Complete Summary

GUIDELINE TITLE

Management of stage I nonseminomatous testicular cancer: guideline recommendations.

BIBLIOGRAPHIC SOURCE(S)

Hotte S, Mayhew LA, Jewett M, Chin E, Winquist E, Genitourinary Cancer Disease Site Group. Management of stage I nonseminomatous testicular cancer: guideline recommendations. Toronto (ON): Cancer Care Ontario (CCO); 2008 Feb 14. 30 p. (Evidence-based series; no. 3-19). [79 references]

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Stage I (CS I) nonseminomatous testicular cancer (NSGCT)

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Management
Treatment

CLINICAL SPECIALTY

Oncology
Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate the optimal management of patients with clinical stage I (CS I) nonseminomatous testicular cancer (NSGCT) after orchidectomy and staging

TARGET POPULATION

Adults with clinical stage I (CS I) nonseminomatous testicular cancer (NSGCT)

INTERVENTIONS AND PRACTICES CONSIDERED

1. Surveillance with computerized tomography scans (CTs) of the abdomen and pelvis and measurement of blood tumor markers
2. Adjuvant chemotherapy with bleomycin, etoposide, and cisplatin (BEP) or other cisplatin-based regimen
3. Retroperitoneal pelvic lymph node dissection (RPLND)
4. Informing patients of risks and benefits of management options

MAJOR OUTCOMES CONSIDERED

- Relapse-free survival
- Cancer-specific survival
- Overall survival

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Literature Search Strategy

The MEDLINE and EMBASE databases were searched for evidence during the month of May 2007 using the following text, medical subject headings (MeSH), and Excerpta Medica tree terms: 'testicular neoplasms', 'testicular cancer', 'neoplasms, germ cell and embryonal', 'germinoma', 'dysgerminoma', and 'germ cell tumo?r'. The results were combined with the terms 'lymph node excision', 'plnd', 'pelvic lymph node dissection', 'surveillance', 'watchful waiting', 'wait-and-see', 'chemotherapy', and 'drug therapy'. The search results were limited to human studies published from 1981 through to May 2007. The complete MEDLINE and EMBASE search strategies are available in Appendix A of the original guideline document. The proceedings of the annual meeting of the American Society of Clinical Oncology (ASCO) were hand searched for the years 1995 to 2007. The bibliographies of reports were also searched for additional references.

Selection Criteria

Inclusion Criteria

Studies were selected for inclusion in the systematic review if they met the following criteria:

Patient Criteria

- They included patients with clinical stage I nonseminomatous testicular cancer (CS I NSGCT) or a mixed seminoma/nonseminoma diagnosis.
- They included patients who had multiple stages of NSGCT, but outcomes were reported separately for CS I patients.
- They included seminoma patients, but outcomes were reported separately for CS I NSGCT patients.

Patient Outcomes

- They reported survival (10 years or greater), recurrence, toxicity and/or quality of life.

Year of Publication

- They were published from 1981 to present.

Study Designs/Types

- They were clinical practice guidelines, systematic reviews, randomized controlled trials (RCTs), or non-randomized prospective studies.

Exclusion Criteria

Studies were excluded if they:

- Were published in languages other than English, because of a lack of translation resources
- Were conducted in narrow patient groups (e.g., human immunodeficiency virus [HIV]+)

- Examined radiotherapy, as it is no longer used in the treatment of NSGCT

References identified by the literature search were reviewed by three of the authors. All references were reviewed initially by one author, but where there was a question concerning inclusion, advice was sought from two authors.

NUMBER OF SOURCE DOCUMENTS

Of the total 2934 references identified, 285 were obtained for full review. Of those, 37 papers representing 32 unique reports met the selection criteria and include eight clinical practice guidelines, one systematic review, two randomized controlled trials (RCTs), and 21 non-randomized studies.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

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

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Quality Appraisal of Clinical Practice Guidelines

The Appraisal of Guidelines for Research & Evaluation (AGREE) tool was used by two independent raters to evaluate the quality of all the clinical practice guidelines identified by the literature search. While all the AGREE tool domains were considered in the evaluation, the rigour of development domain and the overall rating were considered to be most relevant to this review.

