherapy. Furthermore the long-term 3.6-year durability of response to BCG was significantly better than with mitomycin (47 versus 26 percent) [65].

All intravesical therapies can cause symptoms of bladder irritation (dysuria and frequency). In addition, systemic effects may occur if the agent is absorbed through the mucosa. The latter phenomenon depends partly upon the size of the molecule and the pH in the bladder at the time of instillation.

The presence of mucosal damage at the time of instillation can permit systemic absorption of the agent. Deferring intravesical therapy for two to three weeks following TURBT allows healing and reduces the likelihood of severe local or systemic toxicities.

The most commonly used agent for intravesical therapy is Bacillus Calmette-Guerin (BCG). A number of other agents also have activity, including mitomycin, the anthracyclines, thiotepa, gemcitabine, interferon, and docetaxel.

INTRAVESICAL BCG — BCG, a live attenuated form of Mycobacterium bovis, is the most commonly used agent for intravesical therapy. A number of other intravesical agents have been compared to BCG, but none has proved consistently superior [65-69].

Mechanism of action — Although the exact mechanism of its antitumor action is unknown, intravesical instillation of BCG triggers a variety of local immune responses which appear to correlate with antitumor activity [70-72].

These include:

- Intravesical BCG causes a mononuclear cell infiltrate that consists predominantly of CD4 T cells and macrophages.
- BCG treatment is associated with the presence of interferon-gamma (IFNg) in the bladder. IFNg induces bladder cancer cell expression of class II MHC molecules, such as HLA-DR and intercellular adhesion molecule (ICAM)-1, which are absent prior to treatment. IFN-gamma also can cause bladder tumor cells to become sensitive targets for lymphokine-activated killer (LAK) cells and antigen-presenting cells for BCG.
- Cytokine levels, such as interleukin (IL)-1, IL-2, IL-6, IL-8, IL-12, IFNg, tumor necrosis factor

(TNF)-alpha, and tumor necrosis factor apoptosis inducing ligand (TRAIL) are increased in the urine following treatment.

Immune activation may persist for a number of months. In one study of uncomplicated intravesical instillation in 49 patients, BCG was detected in 96, 68 and 27 percent of urine specimens from two hours, 24 hours, and seven days following instillation, respectively [73]. 16S ribosomal DNA was demonstrated in bladder wall biopsy specimens up to 24 months later in 4 to 38 percent by polymerase chain reaction (PCR). The persistence of BCG in the bladder may facilitate an ongoing immune activation but also potentially increases the risk of a late systemic infection. (See "Complications of intravesical BCG immunotherapy".)

BCG may also directly suppress growth of tumor cells in a dose-dependent fashion. One study has shown that heat-inactivated BCG can cause this same effect although to a lesser degree [74].

Dose and schedule — BCG is typically instilled into the bladder weekly for six weeks. Each dose consists of a vial of reconstituted Theracys® (81 mg) or one 2 mL ampule of TICE® BCG (50 mg), plus 50 mL of sterile saline injected into the bladder through a catheter and retained for two hours.

To diminish the risk of systemic infection, intravesical BCG should not be administered to patients with traumatic catheterization, active cystitis, or persistent gross hematuria following TURBT [75]. (See "Complications of intravesical BCG immunotherapy".)

Several trials suggest that a lower dose of BCG may be as effective but less toxic [76-78]. The effect of dose was illustrated by a trial in which 155 patients with non-muscle invasive bladder cancer (T1 grade 3 or Tis, (table 1)) were randomly assigned to six weekly instillations of standard or reduced dose BCG (81 and 27 mg, respectively) following complete TURBT [76]. At a median follow-up of 61 months, there were no differences between the groups with respect to disease recurrence, time to recurrence, need for deferred cystectomy, or disease-specific survival. Rates of grade 3 or 4 toxicity were lower with the reduced dose (local, 37 versus 50 percent; systemic, 4 versus 16 percent, respectively).

Although these results are encouraging, further confirmatory trials are needed before a reduced dose of BCG can be considered standard.

Efficacy — Intravesical BCG is the most efficacious agent for non-muscle invasive bladder cancer. BCG therapy has been shown to delay (although not necessarily prevent) tumor progression to a more advanced stage, decrease the need for subsequent cystectomy, and improve overall survival.

In a systematic review, the activity of intravesical BCG was analyzed in six randomized trials that included 585 eligible patients with Ta or T1 disease [79]. Those treated with TURBT plus BCG had significantly fewer recurrences at 12 months compared to those managed with TURBT alone (odds ratio 0.30; 95% CI 0.21-0.43).

