Complete Summary

GUIDELINE TITLE

Guideline for the management of nonmuscle invasive bladder cancer: (stages Ta,T1, and Tis): 2007 update.

BIBLIOGRAPHIC SOURCE(S)

Bladder Cancer Clinical Guideline Update Panel. Guideline for the management of nonmuscle invasive bladder cancer: (stages Ta, T1, and Tis): 2007 update. Linthicum (MD): American Urological Association Education and Research, Inc; 2007. 133 p. [31 references]

GUIDELINE STATUS

This is the current release of the guideline.

This is an update of a previous version: American Urological Association, Inc. Report on the management of non-muscle-invasive bladder cancer. Baltimore (MD): American Urological Association, Inc.; 1999. 66 p. [108 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Nonmuscle-invasive bladder cancer (stages Ta, T1 and Tis)

GUIDELINE CATEGORY

Management
Treatment

CLINICAL SPECIALTY

Internal Medicine
Oncology
Urology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To analyze the literature to determine the impact of the various available treatments on outcomes of importance to patients
- To estimate the occurrence of side effects and complications of treatments, focusing on post-transurethral resection of bladder tumor treatments
- To support optimal clinical practices in the management of nonmuscle invasive bladder cancer

TARGET POPULATION

Patients with nonmuscle invasive transitional cell carcinoma of the bladder including Tis as well as stages Ta and T1 tumors (see Table 1 in the original guideline document for staging of primary tumors in bladder cancer)

INTERVENTIONS AND PRACTICES CONSIDERED

1. Biopsy and pathologic analysis of tissue
2. Transurethral resection of bladder tumor (TURBT)
3. TURBT plus mitomycin C
4. TURBT plus bacillus Calmette-Guerin
5. Intravesical chemotherapy
6. Cystectomy
7. Periodic surveillance cystoscopy

MAJOR OUTCOMES CONSIDERED

- Probability of tumor recurrence
- Probability of overall progression (progression in stage or to cystectomy)

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The review of the evidence began with a literature search and data extraction. Articles were selected from a database, based on a series of four MEDLINE

searches beginning in October 2004 and concluding in February 2006, Articles published between January 1, 1998 (the closing date of the search for the previous guideline) and December 31, 2005 were included in the analysis. The searches were limited to human subjects, English language, and contained the Medical Subject Heading (MeSH) heading "bladder neoplasms." Additional searches were conducted using various treatment options and the term "bladder cancer," but no additional records were detected. Finally, a review of existing meta-analyses revealed two articles published during the time period captured in the previous guideline that had been missed and were thus included in the dataset for the update.

A data extraction form was developed, tested, and revised (see Appendix 4 in the original guideline document). The Panel was trained in data extraction. After double review and quality control of the initial extractions, single Panel members extracted data from the articles. The final versions of the extracted data were entered into a Microsoft Access® (Microsoft, Redmond, WA) database. The Panel met in person and via conference calls to review the extracted data. Inconsistencies in data recording were reconciled, extraction errors were corrected, and some articles were excluded.

Reasons for excluding articles from further analysis were as follows:

1. The article was included in the previous guideline.
2. The article did not provide usable data on the outcomes of interest.
3. Results for patients with muscle invasive tumors could not be separated from those without muscle invasion.
4. Either the treatments used were not current or they were not the focus of this analysis.
5. The article was a review article or only provided data reported elsewhere.

NUMBER OF SOURCE DOCUMENTS

The searches identified 5,020 articles, from which the Panel ultimately selected 322 for data extraction. A total of 158 articles were accepted for data analysis.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Not stated

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Observational Trials
Meta-Analysis of Randomized Controlled Trials
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The analytic goals were expanded from the previous guideline. In addition to meta-analyzing the randomized controlled trials to determine if there were significant differences among the treatments, the Panel also decided to develop outcomes tables and to actually provide estimates of outcomes for the different treatment modalities. To generate an outcome table, estimates of the probabilities and/or magnitudes of the outcomes are required for each intervention. Ideally, these come from a synthesis or combination of the evidence. Such a combination can be performed in a variety of ways depending on the nature and quality of the evidence. For example, if there is one good randomized controlled trial, the results of that trial alone may be used in the outcome table while findings of other studies of lesser quality are ignored. Alternatively, if there are no studies of satisfactory quality for certain outcome table cells or if available studies are not commensurable, expert opinion may be used to complete those cells. Finally, if a number of studies have some degree of relevance to a particular cell or cells, then meta-analytic mathematical methods may be used.

