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Evidence-Based Series 3-19 EDUCATION AND INFORMATION 2012

Management of Stage I Nonseminomatous Testicular Cancer

*S. Hotte, L.A. Mayhew, M. Jewett, J. Chin, E. Winquist, and
Members of the Genitourinary Cancer Disease Site Group*

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: February 14, 2008

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Section 1: Guideline Recommendations

Section 2: Evidentiary Base

Section 3: EBS Development Methods and External Review Process

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Evidence-Based Series #3-19: Section 1

Management of Stage I Nonseminomatous Testicular Cancer: Guideline Recommendations

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Section 1: Guideline Recommendations

Section 2: Evidentiary Base

Section 3: EBS Development Methods and External Review Process

QUESTION

What is the optimal management of patients with clinical stage I (CS I) nonseminomatous testicular cancer (NSGCT) after orchidectomy and staging? Outcomes of interest include cancer cure, long-term toxicity, and quality of life.

TARGET POPULATION

Adults with CS I NSGCT.

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 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.

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/m²/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 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 CT scans at three and 12 months.

KEY EVIDENCE

- Eight clinical practice guidelines were reviewed (1-9) and their recommendations for management of 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 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 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 (10-11).
 - In the trial of two 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 (12).
- Twenty-one additional non-randomized studies were reviewed (13-32), 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 (33).

RELATED GUIDELINES

- Practice Guideline Report #3-5: *Surveillance Programs for Early Stage Non-seminomatous Testicular Cancer*.
- Evidence-based Series #3-18: *Management of Stage 1 Seminoma*.

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Evidence-Based Series #3-19: Section 2

Management of Stage I Nonseminomatous Testicular Cancer: Evidentiary Base

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QUESTION

What is the optimal management of patients with clinical stage I (CS I) nonseminomatous testicular cancer (NSGCT) after orchidectomy and staging? Outcomes of interest include cancer cure, long-term toxicity, and quality of life.

INTRODUCTION

Testicular cancer is uncommon, affects primarily young men, and is potentially highly curable with chemotherapy even when widely metastatic. Approximately 830 cases of testicular cancer were expected in Canada in 2007 [1], and about half of these are NSGCT. The incidence of testicular cancer rises through adolescence, peaks at ages 25 to 29, and declines thereafter [2]. Between 1964 and 1996, the incidence of testicular germ cell cancer in Ontario increased by 59.4% from 4.01 to 6.39 per 100,000, with an annual increase of about 2% for nonseminoma. Rates were highest among males aged 15 to 29 years. Testicular cancer is classified as nonseminoma if histologically the tumour contains any component of embryonal carcinoma, yolk sac tumour, choriocarcinoma, or immature teratoma. Patients with histologically pure seminoma but elevated blood alpha-feto protein (AFP) or highly elevated β -human chorionic gonadotropin (β -hCG) levels may also be considered to have nonseminoma. Men are considered to have CS I disease after radical orchidectomy when imaging investigations (including a computerized tomography [CT] scan of the abdomen and pelvis) and blood tumour markers (AFP, β -hCG, lactate dehydrogenase [LDH]) are negative. Pathological stage I disease (PS I) is similarly defined except that the men have also had a retroperitoneal lymphadenectomy (RPLND) without pathological evidence of metastases. If metastases are present and completely excised, the patient is considered to have pathological stage II (PS II) disease. Most men with CS I NSGCT are cured with their orchidectomy; however, a significant minority (20 to 30%) of patients will experience metastatic recurrence and require additional treatment for cure. With modern chemotherapy, long-term cure rates in men with good prognosis metastatic NSGCT approach 100% [3]. Thus, men with CS I and PS II NSGCT provide a unique circumstance in solid tumour cancer care, where the desire to optimize cure

and expeditiously allow all patients to return to a usual life must be weighed against the need for all patients to be treated and the potential long-term and permanent adverse effects of these treatments. Historically, RPLND has been used for both staging and therapeutic purposes, with patients with PS II disease being offered adjuvant chemotherapy. However, with the emergence of highly effective cisplatin-based chemotherapy, the necessity of RPLND has been questioned, and either adjuvant chemotherapy treatment alone or active surveillance, with treatment held in reserve for those who relapse, has become the management option for CS I NSGCT, recommendations from contemporary clinical practice guidelines, as well as data from randomized clinical trials (RCTs) and clinical reports, were reviewed to create a clinical practice guideline.

METHODS

The evidence-based series (EBS) guidelines developed by Cancer Care Ontario's Program in Evidence-Based Care (PEBC) use the methods of the Practice Guidelines Development Cycle [4]. For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by three members of the PEBC Genitourinary Disease Site Group (GU DSG) and one methodologist.