Patients with high-risk bladder cancer who are disease-free following an induction course of BCG therapy have a better prognosis than those in whom residual disease is detected. In an analysis of 341 patients who were treated with a course of induction BCG and did not receive maintenance therapy, the five-year survival was better for those who were disease-free (77 versus 62 percent in those who were not disease-free, hazard ratio 0.60, 95% CI 0.44-0.81) [80].

Maintenance therapy — The role of maintenance BCG for longer than six weeks has been considered controversial. Longer treatment may further delay tumor recurrence [12,16]. However, the frequency of complications is higher, and four of five randomized studies have shown no significant impact of maintenance treatment on tumor progression [81-84].

The largest trial, from the Southwest Oncology Group (SWOG), was the only report to show a possible benefit from maintenance therapy [85]. In this trial, 660 patients with high-risk disease were treated with a six-week induction course of BCG following TURBT. At three months, 550 patients were randomly assigned to receive either no additional BCG or maintenance BCG (each week for three

weeks given at 3, 6, 12, 18, 24, 30, and 36 months after the initiation of induction therapy).

Although maintenance therapy was associated with significantly better median recurrence-free survival (77 versus 36 months without BCG) in this trial, the five-year survival rate was not significantly improved (83 versus 78 percent). No toxicities greater than grade 3 were noted in the 243 patients in the maintenance therapy arm, but cumulative toxicity resulted in only 16 percent of patients completing the three-year course of maintenance therapy. However, improvement in the rate of completing BCG therapy has been improved with reduction in the dose of BCG during maintenance therapy and the use of the fluoroquinolone ofloxacin given 8 and 20 hours after BCG dosing [86,87].

Both the AUA and EAU bladder cancer guidelines commissions now recommend at least a year of BCG maintenance therapy for all high-risk patients who initiate with BCG [40,41]. The rationale for this recommendation has been a series of meta-analyses demonstrating that the superior results in terms of prevention of recurrence and progression with BCG compared to chemotherapy are only observed in studies in which at least a year of maintenance therapy is provided [16,65,68,88].

A repeat cystoscopy is indicated approximately six weeks after completing the induction cycle with BCG (three months after the start of treatment). For patients with high-risk tumors, rebiopsy of the original tumor sites or random biopsies of the bladder are often performed.

If an initial course of intravesical BCG is unsuccessful, based upon either recurrent visible tumor or a positive biopsy or urine cytology, a repeat induction course of six weekly BCG treatments should be performed [89]. The diagnosis of BCG-refractory disease, and consideration of alternative therapies, requires a minimum treatment and follow-up time of six months [90].

Long-term outcome — The 70 to 86 percent survival rate at four to five years following BCG is similar that achieved after immediate cystectomy and supports the choice of TURBT plus BCG rather than cystectomy for the initial management in these patients [91,92]. Although additional late relapses are observed, intravesical BCG does delay tumor progression and death in patients who present with non-muscle invasive bladder cancer.

The long-term outcome following intravesical BCG therapy for non-muscle invasive bladder cancer has been assessed in a number of trials [93-95]. As an example, 86 high-risk patients (Ta, Tis, or T1) were randomly assigned to BCG or no BCG following TURBT [93]. At 10-year follow-up, the progression-free rate was longer for patients who had received BCG (62 versus 37 percent without BCG). Disease-specific survival was also significantly increased (75 versus 55 percent).

Similar results have been reported in observational studies [94,95]. As an example, in one report of 98 patients with high-risk or recurrent non-muscle invasive bladder cancer and a minimum follow-up of ten years, 67 percent were progression-free, 59 percent had a retained bladder, and the disease-specific survival was 85 percent [94].

Complications — In a Cochrane database review of six randomized trials involving 585 eligible patients, toxicities associated with intravesical BCG included frequency (71 percent), cystitis (67 percent), fever (25 percent), and hematuria (23 percent) [79]. There were no reported BCG-associated deaths.

In addition to acute toxicities, both localized and systemic infectious complications can occur after intravesical administration of BCG. The infectious complications of intravesical BCG are discussed elsewhere. (See "Cystitis in patients with cancer", section on 'BCG immunotherapy' and "Complications of intravesical BCG immunotherapy".)

