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## Evidence-Based Series #3-18: Section 1

# Management of Stage I Seminoma: Guideline Recommendations

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

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The full Evidence-based Series #3-18 is comprised of 3 sections  
and is available on the CCO website (<http://www.cancercare.on.ca>)

PEBC Genitourinary Cancer DSG page at:

<http://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/genito-ebs/>

Section 1: Guideline Recommendations

Section 2: Evidentiary Base

Section 3: EBS Development Methods and External Review Process

### QUESTION

What is the optimal post-orchidectomy management strategy for stage I testicular seminoma? Outcomes of interest include cancer-specific survival, long-term toxicity (including second malignancy), and quality of life.

### TARGET POPULATION

Adult patients with stage I testicular seminoma.

### RECOMMENDATIONS AND KEY EVIDENCE

The DSG recommends surveillance as the preferred option, because adjuvant therapy is associated with important short and long-term toxicities and second malignancy risks with no evidence of improved survival.

- Surveillance or adjuvant therapy (radiation therapy [RT]) ultimately yields equivalent disease control in stage I seminoma.
- Patients should be informed of all treatment options, including the potential benefits and side effects of each treatment. A table of benefits and risks associated with each management option is available in Section 1: Appendix A.

- **A treatment plan should be developed that includes the patient’s preferences and clinical judgement of that specific case.**

### Qualifying Statements

- The minimum surveillance program should be a physical examination every three to four months, chest X-ray every six to twelve months, and computerised tomography (CT) of the abdomen and pelvis every three to four months in the first three years and then less often thereafter.
- In addition, follow-up should include appropriate investigations of sites at risk of relapse. This approach can be based on the risk of relapse with the frequency as suggested in the evidence-based guidelines outlined by Martin et al. (1).
- When a primary surveillance approach is adopted, patients should be informed of their estimated risk of recurrence and the need for frequent surveillance as described above.
- Prognostic factors for relapse on surveillance have been identified (tumour size, rete testis invasion) and low, intermediate, and high-risk groups for disease progression defined. This has led to the introduction of a risk-adapted approach by some groups. However, the prognostic model underlying this risk-adapted strategy has not been prospectively validated. In addition, the risk stratification provided is limited, as even in the highest risk group over 65% of patients do not require additional therapy after orchidectomy. Thus, a risk-adapted approach cannot be recommended at this time.
- Due to the low incidence of testicular cancers, management is best performed in a multidisciplinary environment within centres familiar with the management of the disease.

### Key Evidence

- Data from large prospective randomized controlled trials (RCTs) and large prospective cohorts of stage I seminoma patients identified in a systematic review of the evidence indicate that overall survival at five years is greater than 95%, regardless of the initial treatment strategy adopted. The challenge remains to define the optimal management approach to minimize toxicity while maintaining excellent results.
- Data from large prospective cohorts of primary surveillance identified in a systematic review of the evidence indicate that surveillance is safe and that 80-85% of patients do not require any post-orchidectomy treatment. In addition, when a policy of routine radiation therapy (RT) for relapse is utilised, there is no increase in the proportion of patients requiring systemic chemotherapy compared to those treated with adjuvant RT.

**For patients who prefer immediate treatment, or who are unsuitable for primary surveillance, adjuvant RT is the recommended option.**

- **When adjuvant RT is the preferred option, a radiation dose of at least 20 Gy and no more than 30 Gy is recommended.**
- **When adjuvant RT is the preferred option, para-aortic and extended-field (i.e., “dogleg”) RT are equivalent in prevention of para-aortic recurrence, but are different in terms of short- and long-term toxicity and follow-up requirements.**
- **In patients treated with adjuvant therapy, post treatment monitoring for disease relapse is still necessary. Except in the specific case of extended-field radiotherapy, the follow-up after adjuvant therapy should be as thorough as the surveillance conducted in the absence of adjuvant therapy.**

### Qualifying Statements

- If adjuvant therapy is planned, sperm banking (and scrotal shielding with RT) should be offered if future fertility is of concern to the patient.
- With extended-field RT, there is evidence from RCTs and non-randomized trials (2-7) that the risk of pelvic recurrence is greatly reduced, and therefore regular abdominal/pelvic computerized tomography (CT) is not necessary as part of the ongoing surveillance/follow-up program.
- With para-aortic RT, the continuation of pelvic CT scanning on a routine basis is necessary. However, there is also evidence that short-term toxicity is reduced with para-aortic RT compared to extended-field RT. This trade-off should be discussed with the patient as part of the decision-making process.
- The main concern with adjuvant RT is the potential for the induction of second non-testicular malignancies. In addition, long-term survivors of testicular seminoma treated with adjuvant RT are at an excess risk of death as a result of cardiac disease. These toxicities should be discussed fully with the patient.