This systematic review is a convenient and up-to-date source of the best available evidence on the management of CS I NSGCT. The body of evidence in this review is primarily comprised of prospective trials and retrospective long-term toxicity data. That evidence forms the basis of a clinical practice guideline developed by the Genitourinary DSG found in Section 1 of this evidence-based series. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

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 tumor'. 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. 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 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, 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., 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 (LM), but where there was a question concerning inclusion, advice was sought from two authors (SH, EW).

Quality Appraisal of Clinical Practice Guidelines

The Appraisal of Guidelines for Research & Evaluation (AGREE) tool [5] 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 [6] and Brown [7] (where p is the corrected proportion, n the corrected number of patients, and L the transformed proportion):

$$ES_l = \log_e \left[\frac{p}{1 - p} \right]$$

and $SE(L)$ the standard error:

$$SE_l = \sqrt{\frac{1}{np} + \frac{1}{n(1 - p)}}$$

The Generic Inverse Variance method of Review Manager 4.2 [8] 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.

RESULTS

Literature Search Results

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 RCTs, and 21 non-randomized studies (Table 1).

Table 1: Literature search results.

Study Type	Number (references)
Clinical Practice Guidelines	8 [9-17]
Systematic Reviews <i>Management of Testicular Cancer</i>	1 [18]
Randomized Controlled Trials <i>BEP vs. RPLND</i> <i>Surveillance 2-CT vs. surveillance 5-CT</i>	1 [19,20] 1 [21]
Non-randomized Studies <i>Chemotherapy</i> <i>Surveillance</i> <i>RPLND</i>	8* [22-31] 11* [24,27,30,32-40] 2* [27,41]

Abbreviations: BEP – bleomycin, etoposide and cisplatin; CT – computed tomography; RPLND - retro retroperitoneal lymphadenectomy; vs. – versus.

* Three studies of risk-adapted management appear in multiple treatment categories.

Clinical Practice Guidelines

Eight guidelines concerning the management of NSGCT were identified [9-17] and were evaluated using the AGREE tool. The quality of the guidelines was modest, with AGREE scores for the rigour quality domain ranging between 14.3% and 61.9%. No guideline was recommended without provisos by either reviewer (see Appendix B for the complete evaluation).

Guideline Recommendations

The guideline recommendations are summarized in Table 2. Some of the guidelines were based on the consensus of experts, while others attempted an evidence-based approach. There was some variability in the recommended surveillance schedules. Additionally, some guidelines listed treatments in order of preference, while others appear to give equal weight to all treatments. 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. Based on the results of the AGREE quality evaluation, the authors decided that none of the guidelines were suitable for adaptation or endorsement in Ontario.

Table 2: Guideline recommendations.

Guideline	Recommendations							
	Radiotherapy should not be used.	Appropriate management options were surveillance, chemotherapy, and RPLND.	Recommended surveillance for appropriate low risk patients.	Recommended chemotherapy with 2 cycles of BEP for high-risk patients.	Recommended primary surveillance for high-risk patients.	RPLND for high-risk patients.	Recommended a risk-adapted approach.	Recommended that all patients should be treated similarly.
NCCN (2007) [9]	X	X	X					X
EAU (2005, 2001) [10]	X	X	X	X	X	X	X	
ESMO (2005) [11]	X	X	X	X	X	X	X	
CCNS (2005) [12]	X	X	X					X
EGCCCG (2004) [13]	X	X	X	X	X	X	X	
NICE (2002) [14,15]	X	X	X					X
Interdisciplinary Consensus on Diagnosis and Treatment of Testicular GCT (2001) [16]	X	X	X					X
Segal (2001) [17]	X	X	X					X

Abbreviations: BEP – bleomycin, etoposide and cisplatin; CCNS – Cancer Care Nova Scotia; EAU – European Association of Urology; EGCCCG -European Germ Cell Cancer Consensus Group; ESMO –European Society for Medical Oncology; GCT – germ-cell tumour; NCCN – National Comprehensive Cancer Network; NICE - National Institute for Clinical Excellence; RPLND - retro retroperitoneal lymphadenectomy.

Systematic Reviews

The one relevant systematic review identified, a Cochrane systematic review by Shelley et al [18], addressed the management of all stages and types of testicular germ cell cancer. This report is not considered further, however, as the majority of included studies either did not meet the selection criteria of this review or had more recent data available.

Randomized Controlled Trials

Two RCTs met the inclusion criteria; one compared bleomycin, etoposide, and cisplatin (BEP) to RPLND [19,20] and the other compared two surveillance programs [21]. No studies were identified that compared surveillance to CT or to RPLND. Generally, the overall quality of the RCTs was poor (Table 3). Given the nature of the treatment options compared, blinding to treatment allocation was not feasible in either trial.