A variety of specific meta-analytic methods are available, and selection of a particular method depends on the nature of the evidence. For this guideline, the Panel elected to use the confidence profile method, which provides methods for analyzing data from studies that are not randomized controlled trials.

Three different meta-analyses of the efficacy data were performed:

1. Meta-analysis of the comparable randomized controlled trials to determine the differences between pairs of available treatments. This analysis provides estimates of the absolute differences.
2. Meta-analysis of the individual arms of the randomized controlled trials to combine all the data from such trials for each treatment. This "single-arm" analysis provides an estimate of the actual rate of occurrence of each outcome.
3. Meta-analysis of the individual arms from all studies regardless of study design. For complications and side effects, only this method was used.

The Fast*Pro software was used to perform the meta-analyses. Many of the studies included in the meta-analysis had varying results. The variation in outcomes from study to study may have resulted from differences in patient populations, in how the intervention was performed, or in the skill of those performing the intervention. Given these differences, a random effects or hierarchical model was used to combine the studies. A random-effects model assumes that there is an underlying true rate for the outcome being assessed for each study. It further assumes that this underlying rate varies from site to site. This site-to-site variation in the true rate is assumed to be normally distributed. The method of meta- analysis used in analyzing the data attempts to determine this underlying distribution.

The results of the Confidence Profile Method are probability distributions that are described using the median of the distribution with a confidence interval. In this case, the 95% confidence interval indicates that the probability (Bayesian) of the true value being outside the interval is 5%. These Bayesian confidence intervals are sometimes called credible intervals.

The Bayesian method of computation assumes a "prior" distribution that reflects knowledge about the probability of the outcome before the results of any experiments are known. The prior distributions selected for this analysis are among a class of "noninformative" prior distributions, which means that they correspond to little or no prior knowledge. The existence of such a prior distribution can cause small changes in results, particularly for small studies. The prior distribution for all probability parameters is Jefferey's prior (beta distribution with both parameters set to 0.5). The prior for the variance for the underlying normal distribution is gamma distributed with both parameters set to 0.5.

In addition to the outcomes tables, graphs (Appendices 6 to 8 in the original guideline document) were developed to visually show selected treatment differences.

Efficacy Analysis

The outcomes analyzed for efficacy included recurrence and progression. A variety of methods of measuring recurrence were extracted, including probability of recurrence (percentage of patients with recurrence), time to recurrence, and time between recurrences. However, only probability of recurrence provided sufficient data for analysis. Similar measures also existed for progression, including time to progression and probability of progression. Moreover, there were different types of progression recorded including stage, grade, metastasis, and cystectomy. Ultimately, the Panel decided that only probability of progression could be analyzed. Progression was defined as progression in stage or to cystectomy.

The meta-analyses were conducted in three ways:

1. Meta-analysis of comparable randomized controlled trials—this method used controlled trial data as reported to determine the difference between two treatments. The meta-analytic result gives an estimate of the absolute magnitude of the difference and whether it reaches statistical significance ($p<0.05$).
2. Meta-analysis of comparable arms of randomized controlled trials—this method combines the individual arms reflecting the same treatment from controlled trials. For example, if one randomized controlled trial compared transurethral resection of bladder tumor (TURBT) alone to mitomycin C and another compared mitomycin C to bacillus Calmette-Guérin (BCG), the two mitomycin C arms would both be included in creating the mitomycin C estimate.
3. Meta-analysis of comparable arms from all studies—this method combines arms as in method two but includes data from clinical series as well as randomized controlled trials.

Thus three outcomes tables exist for the efficacy data. The outcomes tables for methods two and three are formatted the same. Because the first method produces pair-wise results, the table is necessarily formatted differently.

Data from randomized controlled trials dealing with mitomycin C and/or BCG from the data extracted for the previous guideline were included in all three analyses. Other data from the previous guideline were not included.

One issue that is problematic when meta-analyzing data about time points is how to deal with losses to follow-up. Although most studies reported Kaplan-Meier data for recurrence (fewer for progression), not all studies provided the number of patients at risk. In order to avoid penalizing those studies which included numbers at risk, the initial study size was used as the denominator in all meta-analyses at all time points.

Complications

Different studies grouped complications into varying categories. They also used different terms for similar complications. The Panel grouped complications in an attempt to include all similar complications. Complications were variably reported. Only studies that specifically reported data concerning occurrences of complications were included in complication analyses. The Panel did not assume that the lack of reporting implied the lack of occurrence of any specific complication.