### Key Evidence

- An RCT (2) compared 20 Gy to 30 Gy in a non-inferiority design and found no difference in relapse-free survival between the methods (hazard ratio [HR] for relapse, 1.11; 90% confidence interval [CI], 0.54 to 2.28; log rank  $p=0.81$ ).
- An RCT (3) compared para-aortic to “dogleg” radiotherapy in a non-inferiority design, and found no difference in three-year relapse-free survival.
- Evidence from RCTs (2,3) supports the conclusion that para-aortic RT leads to a greater risk of pelvic recurrence but also less short-term toxicity than does extended-field RT. This has also been confirmed in non-randomized trials (8-10).
- Twelve population-based studies (11-22) demonstrated a consistent increase in the risk of second malignancy associated with RT compared to population expected rates. The largest of these (18,19) combined fourteen population-based registries including 10,534 patients with seminoma (all stages) treated with RT and no chemotherapy who had at least 10 years follow-up. Compared with matched cohorts from corresponding registries, the overall relative risk for a second non-testicular malignancy was 2.0 (95% CI, 1.8-2.2). For a 35-year-old patient with seminoma (most treated with RT), the cumulative 40-year risk of a second malignancy was 36%, compared with 23% in the normal population. Another study compared 5,265 stage I seminoma patients treated with adjuvant RT against 1,499 patients managed with surveillance and found a second malignancy observed-to-expected ratio of 1.93 ( $p<0.05$ ) (1, 21).
- Two studies addressed the cardiac toxicity associated with RT. In the MD Anderson series (23), 453 patients treated between 1951 and 1999 had a standardized cardiac mortality ratio of 1.80 (95% CI, 1.01-2.98) after 15 years if only infradiaphragmatic and no mediastinal RT was used. A similar increase in cardiac events (risk ratio, 2.4 [95% CI, 1.04-5.45]) was reported in a cohort of 992 patients treated at the Royal Marsden Hospital (2,24). The etiology of this effect is currently unclear.

**When neither surveillance nor RT is suitable, adjuvant chemotherapy is the preferred option. Single-agent carboplatin is typically used.**

- **In patients treated with adjuvant therapy, post-treatment monitoring for disease relapse is still necessary. The follow-up after adjuvant therapy should be as thorough as the surveillance conducted in the absence of adjuvant therapy.**

### Qualifying Statements

- The follow-up of patients treated with carboplatin in a randomized trial (4) is still relatively short, and the long-term toxic effects of carboplatin are not yet fully known. Additionally, evidence from the randomized trial suggests that the risk of para-aortic recurrence is sufficiently high to warrant abdominal/pelvic CT on a regular basis.
- The use of carboplatin may be restricted to specific situations outside a clinical trial, for instance where adjuvant therapy is preferred and there is a contraindication to RT. Patients should be informed of these possible risks in order to fully consider their options, particularly in comparison to surveillance.
- The authors suggest that the optimal dose is not yet known and may be higher than that used in the trial.

### Key Evidence

- An RCT (4) compared RT at 20 Gy or 30 Gy with a single cycle of carboplatin (area under curve [AUC]=7) in a non-inferiority design, and found no difference in three-year relapse-free survival (HR, 1.28; 90% CI, 0.85-1.93; p=0.32).