Table 3: Methodological quality of eligible randomized trials.

Trial Characteristic	Rustin (2007) [21]	Albers (2006) [19,20]
Description of random allocation	Met	Not Recorded
Power	90% power 5% significance One-sided	80% power 5% significance One-sided
Planned sample size	400 patients required	360 patients required
Sample size met	Met	Not Met
Intention-to-treat analysis	Not Recorded	No
Details of withdrawals and exclusions	Unclear	Unclear

BEP versus RPLND

An RCT by Albers et al [19,20] compared one course of adjuvant BEP (n=178) to RPLND (n=188). In both arms, the percentage of patients with MVI was less than 50%. At a median follow-up of 47 months, two recurrences occurred in the chemotherapy arm (1.1%) and 14 occurred in the RPLND arm (7.5%) (p=0.0025). Chemotherapy was well tolerated. The authors concluded that, while BEP was more efficacious than RPLND, the follow-up period was short and whether the results are generalizable to patients with high-risk features remains uncertain. Survival outcomes are summarized in Table 4.

Surveillance 2-CT Scans versus Surveillance 5-CT Scans

Rustin et al [21] randomized 414 patients in a 3:2 ratio to surveillance with either two CT scans (2-CT) (at three and 12 months) or five (5-CT) (at three, six, nine, 12, and 24 months) to determine whether the number of required CT scans could be reduced without increasing the risk of relapse in the proportion of patients with intermediate or poor prognosis disease. The relapse-free rate at two years was 84.7% (95% CI, 79.5% to 88.8%) in the 2-CT group and 79.6% (95% CI, 72.6% to 85.1%) in the 5-CT arm (two-sided log-rank p=0.21). Considering all randomized patients, a total of nine relapses were identified by the 12-month CT scan, with two relapses occurring after that time. No relapses were identified by the 24-month CT scan. Survival outcomes are summarized in Table 4.

A subgroup analysis showed patients with MVI had a two-year relapse-free rate of 67.9% (95% CI, 46% to 82%) in the 2-CT arm and 63.6% (95% CI, 36% to 82%) in the 5-CT arm. In contrast, patients without MVI had a two-year relapse rate of 86.7% (95% CI, 81% to 91%) in the 2-CT arm and 81.4% (95% CI, 74% to 87%) in the 5-CT arm.

There were no relapses among patients with poor prognosis disease; however, three patients had intermediate prognosis at relapse. Two occurred in the 2-CT arm and one in the 5-CT arm. Considering all randomized patients, the relapse rate among intermediate-risk patients was 0.8% (90% CI, 0.14% to 2.5%) with 2-CT scans and 0.6% (90% CI, 1.2% to 1.6%) with 5-CT scans, a difference of 0.2%.

The authors concluded that, because reducing the number of CT scans was associated with a very minute increase ($\leq 1.6\%$) in relapses among patients with intermediate or poor prognosis disease, CT scans at three and 12 months after orchidectomy should be considered a reasonable option in low-risk patients.

Table 4: Survival data from eligible randomized trials.

Trial	Relapse-free Survival	Cancer-specific Survival	Overall Survival
Rustin (2007) [21] N=414	At 2 years median follow-up: 2-CT: 84.7% 5-CT: 79.6%	At 40 months median follow-up: 100%	At 40 months median follow-up: 100%
Albers (2006) [19,20] N=346	At 5 years: BEP: 98.9% RPLND: 92.5%	At 5 years: 100%	At 5 years: 100%

Abbreviations: BEP - bleomycin, etoposide, and cisplatin; RPLND - retroperitoneal pelvic lymph node dissection.

Non-randomized Studies

Chemotherapy

Eight studies (reported in ten papers) were identified that examined the use of chemotherapy in CS I NSGCT [22-31]. Five of those were single arm studies [22,25,26,28,31], and three were chemotherapy arms of risk-adapted management trials [24,27,29]. Six examined PVB (cisplatin, vinblastine, and bleomycin) or BEP [24,26-29,31], one assessed CEB (carboplatin, etoposide, and bleomycin) [25], and one studied BOP (bleomycin, vincristine, and cisplatin) [22,23]. Survival outcomes are summarized in Table 5.

Table 5: Survival data from non-randomized chemotherapy studies.