To diminish the risk of systemic infection, intravesical BCG should not be administered to patients with traumatic catheterization, active cystitis, or persistent gross hematuria following TURBT, which appears to be associated with the greatest risk of systemic infection with BCG [75]. The presence of a prosthetic device (pacemaker, artificial heart valve, orthopedic hardware) is not an absolute contraindication to intravesical BCG. In a series of 143 patients with a prosthetic device (part of a larger, prospective cohort of 1045 patients) who were treated with intravesical BCG, there were three

cases in which BCG had to be discontinued because of fever [96]. In all three cases, fever resolved within 24 hours without long-term complications. Furthermore, this rate of fever was no different than what occurred in patients without prosthetic devices.

Interactions with statins — Statins (HMG CoA reductase inhibitors) are known to have immunosuppressive effects that might theoretically counteract the immunotherapeutic effect of BCG [97,98]. Whether or not this has clinical implications for patients with bladder cancer remains uncertain. Retrospective studies have given conflicting results. Although one study initially suggested that statins may be harmful in patients receiving BCG [99], two other studies found no effect [100,101]. Furthermore, a fourth study in patients with more advanced bladder cancer suggested that these agents might have antitumor effects [102].

INTRAVESICAL CHEMOTHERAPY — Although no agent has been shown to be superior to BCG in head to head studies [65-68], single-dose intravesical chemotherapy, given in the immediate post-operative period for low-risk papillary disease, does have a clear role. A meta-analysis of seven randomized trials that included 1476 patients found a statistically significant decrease in the risk of recurrence (48 versus 37 percent, odds ratio 0.61) [103]. Agents that have been evaluated in the trials included in the meta-analysis were mitomycin, epirubicin, thiotepa, and pirarubicin.

An even greater absolute reduction (about 17 percent) was observed for patients with multifocal tumors, but this was felt to be insufficient therapy, since 65 percent of patients still recurred. For patients with low-grade disease that has previously recurred or is multifocal, six weekly courses of intravesical chemotherapy is considered a reasonable alternative to BCG for initial management [41]. Failure on such a regimen does not appear to adversely affect subsequent response to BCG.

Mitomycin

Activity — Intravesical mitomycin has been used with multiple schedules, including single dose, multiple weekly administrations, or with a maintenance regimen. Mitomycin is the most commonly used intravesical chemotherapeutic agent, although the optimal schedule is not known and it has not been approved by the Food and Drug Administration for intravesical use.

In a meta-analysis that was included in the American Urological Association guidelines, a single dose post-operative instillation of mitomycin provided an average absolute benefit of a 17 percent reduction in early tumor recurrence [40].

The activity of mitomycin with extended maintenance therapy was illustrated in a multicenter trial in which 495 patients were randomly assigned to intravesical therapy with BCG (weekly for six doses), mitomycin (20 mg weekly for six weeks), or mitomycin (20 mg weekly for six weeks, then monthly for three years) [104]. The three-year recurrence-free rates with six-week courses of either BCG or mitomycin were inferior to that achieved with maintenance mitomycin (66 and 69 percent versus 86 percent).

Other randomized trials have suggested improved results with a variety of approaches to enhance the efficacy of mitomycin. These approaches have included an "optimized" regimen using a longer dwell time [105], increasing the intravesical drug concentration by decreasing the volume in which the drug is instilled (40 mg in 20 cc), decreasing urine volume by dehydration and complete emptying, and by alkalinizing the urine to stabilize the drug [106], electromotive instillation to accelerate drug delivery into and across biologic membranes [107], and microwave hyperthermia [108]. The optimized regimen was proven superior to standard administration of 20 mg diluted in 20 cc volume in a randomized clinical trial, and many have adopted this as the standard of care [106]. Although the other variations have shown benefits compared to standard intravesical mitomycin or BCG, confirmatory trials are required before they can be adopted as standard therapy.

Toxicity — Mitomycin is an alkylating agent that is minimally absorbed from the bladder into the systemic circulation. As a result, myelosuppression following the intravesical use of this agent is uncommon [109].

Other toxicities which have been reported following intravesical administration include:

- A self-limited chemical cystitis has been reported in approximately 40 percent of patients receiving intravesical mitomycin [88]. Only rarely does this progress to shrunken, contracted bladder.
- A rash primarily involving the palms, soles, and genitalia is thought to be a manifestation of a hypersensitivity reaction [110].

Both the chemical cystitis and the rash generally respond to treatment with corticosteroids.

In addition, wounds in the bladder do not heal properly once intravesical mitomycin is started. Such areas do not completely epithelialize and can undergo dystrophic calcification. Although usually asymptomatic, these lesions can take months or years to fully resolve.

Anthracyclines — Epirubicin, doxorubicin, and valrubicin are anthracyclines with limited systemic absorption following intravesical instillation. Studies have demonstrated activity for these agents but the role of anthracyclines remains limited.