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## REFERENCES

1. Martin JM, Panzarella T, Zwahlen DR, Chung P, Warde P. Evidence-based guidelines for following stage 1 seminoma. *Cancer*. 2007;109(11):2248-56.
2. Jones WG, Fossa SD, Mead GM, Roberts JT, Sokal M, Horwich A, et al. Randomized trial of 30 versus 20 Gy in the adjuvant treatment of stage I Testicular Seminoma: a report on Medical Research Council Trial TE18, European Organisation for the Research and Treatment of Cancer Trial 30942 (ISRCTN18525328). *J Clin Oncol*. 2005;23(6):1200-8.
3. Fossa SD, Horwich A, Russell JM, Roberts JT, Cullen MH, Hodson NJ, et al. Optimal planning target volume for stage I testicular seminoma: A Medical Research Council randomized trial. Medical Research Council Testicular Tumor Working Group. *J Clin Oncol*. 1999;17(4):1146.
4. Oliver RT, Mason MD, Mead GM, von der MH, Rustin GJ, Joffe JK, et al. Radiotherapy versus single-dose carboplatin in adjuvant treatment of stage I seminoma: a randomised trial. *Lancet*. 2005;366(9482):293-300.
5. Sommer K, Brockman WP, Hubener KH. Treatment results and acute and late toxicity of radiation therapy for testicular seminoma. *Cancer*. 1990;66(2):259-63.
6. Warde P, Gospodarowicz MK, Panzarella T, Catton CN, Sturgeon JF, Moore M, et al. Stage I testicular seminoma: results of adjuvant irradiation and surveillance. *J Clin Oncol*. 1995;13(9):2255-62.
7. Warde P, Gospodarowicz MK, Panzarella T, Chow E, Murphy T, Catton CN, et al. Long term outcome and cost in the management of stage I testicular seminoma. *Can J Urol*. 2000;7(2):967-72.
8. Classen J, Schmidberger H, Meisner C, Winkler C, Dunst J, Souchon R, et al. Para-aortic irradiation for stage I testicular seminoma: results of a prospective study in 675 patients. A trial of the German testicular cancer study group (GTCSG). *Br J Cancer*. 2004;90(12):2305-11.
9. Livsey JE, Taylor B, Mobarek N, Cooper RA, Carrington B, Logue JP. Patterns of relapse following radiotherapy for stage I seminoma of the testis: implications for follow-up. *Clin Oncol (R Coll Radiol)*. 2001;13(4):296-300.
10. Logue JP, Harris MA, Livsey JE, Swindell R, Mobarek N, Read G. Short course para-aortic radiation for stage I seminoma of the testis. *Int J Radiat Oncol Biol Phys*. 2003;57(5):1304-9.
11. Bokemeyer C, Schmoll HJ. Secondary neoplasms following treatment of malignant germ cell tumors. *J Clin Oncol*. 1993;11(9):1703-9.
12. Hay JH, Duncan W, Kerr GR. Subsequent malignancies in patients irradiated for testicular tumours. *Br J Radiol*. 1984;57(679):597-602.
13. Horwich A, Bell J. Mortality and cancer incidence following radiotherapy for seminoma of the testis. *Radiother Oncol*. 1994;30(3):193-8.
14. Jacobsen GK, Mellempgaard A, Engelholm SA, Moller H. Increased incidence of sarcoma in patients treated for testicular seminoma. *Eur J Cancer*. 1993;29A(5):664-8.
15. Moller H, Mellempgaard A, Jacobsen GK, Pedersen D, Storm HH. Incidence of second primary cancer following testicular cancer. *Eur J Cancer*. 1993;29A(5):672-6.
16. Richiardi L, Scelo G, Boffetta P, Hemminki K, Pukkala E, Olsen JH, et al. Second malignancies among survivors of germ-cell testicular cancer: a pooled analysis between 13 cancer registries. *Int J Cancer*. 2007;120(3):623-31.
17. Robinson D, Moller H, Horwich A. Mortality and incidence of second cancers following treatment for testicular cancer. *Br J Cancer*. 2007;96(3):529-33.
18. Travis LB, Curtis RE, Storm H, Hall P, Holowaty E, van Leeuwen FE, et al. Risk of second malignant neoplasms among long-term survivors of testicular cancer. *J Natl Cancer Inst*. 1997;89(19):1429-39.

19. Travis LB, Fossa SD, Schonfeld SJ, McMaster ML, Lynch CF, Storm H, et al. Second cancers among 40,576 testicular cancer patients: focus on long-term survivors. *J Natl Cancer Inst.* 2005;97(18):1354-65.
20. van Leeuwen FE, Stiggelbout AM, van den Belt-Dusebout AW, Noyon R, Eliel MR, van Kerkhoff EHM, et al. Second cancer risk following testicular cancer: a follow-up study of 1,909 patients. *J Clin Oncol.* 1993;11(3):415-24.
21. Vudarla, N., Jawed, I., Kaya, H., Tward, J. D., Macdonald, O. K., Martincic, D., Gaffney, D. K., Shivnani, A. T., Odom-Maryon, T. L., Lee, C. M. Survival and secondary malignancy rates for adjuvant radiation therapy versus observation in stage I testicular seminoma: A Surveillance, Epidemiology, and End Results (SEER) analysis [abstract]. *J Clin Oncol.* 2007;25(18S):A5020.
22. Wanderas EH, Fossa SD, Tretli S. Risk of a second germ cell cancer after treatment of a primary germ cell cancer in 2201 Norwegian male patients. *Eur J Cancer.* 1997;33(2):244-52.
23. Zagars GK, Ballo MT, Lee AK, Strom SS. Mortality after cure of testicular seminoma. *J Clin Oncol.* 2004;22(4):640-7.
24. Huddart RA, Norman A, Shahidi M, Horwich A, Coward D, Nicholls J, et al. Cardiovascular disease as a long-term complication of treatment for testicular cancer. *J Clin Oncol.* 2003;21(8):1513-23.