Synthesizing the Evidence

A meta-analysis of overall and treatment-specific (i.e., type of chemotherapy) recurrence rates, if appropriate, was planned. First, 0.5 was added to both the total number of recurrences and the total number of patients for each study, to allow studies with zero recurrences to be included in the meta-analysis. Then, a corrected recurrence proportion was calculated as corrected total recurrences divided by corrected total patients. This proportion was logit transformed, and the standard error was calculated for the logit transformed proportion, as suggested by Lipsey and Wilson and Brown (where p is the corrected proportion, n the corrected number of patients, and L the transformed proportion):

$ES_l = \log_e [p/1\text{-}p]$

and SE(L) the standard error:

SE_l = sqrt [(1/np) + (1/n(1-p))]

The Generic Inverse Variance method of Review Manager 4.2 was used to logit transform proportions. The resulting summary estimates and their corresponding 95% confidence intervals (CI) were back-transformed into proportions. The summary estimates were combined using a random effects model. The meta-analysis results were assessed for heterogeneity by calculating the Chi-square test for heterogeneity and the I^2 percentage. A probability level for the Chi-square statistic of less than or equal to 10% ($p \leq 0.10$) was considered indicative of statistical heterogeneity, and I^2 values of 25%, 50%, and 75% indicative of low, moderate, and high degrees of heterogeneity, respectively.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Few randomized controlled trials (RCTs) are available to inform clinicians on the management of clinical stage I nonseminomatous testicular cancer (CS I NSGCT). Guidelines based on expert opinion are consistent in acknowledging the importance of microscopic vascular or lymphatic invasion (MVI) as a prognostic factor and in stating that CS I NSGCT can be managed with surveillance, adjuvant chemotherapy, retroperitoneal pelvic lymph node dissection (RPLND), or combinations of these approaches. It is generally agreed that all approaches ultimately result in similar cancer cure rates. Cancer cure rates are excellent regardless of the management option selected. Overall and disease-free survival rates are over 95% for all management approaches, even though recurrence rates are higher in the patients managed by surveillance.

To address the efficacy of adjuvant chemotherapy, a meta-analysis of recurrence rate data from eligible trials was performed. These data must be interpreted with caution, as a proportion of patients would be expected to be cured by orchidectomy alone, and, by including them in the calculation of recurrence rates, the true efficacy of chemotherapy to eradicate micrometastatic disease is overestimated. The analysis also does not account for differences in recurrence risk over time. While the lack of statistical heterogeneity might imply a strong consistency among the studies, it actually might more strongly reflect the fact that the numbers of recurrences are very low in all the studies. Finally, there are some limitations to the meta-analysis method used. First, the logit method used to calculate the confidence intervals is a conservative one, and likely overestimates these intervals. Second, the addition of 0.5 to the number of recurrences and total patients, while necessary to perform the meta-analysis, does inflate the resulting estimate of recurrence by a small but not trivial amount, given the small number of recurrences. A sensitivity analysis not reported here suggested that this inflation might be in the order of 0.5%.

In this setting, clinicians expect adjuvant chemotherapy to provide at least 95% efficacy in the eradication of micrometastatic disease. The upper 95% confidence

limits of the estimated recurrence rates exceed 5% for all regimens reported. Closest to this benchmark are two cycles of bleomycin, etoposide, and cisplatin (BEP) or cisplatin, vinblastine, and bleomycin (PVB) with an upper confidence limit of 7%. The small numbers of patients treated with each type of adjuvant approach certainly accounts for much of this lack of precision; however, it must be remembered that these estimates represent a "best case" scenario, and inadequate antitumour efficacy cannot be ruled out. The limitations of these data would support a default approach using three cycles of adjuvant BEP, as this is considered adequate therapy for patients with good prognosis metastatic NSGCT who are at higher risk of disease recurrence compared to CS I patients. However, the case for two cycles of adjuvant BEP is supported by the observation that two of the eight recurrences in this group consisted of mature teratoma only. There is also indirect evidence from another RCTl. Williams et al randomized 195 patients with PS II NSGCT to observation or two cycles of adjuvant BEP. The relapse rate in observation patients was 49% compared to 6% in patients treated with adjuvant chemotherapy. Five of the six recurrences in the adjuvant chemotherapy arm occurred before adjuvant chemotherapy was given. Evaluating only patients who received adjuvant chemotherapy, the recurrence rate was 1.1% (95% confidence interval [CI], 0.15% to 7.31%). Based on these additional data, it was the consensus of the Genitourinary Disease Site Group (GU DSG) that two cycles of BEP (with etoposide 500 mg/m^2/cycle) represented adequate adjuvant chemotherapy in CS I NSGCT patients.