Although epirubicin is more active than either placebo or interferon (IFN) alfa [23,111,112], it was less active than BCG in a trial of 957 patients with intermediate and high-risk Ta and T1 papillary bladder cancer [113]. Patients were randomly assigned to intravesical epirubicin (50 mg weekly for six weeks) or BCG (Tice strain, weekly for six weeks). Both groups then received maintenance treatment with three weekly intravesical doses of either agent every three months for 36 months. Treatment with BCG resulted in a significantly longer time to first recurrence compared to epirubicin and a higher three-year recurrence-free survival (65 versus 49 percent). Furthermore, at a median follow-up of 9.2 years, risks of first recurrence and distant metastases were significantly lower with BCG compared to epirubicin (38 versus 53 percent and 5.0 versus 8.6 percent, respectively); death from all causes and death from bladder cancer were significantly reduced with BCG compared with epirubicin (31 versus 38 percent and 3.4 versus 6.8 percent, respectively) [114].

The anthracycline valrubicin is approved by the United States Food and Drug Administration (FDA) for intravesical use in patients with Tis lesions who have failed intravesical BCG, and in whom immediate cystectomy is either refused or contraindicated. The efficacy of valrubicin in this setting was supported by a series of 90 patients with recurrent Tis after multiple prior courses of intravesical therapy, including BCG [115]. Each patient received six weekly instillations (800 mg) and was evaluated at three-month intervals following treatment. Complete remission was noted in 19 patients (21 percent). Median time to failure or last follow-up for complete responders was more than 18 months. The main side effects are reversible local bladder symptoms.

Gemcitabine — Based upon results from small, nonrandomized studies [116-119], intravesical gemcitabine has been proposed as an alternative to BCG or for patients who have progressed on BCG. As an example, the activity of intravesical gemcitabine was illustrated by a series of 30 patients who were refractory or intolerant to intravesical BCG and who refused cystectomy [118]. Patients were treated with a dose of 2000 mg twice weekly for three weeks. A complete response was observed in 15 patients (50 percent). However, 12 of these relapsed at a median of 3.6 months.

Single instillation after TURBT — The role of a single instillation of gemcitabine following TURBT is being investigated in a phase III trial conducted by the Southwest Oncology Group (S0337, NCT00445601) [120]. In this trial, patients receive an immediate single instillation of gemcitabine (2000 mg) or placebo after resection of a grade 1 or 2 Ta or T1 TCC. Patients will then be followed for four years, to determine whether the percentage of patient recurrences and/or the time to first recurrence has been favorably affected.

In another phase III trial, 355 patients were randomly assigned to one instillation of gemcitabine (2000 mg) or placebo following TURBT [121]. A second TUR without drug instillation and adjuvant bacillus Calmette-Guerin (BCG) instillations were allowed at the physician's discretion. There was no significant difference in the 12-month relapse-free survival rate (78 versus 75 percent with

placebo). The activity of gemcitabine relative to placebo is uncertain in this setting because of the use of a potential second TUR and BCG after the initial instillation.

After recurrence on BCG — Intravesical gemcitabine has been studied in two randomized trials in patients with recurrent disease following treatment for non-muscle invasive bladder cancer:

- In one trial, 109 evaluable patients were randomly assigned to intravesical gemcitabine (six weekly instillations of gemcitabine followed by monthly maintenance for 10 months) or intravesical mitomycin [122]. Gemcitabine was at least as effective as mitomycin and had a significantly lower incidence of chemical cystitis.
- In a second trial, 80 patients with high-risk features were randomly assigned to either intravesical gemcitabine or retreatment with BCG [123]. The two-year recurrence-free survival rate was significantly better in those given gemcitabine (19 versus 3 percent).

The Southwest Oncology Group (SWOG) is also evaluating the role of gemcitabine for patients with non-muscle invasive bladder cancer who have progressed on BCG in a single-arm phase II trial (NCT00234039) [120]. This study is to evaluating six weekly instillations of gemcitabine followed by monthly maintenance for 10 months.

Interferon — IFNs directly inhibit the proliferation of bladder tumor cells in vitro [124] and increase bladder tumor cell surface antigen expression [125]. This improved antigenic recognition of tumor cells, as well as the antiproliferative and immunostimulatory effects of IFN may account for their activity in bladder cancer [126].

Initial studies using intravesical instillations of IFN alfa (IFNa) reported that treatment was well tolerated and associated with a dose-related decrease in the recurrence rate [127,128]. However, randomized trials comparing IFNa with either BCG or with epirubicin have shown that it has less activity than either of those agents [111,129].