Also, some investigators may only have reported complications that had occurred and did not report that a complication did not occur. Combining complications into categories reduced the possibility of an overestimation of the complication rate. The probability that a patient would have a complication was still most likely slightly overstated because some patients experienced multiple complications. Thus, the result of the meta-analysis was best interpreted as the mean number of complications the patient may experience rather than as the probability of having a complication. There were insufficient data to permit meaningful meta-analyses of patient deaths. The estimates of death rates provided in the guideline result from the Panel's expert opinion and the limited available data.

Patient Groups

The Panel attempted to evaluate outcomes based on a variety of patient characteristics including stage, grade, tumor multiplicity, and recurrence. However, in most cases, the outcomes data were not fully or consistently stratified by these conditions. Ultimately, the Panel elected to analyze the combined data from all studies and also the individual data sets for high- and low-risk patients. Low risk was defined as Grade 1. High risk included groups that had no Grade 1 patients or were entirely carcinoma in situ and/or T1.

Treatments

The Panel considered a wide variety of treatments. However, limited data were available for many of the treatments of interest. Ultimately, the Panel decided that it could not distinguish between the different types of TURBT, including repeat TURBT. All forms of TURBT were considered the same. The Panel also considered maintenance therapy versus induction only. A wide variety of induction and maintenance schedules have been used and reported in the literature. The Panel ultimately decided that any treatment administered for a longer time period than an initial induction regimen would be considered as maintenance therapy. Finally, a single postoperative dose of mitomycin C was examined as a third alternative dosing regimen.

Because the issues surrounding the comparison of BCG and mitomycin C maintenance therapy and induction alone were so important, the Panel elected to combine data from the randomized controlled trials included in the original guideline with the data from the current analyses. Nonrandomized studies or studies of other regimens from the earlier guideline were not included.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

To develop the recommendations, the American Urological Association (AUA) Bladder Cancer Clinical Guidelines Panel used an explicit approach to address the relevant factors for choosing among alternative interventions. These factors included outcomes of the interventions, patient preferences, and the relative priorities of interventions given limited health care resources. In developing the guideline, the Panel used scientific evidence to estimate outcomes of treatment modalities as accurately as possible. Panel members themselves served as proxies for patients in considering preferences with regard to health and economic outcomes. The steps taken to develop this guideline included problem definition, literature search, data extraction, systematic evidence combination, guideline generation, approval, and dissemination.

This guideline update was based on the original AUA guideline, *Report on The Management of Non-Muscle-Invasive Bladder Cancer (Stages Ta, T1 and Tis)* published in 1999. The methodology was similar to that used in the previous guideline. The intention was to determine the impact of the various available treatments on outcomes of importance to patients. The efficacy outcomes examined were recurrence of bladder tumors and progression in stage or to cystectomy. The Panel also attempted to estimate the occurrence of side effects and complications of treatments. The Panel focused on treatments given to patients after transurethral resection of bladder tumor (TURBT). It was assumed that all patients had TURBT eradication of all visible tumors. The Panel examined the efficacy of alternative follow-on treatments including repeat TURBT, phototherapy, intravesical chemotherapy, and intravesical immunotherapy. The Panel also considered the impact of tumor stage, grade, multiplicity, and recurrence status on outcomes. Treatments that were not generally available in the United States and were not expected to be approved for general use by the time of the release of the guideline were excluded from the analysis. The Panel also decided not to update outcomes for treatments that were deemed less effective in the previous guideline, namely thiotepa and doxorubicin.

After the evidence was combined and outcome tables were produced, the Panel met to review the results and identify anomalies. From the evidence in the outcome tables and expert opinion, the Panel drafted the treatment guideline. As in the previous guideline, the guideline statements were graded with respect to the degree of flexibility in their application. Although the terminology has changed slightly, the current three levels are essentially the same as in the previous guideline. A "standard" has the least flexibility as a treatment policy; a

"recommendation" has significantly more flexibility; and an "option" is even more flexible. See the "Rating Scheme for the Strength of the Recommendations" field.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

The guideline statements were graded with respect to the degree of flexibility in their application. The three levels of flexibility are defined as follows:

Standard: A guideline statement is a standard if: (1) the health outcomes of the alternative interventions are sufficiently well known to permit meaningful decisions and (2) there is virtual unanimity about which intervention is preferred.