Trial	Chemotherapy/ No. of Cycles (N)	Relapse-free Survival	Cancer-specific Survival	Overall Survival
Dearnaley (2005) [22,23] N=115	BOP/2	At 5 years: 98.3% (95% CI, 95.5%-99.9%)	N/A	N/A
Klepp * (2003) [24] N=291	BEP/1 (152) BEP/2 (40) PVB/1 (43) PVB/2 (56)	At 46 months median follow-up: 96.3%*	At 46 months median follow-up: 100%	At 46 months median follow-up: 100%
Pectasides (2003) [25] N=52	CEB/2	At 5 years: Stage I: 100% Stage IM: 93%	At 5 years: Stage I: 100% At 112 months median follow-up: Overall: 96% Stage I: 100% Stage IM: 93%	At 5 years: Stage I: 100% Stage IM: 97% At 112 months median follow-up: Overall: 96% Stage I: 100% Stage IM: 93%
Böhlen (1999) [26] N=60	BEP/2, PVB/2	At 93 months: 95%	At 93 months: 100%	At 93 months: 100%
Klepp * (1997) [27] N=34	BEP/3	At 40 months median follow-up: 97%	At 40 months median follow-up: 100%	At 40 months median follow-up: 100%
Cullen (1996) [28] N=114	BEP/2	At 2 years: 98.4% At 4 years median follow-up: 98.4%	At 4 years median follow up: 99.1%	At 4 years median follow up: 99.1%
Pont * (1996) [29,30] N=29	BEP/2	At median 79 months: 93.1%	At median 79 months: 96.6%	At median 79 months: 93.1%
Studer (1993) [31] N=43	BEP/2	At 42 months median follow-up: 97.6%	At 42 months median follow-up: 100%	At 42 months median follow-up: 100%

Abbreviations: BEP – bleomycin, etoposide and cisplatin; BOP – bleomycin, vincristine, and cisplatin; CEB – cisplatin, etoposide and bleomycin; n/a - not available; PVP – cisplatin, vinblastine and bleomycin.

* Indicates single arm of a risk-adapted study.

Meta-analysis

To assess the efficacy of adjuvant chemotherapy on overall and treatment-specific recurrence rates, a meta-analysis of eligible studies was performed (see description of Methods on p. 3). One RCT and seven non-randomized studies with ten treatment arms, and a total of 873 evaluable patients contributed to the meta-analysis [19,20,22,24-29]. Because the RCT compared adjuvant chemotherapy to RPLND, only the chemotherapy arm was included in the meta-analysis. Although the follow-up times of the included studies varied (as shown in Table 5), all had sufficient follow-up that almost all recurrences that would occur among these patients were included.

Across the eight studies, 23 recurrences were reported, corresponding to an overall estimated recurrence rate of 3.8% (95% CI, 2.6% to 5.5%; $p=0.42$; $I^2=2.6\%$). For patients treated with BEP or PVB, the estimated recurrence rates were 3.9% (95% CI, 1.6% to 9%), 3.9% (95% CI, 2.1% to 7%), and 7.2% (95% CI, 2.1% to 22.1%) for one, two, and three cycles of adjuvant chemotherapy, respectively. Two recurrences with two cycles of BEP or PVB and one with three cycles of BEP were pure mature teratoma. For patients treated with two cycles of BOP or CEB, the estimated recurrence rates were 2.2% (95% CI, 0.6% to 7.2%) and 1% (95% CI, 0.1% to 13.5%), respectively. In each analysis, no statistical heterogeneity was detected, with the exception of the subgroup of trials that examined one cycle of BEP/PVB ($p=0.10$; $I^2=57\%$).

Surveillance

Eleven non-randomized trials of surveillance were identified that met the selection criteria [24,27,30,32-40]. Across those studies, a total of 1768 patients were evaluated; however, there may be an overlap of patients in some reports. After a median follow-up range of 19.5 to 76 months, 378 recurrences were reported (21.4%), and 11 contralateral testicular tumours (0.6%) were also detected. A meta-analysis of the recurrence rate data was not performed because of the variability in the risk categories of patients included in the 11 studies. Across the studies, 13 deaths from testicular cancer were reported, along with seven other deaths. One of those deaths was due to treatment toxicity during salvage treatment. Survival outcomes are summarized in Table 6.

Table 6: Survival data from non-randomized surveillance studies.