In a large phase III trial, 670 patients were randomly assigned to BCG alone or BCG plus intravesical IFNa [130]. All patients had newly-diagnosed, histologically confirmed non-muscle-invasive bladder cancer and had not received prior BCG. Patients were simultaneously randomized to recommended daily allowance vitamins or megavitamins. There was no evidence of any reduction in the rate of bladder recurrence associated with the addition of IFNa to BCG, nor was there any benefit attributable to the megadose vitamins.

A multicenter phase II trial has suggested that some patients who recurr on BCG alone may respond if retreated with the combination of BCG plus IFNa [131]. However, there are no randomized trials that have confirmed a benefit from combination therapy in this setting.

IFNa has not been approved for intravesical use in patients with bladder cancer but is commonly used off-label.

Thiotepa — Thiotepa was the first intravesical agent to be used for non-muscle invasive bladder cancer. A randomized trial conducted by the National Bladder Cancer Collaborative Group showed that intravesical thiotepa (30 or 60 mg) was associated with a significant reduction in recurrence rate [132]. However, it can cause irritative voiding symptoms in up to 69 percent of patients [109].

Because of its relatively small molecular weight (186 daltons), thiotepa is absorbed systemically, and the incidence of myelosuppression may be as high as 54 percent [109,133]. Furthermore, thiotepa is a potent carcinogen and has been linked to the development of secondary leukemia in patients treated for non-muscle invasive bladder cancer [134].

Because of these acute side effects and late complications, intravesical thiotepa is seldom used.

Docetaxel — Intravesical docetaxel may have activity in patients with nonmuscle invasive urothelial bladder cancer that is refractory to BCG. In a phase I study of 18 patients, four (22 percent) remained disease-free at a median follow-up of 48 months following one course of six weekly intravesical

installations [135,136]. The addition of monthly maintenance therapy, however, improved the 13-month disease free outcome to 44 percent (6 of 13 patients) [137].

EXPERIMENTAL APPROACHES — Several novel approaches have been evaluated to decrease the incidence of recurrence following initial treatment for non-muscle invasive bladder cancer.

Photodynamic therapy — In addition to its use in the initial management of patients with non-muscle invasive bladder cancer, photodynamic therapy using the photosensitizing agents 5-aminolevulinic acid (ALA) or porfimer (Photofrin) may have a role in patients with refractory non-muscle invasive disease [138-141]. (See 'Fluorescence endoscopy' above.)

Results from the two largest series are summarized:

- In a report of 31 patients with recurrent disease who were followed for 24 months after intravesical application of ALA and transurethral light exposure, 16 were free of tumor recurrence, including four of ten patients with prior BCG treatment [138]. Treatment was well tolerated.
- Long-term benefit was suggested in a series of 34 patients with refractory Tis (n = 29) or multiple small papillary Ta or T1 lesions (n = 5) who underwent therapy with porfimer followed by transurethral light exposure [141]. At three months, a complete or partial response was achieved by 14 and 4 patients, respectively, while 14 were nonresponders (including four of five patients with Ta/T1 disease). With a median follow-up of 52 months, only three complete responders required cystectomy for progressive disease (mean time 20 months).

Photodynamic therapy remains investigational.

Radiation therapy — External beam radiation therapy (RT), with or without platinum-based chemotherapy, has been evaluated as an alternative to intravesical therapy for patients with high-grade T1 lesions following TURBT.

In this setting, RT alone does not appear to have a role. In a randomized trial of 210 patients with high-grade T1NXMO disease, radical RT (60 Gy in 30 fractions) alone had no advantages over observation in terms of progression-free or overall survival for patients with unifocal disease, or over BCG for those with multifocal disease or CIS [142].

A possible role for RT as part of a combined modality approach including chemotherapy for treatment of patients with muscle invasive cancer is discussed separately. (See "Multimodality approaches for bladder preservation in invasive bladder cancer", section on 'Chemoradiotherapy without induction chemotherapy'.)

Chemoprevention — Systemic chemopreventive biologic agents rather than or in addition to intravesical therapy have been evaluated to prevent recurrence of low-risk non-muscle invasive bladder cancers. Although some data supporting these agents are suggestive, no role has been established for any chemopreventive agent in patients with previously treated non-muscle invasive bladder cancer.

Chemopreventive agents to prevent recurrence are discussed elsewhere. (See "Chemoprevention of bladder cancer", section on 'Chemopreventive agents'.)