Recommendation: A guideline statement is a recommendation if: (1) the health outcomes of the alternative intervention are sufficiently well known to permit meaningful decisions, and (2) an appreciable but not unanimous majority agrees on which intervention is preferred.

Option: A guideline statement is an option if: (1) the health outcomes of the interventions are not sufficiently well known to permit meaningful decisions, or (2) preferences are unknown or equivocal. Options can exist because of insufficient evidence or because patient preferences are divided and may/should influence choices made.

COST ANALYSIS

A formal cost analysis was not performed and published cost-analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

After the evidence was combined and outcome tables were produced, the American Urological Association (AUA) Bladder Cancer Clinical Guidelines Panel met to review the results and identify anomalies. Additional teleconferences were held to review updates to the outcomes tables based on the problems identified. From the evidence in the outcome tables and expert opinion, the Panel drafted the treatment guideline. The draft was sent to 88 peer reviewers; the Panel revised the document based on the comments received from 38. The guideline was submitted for approval to the Practice Guidelines Committee of the AUA and then to the Board of Directors for final approval.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Grades of the guideline statements (**Standard, Recommendation, Option**) are defined at the end of the "Major Recommendations" field.

The American Urological Association Bladder Cancer Clinical Guidelines Panel based the majority of the following guideline statements on a careful analysis of comparative outcomes from randomized controlled trials. Included were data published after the previous guideline was completed as well as results from previous studies involving transurethral resection of bladder tumor (TURBT) and intravesical therapies. These statements apply to the treatment of patients with nonmuscle invasive transitional cell carcinoma of the bladder including Tis as well as stages Ta and T1 tumors (see Table 1 in the original guideline document for staging of primary tumors in bladder cancer). Inherent in these guideline statements is the importance of individualizing patient diagnostic evaluation and therapy. Some of the treatment paradigms addressed below were not based on data but on Panel experience alone.

In an attempt to recognize commonly encountered clinical variations, the Panel has designated certain example settings as "index patients." In establishing these index patients, the Panel closely examined pressing questions involving the use of intravesical chemotherapy versus immunotherapy and the role of maintenance therapy. Each guideline statement addresses a specific index patient.

For All Index Patients

Standard: Physicians should discuss with the patient the treatment options and the benefits and harms, including side effects, of intravesical treatment. [Based on Panel consensus.]

For Index Patient No. 1: ***A patient who presents with an abnormal growth on the urothelium but who has not yet been diagnosed with bladder cancer***:

Standard: If the patient does not have an established histologic diagnosis, a biopsy should be obtained for pathologic analysis. [Based on Panel consensus.]

Standard: Under most circumstances, complete eradication of all visible tumors should be performed. [Based on Panel consensus.]

Standard: If bladder cancer is confirmed, periodic surveillance cystoscopy should be performed. [Based on Panel consensus.]

Option: An initial single dose of intravesical chemotherapy may be administered immediately postoperatively. [Based on Panel consensus.]

For Index Patient No. 2: ***A patient with small-volume low-grade Ta cancer***

Recommendation: An initial single dose of intravesical chemotherapy may be administered immediately postoperatively. [Based on review of the data.]

For Index Patient No. 3: ***A patient with multifocal and/or large volume, histologically confirmed, low-grade Ta or a patient with recurrent low-grade Ta bladder cancer.***

Recommendation: An induction course of intravesical therapy with bacillus Calmette-Guérin or mitomycin C is recommended for the treatment of these patients with the goal of preventing or delaying recurrence. [Based on review of the data.]

Option: Maintenance bacillus Calmette-Guérin or mitomycin C may be considered. [Based on review of the data.]

For Index Patient No. 4: ***A patient with initial histologically confirmed high-grade Ta, T1, and/or carcinoma in situ bladder cancer.***

Standard: For patients with lamina propria invasion (T1) but without muscularis propria in the specimen, repeat resection should be performed prior to additional intravesical therapy. [Based on review of the data and Panel consensus.]

Recommendation: An induction course of bacillus Calmette-Guérin followed by maintenance therapy is recommended for treatment of these patients. [Based on review of the data.]

Option: Cystectomy should be considered for initial therapy in select patients. [Based on review of the data and Panel consensus.]

For Index Patient No. 5: ***A patient with high- grade Ta, T1, and/or carcinoma in situ bladder cancer which has recurred after prior intravesical therapy.***

Standard: For patients with lamina propria invasion (T1) but without muscularis propria in the specimen, repeat resection should be performed prior to additional intravesical therapy. [Based on review of the data and Panel consensus.]