With respect to RPLND, because there is very little evidence concerning its efficacy in CS I NSGCT patients, a recommendation cannot currently be made. With respect to primary surveillance as a management option, while surveillance regimes require much more rigorous follow-up than does adjuvant treatment, including more frequent physician visits, computerized tomography (CT) scans, chest x-rays, and serum tumour marker tests, surveillance is generally associated with a lower level of toxicity and has comparable cancer-specific survival. Alternatively, some patients prefer adjuvant treatment, as they may find it difficult to adhere to the strict follow-up regime required by surveillance, or feel like they are waiting for a recurrence ("sword of Damocles" syndrome).

As salvage chemotherapy is able to provide a cancer cure with prompt detection of recurrence in virtually all patients, the Genitourinary Disease Site Group (GU DSG) consensus was that all CS I NSGCT patients be offered surveillance, provided they are considered appropriate for this approach and do not prefer immediate adjuvant treatment. Although not part of the scope of this review, there is evidence from a randomized trial conducted in patients with metastatic disease showing better survival rates among patients treated in multidisciplinary centres of excellence compared to patients treated in community centres. Therefore, it is suggested that primary surveillance be done in collaboration with a cancer centre experienced in the treatment of testicular cancer. The appropriate number of CT scans recommended with primary surveillance is unclear, but two scans at three and 12 months may be adequate in CS I patients without MVI. For patients who decline or who are not candidates for surveillance, immediate adjuvant chemotherapy with two cycles of BEP is recommended. RPLND may also be considered for this subset of men, but its benefits as an alternative or in addition to adjuvant chemotherapy are unclear. The philosophy underpinning these recommendations is to avoid the overtreatment of men cured by

orchidectomy while maintaining the highest possible cancer cure rate in those destined to experience a recurrence.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

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

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Development and Internal Review

This evidence-based series was developed by the Genitourinary Disease Site Group (GU DSG) of Cancer Care Ontario's Program in Evidence-based Care (CCO's PEBC).

External Review

This guideline was reviewed in draft form at the 1st Canadian Germ Cell Cancer Consensus Conference on October 19-20, 2007 in King City, Ontario. Conference attendees consisted of 39 Canadian experts in the field from eight different Canadian provinces (there were no attendees from Prince Edward Island or Newfoundland). The attendees included 14 medical oncologists, 13 radiation oncologists, 11 urologists/urological surgeons, and one pathologist. Also present were one nurse practitioner, one radiation technician, one methodologist from the CCO's PEBC, two invited expert physicians from the United States, two invited expert physicians from Europe, three patients, and the mother of a patient who had passed away from testicular cancer.

Conference attendees were given a presentation on the Ontario draft guideline, as well as presentations on guidelines from Europe and the United States. Conference attendees were given the opportunity to discuss the different guidelines and ask questions of the presenters, and were presented with paper copies of the guidelines. The following day, attendees were asked to come to a consensus concerning recommendations for treatment.

As the conference attendees included a majority of those who would be approached for practitioner feedback, using the PEBC's standard external review methods, no additional practitioner feedback was solicited for this report beyond that obtained at the conference.

Report Approval Panel Review

The draft report was reviewed by the PEBC Report Approval Panel, which consists of three members, including an oncologist, with expertise in clinical and methodology issues.

This report reflects the integration of feedback obtained through the external review process with final approval given by the Genitourinary Disease Site Group and the Report Approval Panel of the PEBC.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- Patients should be made aware of all treatment options and the risks and benefits surrounding each of these options.
- The consensus opinion of the Genitourinary Disease Site Group (GU DSG) is that primary surveillance is recommended for all patients with clinical stage I nonseminomatous testicular cancer (CS I NSGCT), with treatment at relapse. When a primary surveillance approach is adopted, patients should be informed of their estimated risk of recurrence and the need for frequent ongoing investigations, including blood tumour markers and computerised tomography (CT) scans of the abdomen and pelvis, to monitor for recurrence.
- Patients with CS I NSGCT should be assessed and have management plans developed at multidisciplinary centres with experience in the treatment of testicular cancer.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by clinical practice guidelines, one systematic review, randomized controlled trials (RCTs), and non-randomized studies.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Eight clinical practice guidelines were reviewed and their recommendations for management of clinical stage I nonseminomatous testicular cancer (CS I NSGCT) compared.
    - One guideline reported that consensus was not achieved. There was general agreement that adjuvant radiotherapy should not be used and that appropriate management options included primary surveillance, adjuvant chemotherapy, and retroperitoneal lymphadenectomy (RPLND).