POSTTREATMENT MANAGEMENT — Careful follow-up is required for both high- and low-risk patients with non-muscle invasive bladder cancer. Recurrent disease can develop anywhere along the genitourinary epithelium, including the renal pelvis, ureters, and urethra, as well as the bladder. One consequence of the "successful" treatment of tumors in the bladder has been an increase in the frequency of extravesical recurrences [143]. (See "Urethral cancer in men" and "Urethral cancer in women" and "Malignancies of the renal pelvis and ureter".)

Patients should be encouraged to discontinue smoking, because of the association between smoking and urothelial cancer. (See "Epidemiology and etiology of urothelial (transitional cell) carcinoma of

the bladder", section on 'Smoking cessation'.)

Cystoscopy and cytology — Follow-up evaluation with repeat cystoscopy and urinary cytology is necessary three months after therapy. If the bladder is not endoscopically and cytologically free of tumor, a repeat course of intravesical therapy is indicated [144]. Cystectomy should be considered for patients with recurrent or persistent tumor after one or two cycles of intravesical therapy. (See "Radical cystectomy and bladder-sparing treatments for urothelial (transitional cell) bladder cancer".)

If no recurrences are documented, repeat urinalysis and cystoscopy are generally advised at three to six month intervals, depending on the number of tumor recurrences, for the first four years and annually thereafter in the absence of tumor recurrence [145,146].

Adherence to surveillance recommendations is often suboptimal, as illustrated in a series of 6717 patients aged 65 or older with non-muscle invasive bladder cancer identified in the Surveillance, Epidemiology and End Results (SEER)-Medicare linked database of the National Cancer Institute [147]. During the five contiguous six-month intervals following initial diagnosis, only 40 percent of patients had an examination during all five periods, while 18 percent were examined during two or fewer of these periods. Among the factors that were independently associated with a lower intensity of surveillance were age ≥75 years, nonwhite ethnicity, favorable tumor histology (ie, well-differentiated versus poorly differentiated), and a high degree of comorbidity.

Urine biomarkers — A wide range of urinary biomarkers are being evaluated for their utility in surveillance following initial treatment of non-muscle invasive bladder cancer.

In the United States several of these urine tests (eg, bladder tumor antigen [BTA] Stat, BTA TRAK, UroVysion, nuclear matrix protein [NMP] 22) are approved for the detection of tumor recurrence. However, none of these tests has been proven to have sufficient diagnostic reliability to eliminate the need for cystoscopy. Major problems with these assays include the lack of sensitivity for small tumors, particularly low-grade lesions, as well as a large number of false positives.

The data supporting the use of these assays and their potential role in bladder cancer surveillance are discussed elsewhere. (See "Urine biomarkers for the detection of urothelial (transitional cell) carcinoma of the bladder", section on 'Urine biomarkers'.)

Upper urinary tract — In large series the incidence of renal pelvis and ureteral tumors has ranged from 1 to 4 percent [148-152], although a substantially higher incidence has been reported in small series [153,154]. The median time to discovery of such tumors following the diagnosis of bladder cancer has varied from three to seven years [148,149,152,153].

Factors that may increase the risk of developing an upper tract tumor include urethral involvement, vesicoureteral reflux, the presence of multiple tumors or Tis, previous BCG treatment, and occupational exposure [149,150,152-154]. (See "Malignancies of the renal pelvis and ureter", section on 'Diagnosis'.)

For patients with a negative urine cytology and intermediate to high-risk disease after TURBT, imaging of the upper urinary tracts every one to two years is recommended to exclude involvement with metachronous lesions [146,155,156]. This should be continued for five years in patients with intermediate-risk disease and for life in patients with high-risk disease. There are no strong data to support routine upper tract imaging for patients with single, nonrecurrent, low-grade, small, papillary tumors [41]. Imaging options include IVP, CT urography, retrograde pyelography, or magnetic resonance imaging (MRI) urogram. (See 'Risk stratification' above.)

For patients who have positive urinary cytology and no obvious intravesical tumor, careful periodic evaluation of the upper tracts is particularly important [155,157]. CT urography has replaced IVP as the preferred imaging modality in this situation. This may be combined with ureteroscopy for any suspicious lesions. Due to the rarity of this condition, it is unclear how such cytology positive upper tracts should be managed. However, some success has been reported using topically applied drug therapy, particularly BCG [158].