**Appendix A.**

**Table 1. Benefits and risks of different management strategies in the treatment of stage I seminoma.**

<b>Management Option</b>	<b>Benefits</b>	<b>Drawbacks</b>
<b>Surveillance</b>	<ul style="list-style-type: none"> <li>• Excellent cancer cure rate</li> <li>• No treatment-related toxicity</li> <li>• Excellent salvage rate</li> <li>• Avoids overtreatment for the majority of patients</li> </ul>	<ul style="list-style-type: none"> <li>• Requires frequent follow-up CT scans, with associated long-term risks</li> <li>• Some patients may experience anxiety related to risk of recurrence</li> </ul>
<b>Dogleg RT</b>	<ul style="list-style-type: none"> <li>• Excellent cancer cure rate</li> <li>• Eliminates need for routine CT scans</li> <li>• Reduces recurrence rates compared to patients managed by surveillance</li> </ul>	<ul style="list-style-type: none"> <li>• Long-term second cancer risk</li> <li>• Long-term cardiac risk</li> <li>• A large majority of patients are overtreated</li> </ul>
<b>Para-aortic RT</b>	<ul style="list-style-type: none"> <li>• Excellent cancer cure rate</li> <li>• Lower recurrence rate than for patients managed by surveillance</li> </ul>	<ul style="list-style-type: none"> <li>• Requires frequent follow-up CT scans, with associated long-term risks</li> <li>• Long-term second cancer risk</li> <li>• Long-term cardiac risk</li> <li>• A large majority of patients are overtreated</li> </ul>
<b>Chemotherapy</b>	<ul style="list-style-type: none"> <li>• Excellent cancer cure rate</li> <li>• Acute toxicity better than RT</li> </ul>	<ul style="list-style-type: none"> <li>• Long-term survival unknown</li> <li>• Long-term toxicity unknown</li> <li>• Requires frequent follow-up CT scans, with associated long-term risks</li> <li>• A large majority of patients are overtreated</li> </ul>



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## **Evidence-Based Series #3-18: Section 2**

### **Management of Stage I Seminoma: Evidentiary Base**

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**Report Date: January 30, 2008**

#### **QUESTION**

What is the optimal post-orchidectomy management strategy for stage I testicular seminoma? Outcomes of interest include cancer-specific survival, long-term toxicity (including second malignancy), and quality of life.

#### **INTRODUCTION**

Testicular cancer is rare, accounting for only 1% of all cancers diagnosed in male residents in Ontario. However, it is the most commonly diagnosed cancer in men aged 25-34 years. In 2007, approximately 830 new cases of testicular cancer will be reported in Canada, with 30 deaths occurring (3). Overall, approximately 60% of incident cases are seminoma (4). Testicular cancer incidence rises throughout adolescence, peaks at ages 25-29, and declines thereafter (5). There were 2,802 cases of seminoma diagnosed in Ontario residents between 1964 and 1996, and the incidence of seminoma is increasing in the province. 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 seminoma (5). The relative increase was greatest in the 15-29 years age group, and there appears to be a cohort effect, with more recent cohorts of men at increased risk. Stage I seminoma represents the largest subgroup, representing about 70-80% of the total (6).

There are multiple treatment options available for the management of stage I seminoma; this comprises either a surveillance strategy or adjuvant therapy after orchidectomy. Surveillance is defined as the follow-up of the patient, usually with a physical examination, chest X-ray, and computerized tomography (CT) scanning of the abdomen and pelvis to detect relapse, and then the initiation of treatment at relapse, should this occur. Adjuvant therapy may consist of either radiotherapy to the retroperitoneal lymph nodes or chemotherapy with single-agent carboplatin. Follow-up after adjuvant therapy consists of a physical examination, chest X ray and, depending on the type of adjuvant therapy chosen, may include CT scans of the abdomen and/or pelvis. The frequency of this imaging after adjuvant therapy may be reduced, compared to surveillance.