Trial	Relapse-free Survival	Cancer-specific Survival	Overall Survival
Duran (2007) [32,33] N=305	At 5 years: Overall: 75% Initial group: 67.4% Recent group: 81.1%	At 5 years: Initial group: 99.3% Recent group: 99.2%	At 5 years: Initial group: 97% Recent group: 98.4%
Klepp * (2003) [24] N=328	At 46 months median follow-up: 87.8%*	At 46 months median follow-up: 100%	At 46 months median follow-up: 98.8%
Colls (1999) [34] N=248	At 53 months median follow-up: 72%	At 53 months median follow-up: 98.4%	At 53 months median follow-up: 97.6%
Klepp * (1997) [27] N=106	At 40 months median follow-up: 78%	At 40 months median follow-up: 100%	At 40 months median follow-up: 100%
Read (1992) [35] N=396	At 5 years: 73%	At 5 years: 99%	At 5 years: 98%
Sturgeon (1992) [36] N=105	At 5 years: 64.8%	At 5 years: 99%	At 5 years: 99%
Pont * (1990) [30] N=22	At 30 months median follow-up: 95.4%	At 30 months median follow-up: 100%	At 30 months median follow-up: 100%
Peckham (1987) [37] N=132	At 43 months median follow-up: 73%	At 43 months median follow-up: 99.2	At 43 months median follow-up: 99.2
Pizzocaro (1986) [38] N=59	At 30 months median follow up: 69.5%	At 30 months median follow up: 98.3%	At 30 months median follow up: 98.3%
Sogani (1984) [39] N=45	At 19.5 months median follow up: 80%	At 19.5 months median follow up: 100%	At 19.5 months median follow up: 100%
Read (1983) [40] N=45	76%¶	100%¶	100%¶

¶ Median follow up time not given. Range 6-39 months.

* Indicates single arm of a risk-adapted study.

RPLND

Two non-randomized studies were identified that examined the use of RPLND as adjuvant treatment for CS I NSGCT [27,41]. Across the two studies, 344 patients were followed for a median time ranging from 21 to 40 months, and a total of 41 recurrences were found. There was one death from testicular cancer and one other death from unrelated causes. Survival outcomes are summarized in Table 7.

Table 7: Survival data from non-randomized RPLND studies.

Trial	Relapse-free Survival	Cancer-specific Survival	Overall Survival
Klepp * (1997) [27] N=109	At 40 months median follow-up: 88.1%	At 40 months median follow-up: 100%	At 40 months median follow-up: 100%
Weissbach (1990) [41] N=235	At 30 months median follow-up: Modified: 83% Radical: 85%	At 21 months median follow-up: 99.6%	At 21 months median follow-up: 99.1%

* Indicates single arm of a risk-adapted study.

Long-term Outcomes

Studies examining important long-term outcomes relevant to testicular cancer (e.g., long-term survival, quality of life, sexual function and health, adverse events, toxicity related to therapy) were indentified by the primary literature search. However, these studies provided virtually no information on the disease stage of included patients. While long-term data are extremely important to understanding testicular cancer as a whole, none of the identified studies met the patient eligibility criteria specific to this review, and there is currently little information on the long-term outcomes of patients with CS I NSGCT. In addition, it is unclear what can be taken from the identified data and applied to decisions specific to patients with CS I NSGCT. A recommendation has been put forward to the GU DSG to consider this topic for a separate guideline.

DISCUSSION

Few RCTs are available to inform clinicians on the management of CS I NSGCT. Guidelines based on expert opinion are consistent in acknowledging the importance of MVI as a prognostic factor and in stating that CS I NSGCT can be managed with surveillance, adjuvant chemotherapy, 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 [7]. 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 BEP or 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 RCT. Williams et al [42] 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% CI, 0.15% to 7.31%). Based on these additional data, it was the consensus of the GU DSG that two cycles of BEP (with etoposide 500 mg/m²/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, 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 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 [43]. 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.

CONFLICT 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.

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Appendix A: Literature search strategies.