Urethra — In addition to bladder and upper urinary tract recurrences, tumor recurrences in the prostatic urethra and ducts are not uncommon. In a series of 186 men followed for 15 years, 72 (39 percent) had a relapse in the prostatic urethra [159]. More than one-half of the relapses occurred in the first five years, but 39 percent were diagnosed between 5 and 15 years. Only 11 (15 percent) had stromal invasion of the prostate, and the remainder were initially managed with repeat transurethral resection and BCG. However, 61 percent of these patients eventually progressed, either in the prostate or the bladder. (See "Urethral cancer in men".)

TREATMENT OF RECURRENT DISEASE

Non-muscle invasive papillary tumor — Recurrent non-muscle invasive papillary tumors (Ta, (table 1)) can generally be managed with repeat TURBT. Although this is typically performed with the patient under general anesthesia, office fulguration may be appropriate for selected patients with fewer than five small (<0.5 cm), low-grade lesions [160]. It is even possible to safely monitor these patients initially and intervene when size or symptoms dictate in patients with an established pattern of low-grade recurrences [161].

Tis — Tis (carcinoma in situ) cannot be controlled with TURBT alone. If intravesical therapy fails to control disease, cystectomy is indicated [162]. While both standard and novel therapies have been used for patients who have refused cystectomy or are not candidates for surgical resection, there is a real danger of progression when definitive treatment is delayed [163]. (See "Radical cystectomy and bladder-sparing treatments for urothelial (transitional cell) bladder cancer".)

T1 disease — Patients who relapse with recurrent T1 tumors within six months to one year after TURBT and one or two courses of BCG are best treated with cystectomy [91,164]. In an analysis based upon a comparison with a historical cohort, preemptive radical cystectomy was associated with better disease-specific survival than postponing cystectomy until the appearance of T2 disease [165]. (See "Radical cystectomy and bladder-sparing treatments for urothelial (transitional cell) bladder cancer".)

Salvage cystectomy — The optimal timing of salvage cystectomy is controversial. The potential benefits of preserving the bladder must be balanced against the risks of developing metastatic disease and thus decreased survival.

Intravesical therapy with valrubicin or BCG plus interferon may avoid or delay cystectomy, particularly in patients who represent a poor medical risk [166,167]. In one report of 40 patients who had failed one (19) or more (21) induction courses of intravesical BCG, weekly low-dose BCG (one-third dose, or 27 mg) plus interferon-alpha 2b (50 million units) was administered for six to eight weeks and repeated at months 5, 11, and 17 [167]. At 12 and 24 months, 63 and 53 percent of patients were disease-free, respectively, and 12 of 22 patients who were initially planned for cystectomy were cystoscopically disease-free with an intact bladder.

However, other data suggest inferior survival in patients who are treated with continued bladder-sparing strategies and delayed cystectomy [168]. This was illustrated by a report of 90 patients with high-risk non-muscle invasive bladder tumors who underwent salvage cystectomy. The indication for cystectomy was refractory or recurrent non-muscle invasive disease in 35 and progression with either muscle-invasive disease or prostatic stromal invasion in 55. The survival rate was significantly better for patients undergoing cystectomy less than one year after BCG therapy (75 versus 34 percent for delayed cystectomy).

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Beyond the Basics topics (see "Patient information: Bladder cancer treatment; non-muscle invasive (superficial) cancer (Beyond the Basics)" and "Patient information: Bladder cancer treatment; invasive cancer (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- The initial diagnosis and management of patients with non-muscle-invasive bladder tumors (Ta, Tis, and T1, (table 1)) generally includes a complete cystoscopic transurethral resection of the bladder tumor (TURBT). An examination under anesthesia (EUA) should be performed at the same time. For patients with non-muscle invasive disease, TURBT, often in conjunction with intravesical chemotherapy or immunotherapy, may delay or avoid the need for radical cystectomy. Subsequent management requires a consideration of the risk of recurrence or progression as estimated based upon clinical factors. (See 'Transurethral resection' above and "Radical cystectomy and bladder-sparing treatments for urothelial (transitional cell) bladder cancer" and 'Risk stratification' above.)

- For patients at low risk of recurrence following TURBT, we recommend an immediate, single post-operative dose of chemotherapy (**Grade 1A**). This is considered sufficient in itself without the need for additional therapy, and BCG is never given in this setting. (See 'Intravesical therapy' above.)

  - The most extensive data for intravesical chemotherapy are with mitomycin. (See 'Mitomycin' above.)

- For patients at intermediate risk of recurrence following TURBT, we recommend postoperative adjuvant intravesical therapy (**Grade 1B**). This therapy should include:

  - An immediate single post-operative dose of chemotherapy followed by either an induction cycle of further chemotherapy or BCG. (See 'Intravesical therapy' above.)
  - For patients who have failed prior intravesical chemotherapy, further therapy in the form of BCG is indicated. (See 'Intravesical BCG' above.)
  - For those given induction BCG, we recommend that maintenance BCG should be continued for at least one year (**Grade 1A**). (See 'Maintenance therapy' above.)