Recommendation: Cystectomy should be considered as a therapeutic alternative for these patients. [Based on review of the data.]

Option: Further intravesical therapy may be considered for these patients. [Based on review of the data and Panel consensus.]

Definitions:

Rating Scheme for Strength of Recommendations

The guideline statements were graded with respect to the degree of flexibility in their application. The three levels of flexibility are defined as follows:

Standard: A guideline statement is a standard if: (1) the health outcomes of the alternative interventions are sufficiently well known to permit meaningful decisions and (2) there is virtual unanimity about which intervention is preferred.

Recommendation: A guideline statement is a recommendation if: (1) the health outcomes of the alternative intervention are sufficiently well known to permit meaningful decisions, and (2) an appreciable but not unanimous majority agrees on which intervention is preferred.

Option: A guideline statement is an option if: (1) the health outcomes of the interventions are not sufficiently well known to permit meaningful decisions, or (2) preferences are unknown or equivocal. Options can exist because of insufficient evidence or because patient preferences are divided and may/should influence choices made.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence is not specifically stated for each recommendation.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate management of nonmuscle-invasive bladder cancer (stages Ta, T1 and Tis)

POTENTIAL HARMS

- Complications of treatment were combined into several large categories: bladder contracture, epididymitis/prostatitis/urethral infections, hematuria, lower urinary tract symptoms (LUTS), fever/chills/flu symptoms, and systemic infection.
- Lower urinary tract symptoms (including frequency, urgency, dysuria, etc.) were the most common side effects reported with all of the treatment options.

CONTRAINDICATIONS

CONTRAINDICATIONS

Perioperative mitomycin C should not be administered to patients with a known or suspected bladder perforation following transurethral resection of bladder tumor (TURBT) as a small number of serious complications related to mitomycin C extravasation have been reported.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- The final report is intended to provide medical practitioners with a current understanding of the principles and strategies for the management of nonmuscle invasive bladder cancer. The report is based on an extensive

review of available professional literature, as well as clinical experience and expert opinion. Some of the medical therapies currently employed in the management of bladder cancer have not been approved by the U. S. Food and Drug Administration (FDA) for this specific indication. Thus, doses and dosing regimens may deviate from that employed for FDA-approved indications, and this difference should be considered in the risk-versus-benefit assessment.

- This document provides guidance only, and does not establish a fixed set of rules or define the legal standard of care. As medical knowledge expands and technology advances, the guideline will change. Today the guideline statements represent not absolute mandates but provisional proposals or recommendations for treatment under the specific conditions described. For all these reasons, the guideline does not preempt physician judgment in individual cases. Also, treating physicians must take into account variations in resources, and in patient tolerances, needs, and preferences. Conformance with the guideline reflected in this document cannot guarantee a successful outcome.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Bladder Cancer Clinical Guideline Update Panel. Guideline for the management of nonmuscle invasive bladder cancer: (stages Ta, T1, and Tis): 2007 update. Linthicum (MD): American Urological Association Education and Research, Inc; 2007. 133 p. [31 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1999 (revised 2007)

GUIDELINE DEVELOPER(S)

American Urological Association Education and Research, Inc. - Medical Specialty Society

SOURCE(S) OF FUNDING

The American Urological Association (AUA) is the sole source of funding.

GUIDELINE COMMITTEE

Bladder Cancer Clinical Guideline Update Panel

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Members: M. Craig Hall, MD (Chair); Sam S. Chang, MD (Vice-Chair); Guido Dalbagni, MD; Raj Som Pruthi, MD; Paul F. Schellhammer, MD; Jon Derek Seigne, MB; Eila Curlee Skinner, MD; J. Stuart Wolf, Jr., MD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Each panel member disclosed potential conflicts of interest to the AUA. Conflict of interest forms were updated annually or more frequently, as appropriate.

GUIDELINE STATUS

This is the current release of the guideline.

This is an update of a previous version: American Urological Association, Inc. Report on the management of non-muscle-invasive bladder cancer. Baltimore (MD): American Urological Association, Inc.; 1999. 66 p. [108 references]

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the American Urological Association Web site.

Print copies: Available to physicians from the American Urological Association, Inc., 1000 Corporate Boulevard, Linthicum, MD 21090; telephone: (866) RING AUA.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on January 5, 2000. It was verified by the guideline developer on January 14, 2000. This NGC summary was updated by ECRI Institute on February 18, 2008. The updated information was verified by the guideline developer on February 19, 2008.

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