MEDLINE*

1	exp **Neoplasms, Germ Cell and Embryonal"/	58	phase iv.mp.
2	germ cell tumo?r.mp.	50	plnd.mp.
3	intratubular germ cell neoplasm.mp.	51	drug therapy/ or exp chemoprevention/ or exp
4	exp *Seminoma/	52	chemotherapy, adjuvant/ or exp drug therapy, combination/
5	seminoma.mp.	53	drug therapy.mp.
6	exp *Germinoma/	54	chemotherapy.mp.
7	germinoma.mp.	55	or/43-53
8	exp *Dysgerminoma/	56	42 and 54
9	dysgerminoma.mp.	57	phase ii.mp.
10	exp *Carcinoma, Embryonal/	58	phase iii.mp.
11	embryonal carcinoma.mp.	59	phase iv.mp.
12	exp *Endodermal Sinus Tumor/	60	phase 2.mp.
13	yolk sac tumo?r.mp.	61	phase 3.mp.
14	exp *Choriocarcinoma, Non-gestational/ or exp	62	phase 4.mp.
	*Choriocarcinoma/	63	clinical trial:.mp. or exp Clinical Trial/
15	Choriocarcinoma.mp.	64	controlled clinical trial.mp. or exp Controlled Clinical Trial/
16	exp *Trophoblastic Tumor, Placental Site/	65	randomized controlled trial:.mp. or exp Randomized
17	placental site trophoblastic tumo?r.mp.		Controlled Trials/
18	exp *Teratoma/	66	randomized trial.mp.
19	teratoma.mp.	67	random allocation.mp. or exp Random Allocation/
20	polyembryoma.mp.	68	rct.mp.
21	exp *Sex Cord-Gonadal Stromal Tumors/	69	single blind.mp.
22	sex cord-stromal tumo?r.mp.	70	exp Single-Blind Method/ or single-blind.mp.
23	exp *Leydig Cell Tumor/	71	exp Double-Blind Method/ or double blind.mp.
24	leydig Cell Tumo?r.mp.	72	double-blind.mp.
25	exp *Sertoli Cell Tumor/	73	triple blind.mp.
26	sertoli cell tumo?r.mp.	74	triple-blind.mp.
27	exp *Granulosa Cell Tumor/	75	practice guideline:.mp. or exp Practice Guideline/
28	granulosa cell tumo?r.mp.	76	exp Practice Guidelines/ or clinical guideline.mp.
29	exp *Gonadoblastoma/	77	exp Meta-Analysis/
30	gonadoblastoma.mp.	78	meta-anal:.mp.
31	exp *Sarcoma/ or sarcoma.mp.	79	metanal:.mp.
32	plasmacytoma.mp. or exp *Plasmacytoma/	80	metaanal:.mp.
33	lymphoma.mp. or exp *Lymphoma/	81	meta anal:.mp.
34	granulocytic sarcoma.mp. or exp *Sarcoma, Granulocytic/	82	systematic review.mp. or exp "Review Literature"/
35	exp *Adenocarcinoma/ or adenocarcinoma of the rete	83	evidence-based medicine.mp. or exp Evidence-Based
	testis.mp.		Medicine/
36	exp *Carcinoma/ or carcinoma.mp.	84	systematic overview.mp.
37	exp *Mesothelioma/ or malignant mesothelioma.mp.	85	exp databases, bibliographic/ or exp pubmed/ or exp
38	or/1-37	86	medline/
39	testicular neoplasm.mp. or exp *Testicular Neoplasms/	87	medline.ab.
40	testicular cancer.mp.	88	embase.ab.
41	39 or 40	89	quantitative overview.mp.
42	38 and 41	90	quantitative syntheses.mp.
43	radiation treatment.mp.	91	or/56-88
44	exp Radiotherapy, Adjuvant/ or exp Radiotherapy/ or	92	prospective.mp. or exp Prospective Studies/
	radiotherapy.mp.	93	exp Retrospective Studies/ or retrospective.mp.
45	surveillance.mp.	94	exp Cohort Studies/ or cohort.mp.
46	watchful waiting.mp.	95	case control stud:.mp.
47	wait-and-see.mp.	96	exp Follow-Up Studies/
48	(wait and see).mp.	97	exp Longitudinal Studies/ or longitudinal.mp.
49	exp Lymph Node Excision/ or pelvic lymph node	98	case control.mp.
	dissection.mp.	99	cohort anal.mp.
50	plnd.mp.	100	comparative stud:.mp.
51	drug therapy/ or exp chemoprevention/ or exp	101	or/90-98
	chemotherapy, adjuvant/ or exp drug therapy, combination/		89 or 99
52	drug therapy.mp.		55 and 100
53	chemotherapy.mp.		
54	or/43-53		
55	42 and 54		
56	phase ii.mp.		
57	phase iii.mp.		

*This search is a combined search strategy for Evidence-based Series #3-19 and #3-18 (seminoma).