    - All the guidelines recognized the importance of the presence or absence of microscopic vascular or lymphatic invasion (MVI) in the primary tumour as a prognostic factor, and three recommended a risk-stratified approach to management based on this.
    - For low-risk patients (MVI absent), all the guidelines recommended surveillance for patients considered appropriate and motivated for this approach. Some variability in recommended surveillance schedules was present.
    - For high-risk patients (MVI present), three guidelines recommended adjuvant chemotherapy with two cycles of bleomycin, etoposide and cisplatin (BEP), three recommended primary surveillance, and three recommended adjuvant chemotherapy or RPLND.
    - Five guidelines recommended that all patients be treated similarly regardless of risk factor.
- There are no randomized controlled trials (RCTs) that compare the most relevant treatment options for the management of CS I NSGCT.
- Two RCTs were identified that addressed the management of CS I NSGCT:
    - In the trial of chemotherapy (one cycle of adjuvant BEP) versus RPLND, the authors concluded that, while BEP was more efficacious, the follow-up period was short, and generalizability to patients with high-risk features remained uncertain.
    - In the trial of two computerized tomography (CT) scans versus five CT scans in primary surveillance, the authors concluded that the lower frequency of CT scans did not increase the risk of relapse among patients with poor-prognosis disease.
- Twenty-one additional non-randomized studies were reviewed, including eight chemotherapy, 11 surveillance, and two RPLND studies, and three risk-adapted studies that reported findings for more than one treatment type. Patients managed by primary surveillance were found to have equivalent cancer-specific survival rates to those given adjuvant treatment.
- Although not part of the focus of this report, a randomized trial conducted in patients with metastatic disease showed that patients treated in multidisciplinary centres of excellence had better survival rates than those treated in community centres.

POTENTIAL HARMS

Toxicities of treatment

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- As cancer cure rates appear equal with primary surveillance, adjuvant chemotherapy, and retroperitoneal lymphadenectomy (RPLND), patient preference with respect to the risk of recurrence and the timing and toxicities of treatment must be considered.
- For patients who prefer immediate treatment, or who are unsuitable for primary surveillance, adjuvant chemotherapy with two cycles of bleomycin, etoposide (500 mg/m^2/cycle), and cisplatin (BEP) is recommended.
- Surgeons involved in the development of this guideline suggest RPLND may be a useful option for patients at high risk of relapse. There is currently not

enough evidence from prospective trials to support or refute this position. Patients who undergo RPLND should have their surgery performed by surgeons who are experienced with the procedure. Otherwise, RPLND should be offered in the context of a clinical trial.
- Patients with no clinical evidence of nonseminomatous testicular cancer (NSGCT) after orchidectomy other than persistently elevated or rising serum tumour markers should be considered for management as if they have metastatic disease.
- Patients undergoing surveillance could be investigated with only two computerized tomography (CT) scans at three and 12 months.
- Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

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

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Hotte S, Mayhew LA, Jewett M, Chin E, Winquist E, Genitourinary Cancer Disease Site Group. Management of stage I nonseminomatous testicular cancer: guideline recommendations. Toronto (ON): Cancer Care Ontario (CCO); 2008 Feb 14. 30 p. (Evidence-based series; no. 3-19). [79 references]

ADAPTATION

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

DATE RELEASED

2008 Feb 14

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Genitourinary Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The authors of this guideline were asked to disclose potential conflicts of interest relating to this systematic review and declared there were none.

GUIDELINE STATUS

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Management of stage I nonseminomatous testicular cancer: guideline recommendations. Summary. Toronto (ON): Cancer Care Ontario (CCO), 2008 Feb. 6 p. (Practice guideline; no. 3-19). Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on July 16, 2008. The information was verified by the guideline developer on August 20, 2008.

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