- For patients with any high-risk disease features (high-grade, T1, or Tis), we recommend a course of intravesical BCG immunotherapy following a restaging TURBT (**Grade 1B**). Intravesical chemotherapy is generally an inferior alternative to BCG for these patients. (See 'Intravesical BCG' above.)

- For patients given intravesical BCG immunotherapy:

  - The initial course of BCG immunotherapy generally consists of six weekly doses of BCG. (See 'Dose and schedule' above.)
  - Maintenance BCG therapy, treatment should be continued for at least one year if possible. (See 'Posttreatment management' above.)
  - To minimize the risk of systemic infection, intravesical BCG should not be administered to patients with traumatic catheterization, active cystitis, or persistent gross hematuria following TURBT. BCG is never given in the perioperative setting. (See 'Complications' above and "Complications of intravesical BCG immunotherapy".)

- For all patients being treated for non-muscle invasive bladder cancer, careful surveillance with cystoscopy and cytology is required and should begin three months after the initiation of BCG therapy. (See 'Cystoscopy and cytology' above.)

  - If no evidence of disease is found at the three-month evaluation, a reasonable surveillance schedule includes repeat cystoscopy and urine cytology at three month intervals for two years, at six month intervals for another two years, and then annually thereafter. Selected patients with low risk disease may be followed with a less intensive schedule. (See 'Cystoscopy and cytology' above.)
  - Because of the risk of metachronous involvement of the upper urinary tract, surveillance should include imaging of the upper urinary tracts every one to two years for all but the lowest risk patients. This should be continued for five years in patients with intermediate-risk disease and for life in patients with high-risk disease. (See 'Cystoscopy and cytology' above and 'Risk stratification' above.)

- For patients with residual non-muscle invasive disease at the three-month cystoscopy or a subsequent recurrence with non-muscle invasive disease after failing BCG, we suggest another six-week course of either intravesical BCG or BCG plus interferon (**Grade 2C**). For patients whose initial treatment consisted of intravesical chemotherapy and who recur without interval disease progression, we recommend a trial of intravesical BCG (**Grade 2C**). (See 'Cystoscopy and cytology' above and 'Dose and schedule' above.)

  - For patients with high-risk residual non-muscle invasive disease after two initial courses of intravesical BCG and for those requiring multiple courses of intravesical BCG over time, we suggest that cystectomy be strongly considered (**Grade 2C**). (See "Radical cystectomy and bladder-sparing treatments for urothelial (transitional cell) bladder cancer".)

- For patients with recurrent CIS after two courses of BCG, we recommend cystectomy (**Grade 1C**). For patients who refuse cystectomy or who are too ill for major surgery, alternative methods may be considered but at the risk for interval disease progression. (See "Radical cystectomy and bladder-sparing treatments for urothelial (transitional cell) bladder cancer".)

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Topic 2996 Version 12.0

GRAPHICS

TNM staging system for bladder cancer

Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Ta	Noninvasive papillary carcinoma		
Tis	Carcinoma in situ: "flat tumor"		
T1	Tumor invades subepithelial connective tissue		
T2	Tumor invades muscularis propria		
pT2a	Tumor invades superficial muscularis propria (inner half)		
pT2b	Tumor invades deep muscularis propria (outer half)		
T3	Tumor invades perivesical tissue		
pT3a	Microscopically		
pT3b	Macroscopically (extravesical mass)		
T4	Tumor invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall		
T4a	Tumor invades prostatic stroma, uterus, vagina		
T4b	Tumor invades pelvic wall, abdominal wall		
Regional lymph nodes (N)*			
NX	Lymph nodes cannot be assessed		
N0	No lymph node metastasis		
N1	Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)		
N2	Multiple regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node metastasis)		
N3	Lymph node metastasis to the common iliac lymph nodes		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Anatomic stage / prognostic groups			
Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a	N0	M0
	T2b	N0	M0
Stage III	T3a	N0	M0
	T3b	N0	M0
	T4a	N0	M0

Stage IV	T4b	N0	M0
	Any T	N1-3	M0
	Any T	Any N	M1

Note: cTNM is the clinical classification, pTNM is the pathologic classification. * Regional lymph nodes include both primary and secondary drainage regions. All other nodes above the aortic bifurcation are considered distant lymph nodes. *Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer New York, Inc.*