EMBASE*

- 1 exp *Seminoma/ or exp *Germ Cell Tumor/ or exp *Testis Cancer/ or exp *Testis Tumor/
- 2 germ cell tumor?.mp.
- 3 intratubular germ cell neoplasia.mp.
- 4 seminoma.mp.
- 5 germ cell tumor?.mp.
- 6 germinoma.mp.
- 7 dysgerminoma.mp. or exp *DYSGERMINOMA/
- 8 embryonal carcinoma.mp. or exp *Embryonal Carcinoma/
- 9 yolk sac tumor?.mp. or exp *Yolk SAC Tumor/
- 10 choriocarcinoma.mp. or exp *CHORIOCARCINOMA/
- 11 exp *placental site trophoblastic tumor/ or placental site trophoblastic tumor?.mp.
- 12 exp *TESTIS TERATOMA/ or teratoma.mp.
- 13 polyembryoma.mp.
- 14 sex cord-stromal tumor?.mp. or exp *Sex Cord Tumor/
- 15 leydig cell tumor?.mp. or exp *Leydig Cell Tumor/
- 16 sertoli cell tumor?.mp. or exp *Sertoli Cell Tumor/
- 17 granulosa cell tumor?.mp. or exp *Granulosa Cell Tumor/
- 18 gonadoblastoma.mp. or exp *GONADOBLASTOMA/
- 19 sarcoma.mp. or exp *SARCOMA/
- 20 exp *PLASMACYTOMA/ or plasmacytoma.mp.
- 21 lymphoma.mp. or exp *LYMPHOMA/
- 22 granulocytic sarcoma.mp. or exp *Granulocytic Sarcoma/
- 23 exp *Rete Testis/ or exp *Adenocarcinoma/ or adenocarcinoma of the rete testis.mp.
- 24 CARCINOMA/ or exp *TESTIS CARCINOMA/
- 25 malignant mesothelioma.mp. or exp *Malignant Mesothelioma/
- 26 or/1-25
- 27 testicular cancer.mp. or exp *Testis Cancer/
- 28 testicular neoplasia.mp. or exp *Testis Tumor/
- 29 27 or 28
- 30 26 and 29
- 31 limit 30 to (human and english language and yr="1981 - 2007")
- 32 pelvic lymphadenectomy.mp. or exp Pelvis Lymphadenectomy/
- 33 plnd.mp.
- 34 lymph node dissection.mp. or exp Lymph Node Dissection/
- 35 Radiotherapy/
- 36 radiation treatment.mp.
- 37 adjuvant radiotherapy.mp.
- 38 exp drug therapy/ or exp adjuvant therapy/ or exp chemotherapy/ or exp adjuvant chemotherapy/ or exp cancer chemotherapy/ or exp cancer adjuvant therapy/ or exp cancer combination chemotherapy/ or exp combination chemotherapy/
- 39 surveillance.mp. or exp DISEASE SURVEILLANCE/
- 40 watchful waiting.mp.
- 41 wait-and-see.mp.
- 42 (wait and see).mp.
- 43 (watch and wait).mp.
- 44 exp FOLLOW UP/ or exp "EVALUATION AND FOLLOW UP"/ or follow.mp.
- 45 or/32-44
- 46 31 and 45
- 47 phase ii.mp.
- 48 phase 2.mp.
- 49 phase iii.mp.
- 50 phase 3.mp.
- 51 phase iv.mp.
- 52 phase 4.mp.
- 53 exp clinical trial/
- 54 exp controlled trial/
- 55 exp randomized controlled trial/
- 56 clinical trial.mp.
- 57 randomised trial.mp.
- 58 controlled trial.mp.
- 59 rct.mp.
- 60 exp Randomization/
- 61 random allocation.mp.
- 62 single blind.mp.
- 63 single-blind.mp.
- 64 double blind.mp.
- 65 double-blind.mp.
- 66 triple blind.mp.
- 67 triple-blind.mp.
- 68 practice guideline.mp. or exp Practice Guideline/
- 69 clinical guideline.mp.
- 70 meta-analysis.mp.
- 71 meta analysis.mp.
- 72 metaanalysis.mp.
- 73 metanalysis.mp.
- 74 exp meta analysis/
- 75 systematic review.mp. or exp "Systematic Review"/
- 76 systematic overview.mp.
- 77 evidence-based medicine.mp. or exp Evidence Based Medicine/
- 78 evidence based medicine.mp.
- 79 exp embase/ or exp medline/ or exp mesh heading/
- 80 embase.ab.
- 81 medline.ab.
- 82 mesh heading.ab.
- 83 quantitative synthesis.mp.
- 84 quantitative overview.mp.
- 85 or/48-84
- 86 prospective.mp. or exp PROSPECTIVE STUDY/
- 87 exp RETROSPECTIVE STUDY/ or retrospective.mp.
- 88 exp COHORT ANALYSIS/ or cohort.mp.
- 89 exp Case Control Study/ or case control.mp.
- 90 follow-up.mp. or exp Follow Up/
- 91 follow up.mp.
- 92 longitudinal.mp. or exp LONGITUDINAL STUDY/
- 93 comparative study.mp.
- 94 exp COMPARATIVE STUDY/
- 95 or/86-94
- 96 85 or 95
- 97 47 and 96

*This search is a combined search strategy for Evidence-based Series #3-19 and #3-18 (seminoma).

Appendix B: Results of AGREE rating of guidelines.

Guideline	Agree Domain Scores						Overall Rating
	Scope and Purpose	Stakeholder Involvement	Rigour of Development	Clarity and Presentation	Applicability	Editorial Independence	
NCCN (2007) [9]	44.4%	29.2%	19.0%	83.3%	11.1%	66.7%	Recommended with provisos or alterations (1) Not recommended (1)
EAU (2005, 2001) [10]	33.3%	25%	33.3%	58.3%	11.1%	16.7%	Recommended with provisos or alterations (2)
ESMO (2005) [11]	33.3%	0%	14.3%	58.3%	5.6%	16.7%	Not recommended (2)
CCNS (2005) [12]	44.4%	37.5%	38.1%	50%	0%	41.7%	Recommended with provisos or alterations (2)
EGCCCG (2004) [13]	44.4%	25%	42.9%	54.2%	11.1%	16.7%	Recommended with provisos or alterations (2)
NICE Guidance (2002) [14,15]	44.4%	41.7%	45.2%	58.3%	44.4%	16.7%	Recommended with provisos or alterations (1) Not recommended (1)
Interdisciplinary Consensus on Diagnosis and Treatment of Testicular GCT (2001) [16]	16.7%	33.3%	33.3%	29.2%	0%	8.3%	Not recommended (2)
Segal (2001) [17]	66.7%	41.7%	61.9%	50%	33.3%	50%	Recommended with provisos or alterations (2)

Evidence-Based Series #3-19: Section 3

Management of Stage I Nonseminomatous Testicular Cancer: EBS Development Methods and External Review Process

*S. Hotte, L.A. Mayhew, M. Jewett, J. Chin, E. Winquist,
and Members of the Genitourinary Cancer Disease Site Group*

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: February 14, 2008

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

The Evidence-Based Series: A New Look to the PEBC Practice Guidelines

Each Evidence-Based Series is comprised of three sections.

- *Section 1: Guideline Recommendations.* Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.

- *Section 2: Evidentiary Base.* Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- *Section 3: EBS Development Methods and External Review Process.* Summarizes the evidence-based series development process and the results of the formal external review of the draft version of Section 1: Guideline Recommendations and Section 2: Evidentiary Base.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This evidence-based series was developed by the GU DSG of CCO's PEBC. The series is a convenient and up-to-date source of the best available evidence on stage I nonseminomatous testicular cancer, developed through systematic review, evidence synthesis, and input from practitioners in Ontario

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.

During the discussion of the Ontario draft guideline, conference attendees offered the following feedback (response of the GU DSG is italicised):

- It wasn't explicitly stated that patients should be informed of all the treatment options. *This has been addressed in the revised draft.*
- RPLND was dismissed as having no role in the treatment of stage I nonseminoma. Some attendees felt that this was a disservice to patients, as RPLND can provide excellent cancer control rates and reduce the need for CT scans. Other attendees felt that the discussion of RPLND was driven by a fear of late relapse, a deadly consequence but one that happens in only 1 to 2% of patients; however, there is no evidence that RPLND prevents late relapse, and there is significant morbidity associated with the procedure. *The recommendations have been changed to indicate that there is not enough prospective evidence to support a routine role for RPLND, and that further study is needed.*
- Burden of treatment is becoming a more important consideration, and long-term toxicity must be considered early on when initially treating a patient. *Owing to the lack of evidence on the long-term toxicity associated with management options for stage I nonseminoma, the authors have referred this issue back to the GU DSG, with the recommendation they consider writing a guideline on this topic.*

- With respect to the 2-CT vs. 5 CT RCT by Rustin et al (3), the conference attendees felt that the CT recommendations should be stronger and that the number of CT scans recommended be reduced to two. *The recommendations were changed to reflect that two CT scans were recommended.*

With respect to consensus concerning the treatment of stage I nonseminomatous testicular cancer, the conference attendees were split as to whether a risk-adapted or a non-risk-adapted approach should be used. All believed that surveillance should be the primary option in low-risk patients. In high-risk patients, while some felt that primary surveillance was still the best option, other attendees were of the opinion that all three treatment approaches were equal options, or that immediate treatment (chemotherapy or RPLND) was the best option. In terms of immediate treatment, three surgeons thought that RPLND would be the best option in high-risk patients, while others believed chemotherapy was the most appropriate option. All the attendees agreed that patients should be presented with all available treatment options, along with the possible associated benefits and side effects of each.

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. Key issues raised by the Panel included (response of the GU DSG is italicised):

- RAP asked why a meta-analysis of the recurrence data from the surveillance studies was not performed. *The GU DSG deemed a meta-analysis of the surveillance recurrence data inappropriate due to the variability in risk categories of patients included in the surveillance studies.*
- RAP believed that the recommendation concerning RPLND could not be adequately supported by the data. *The recommendation was reworded.*
- RAP commented that the referencing of trials was inconsistent across different sections of the report. *The referencing was standardized across the report.*
- A query was made with regard to blinding in the RCTs. *A phrase was added to establish that, owing to the treatments being compared, blinding was not possible.*

Conclusion

This report reflects the integration of feedback obtained through the external review process with final approval given by the Genitourinary DSG and the Report Approval Panel of the PEBC. Updates of the report will be conducted as new evidence informing the question of interest emerges.

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