Two recent surveys of radiation oncologists' treatment preferences in the management of stage I testicular seminoma have been published. In 2002, Choo et al (7) surveyed radiation oncologists in Canada and the United States. Of the 97 who responded, 78% would offer surveillance to their patients but estimated that only 20% would take up this option. Among four management options (1. surveillance, 2. radiation therapy (RT) to the para-aortic region, 3. RT to the para-aortic and ipsilateral pelvis ("dogleg"), 4. single-agent chemotherapy), the order of first preference was option 1 (44%), 2 (42%), and 3 (14%) for patients who wished to preserve fertility. When fertility was not a major concern, the order was option 2 (43%), 3 (39%), and 1 (17%). Similarly, in 2006, Alomary et al surveyed Canadian radiation oncologists to determine what they thought was the most appropriate treatment for seminoma and also what treatment they would prefer if they themselves were diagnosed with the condition (8). Of the 78 radiation oncologists who responded, 56% thought that surveillance was the most appropriate option, and 52% indicated that they themselves would prefer that treatment approach for themselves. Thirty-one percent thought that adjuvant RT was the most appropriate treatment option, and 27% indicated that it was the treatment option that they would prefer for themselves. Only 1% indicated adjuvant chemotherapy as the most appropriate treatment option, but 8% indicated that it would be their preferred treatment option. Twelve percent of respondents indicated that they were unsure of the most appropriate treatment option, and 13% indicated that they were unsure of which treatment they would wish for themselves. There was a strong association between what respondents thought was the best treatment and what they would choose for themselves ( $\chi^2 [1, n=60] = 36.4, p < 0.001$ ). Provincial location, type of practice (academic versus [vs.] community), or the number of years in clinical practice did not influence management choices; however, the mean age of radiation oncologists who would choose radiation therapy for themselves was greater than for those choosing surveillance (47 years vs. 43 years,  $p = 0.05$ ).

As the optimal management strategy for stage I seminoma appears to be a matter of opinion and debate, this report sought to systematically review the available evidence from the medical literature and develop appropriate clinical practice recommendations.

## **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 (9). For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by two members of the PEBC Genitourinary Disease Site Group (DSG) and methodologists.

This systematic review is a convenient and up-to-date source of the best available evidence on the management of stage I seminoma. The body of evidence in this review is primarily comprised of retrospective studies, with some prospective studies and three randomized controlled trials (RCTs). This evidence forms the basis of the recommendations developed by the Genitourinary DSG and 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, MeSH, and EMBASE subject headings: 'testicular neoplasms', 'testicular cancer', "Neoplasms, germ cell and embryonal", 'seminoma', 'germinoma', 'dysgerminoma', and 'germ cell tumor?r'. These results were combined with the terms 'radiotherapy', 'surveillance', 'watchful waiting', 'chemotherapy', and 'drug therapy' to

provide a base pool of literature on the treatment of testicular cancer, with the total results being limited to human studies published from 1981 through to May 2007. These searches produced a total of 2,913 references. One further reference not published at the time of the literature search but published shortly afterwards was suggested by an author (PW). The American Society of Clinical Oncology (ASCO) abstracts were hand searched for references related to seminoma. Four relevant ASCO abstracts were found, one of which was an update of a previously published paper.

### **Study Selection Criteria**

Studies were selected if they met the following criteria:

#### ***Patient criteria***

- Studies with patients with stage I seminoma diagnosis.
- Studies with multiple stages of seminoma disease where survival and recurrence data were reported separately for stage I patients.
- Studies that included nonseminoma patients, provided that the survival and recurrence data for seminoma patients were reported separately for stage I patients.

#### ***Patient outcomes***

- Studies reporting at least one of survival, recurrence, second malignancy, cardiac toxicity, or quality of life.

#### ***Year of Publication***

- Studies published after 1981.

#### ***Study Designs/Types***

- Clinical practice guidelines, systematic reviews, RCTs, and non-randomized prospective and retrospective studies.

The following types of articles were excluded:

- Articles published in languages other than English, because of the lack of translation resources.
- Editorials, comments, and case studies.
- Studies conducted in narrow patient groups (e.g., HIV+).
- Non-RCT studies with less than 100 patients, or less than 400 patients if examining long-term toxicity or quality of life, as these were considered underpowered to inform the development of clinical practice guidelines.
- Studies in which staging was performed by lymphangiogram, as the more accurate staging results of CT scans may have resulted in a stage migration of patients.

The references were jointly reviewed by two authors (LM and PC).

### **Quality Appraisal**

The Appraisal of Guidelines for Research & Evaluation AGREE tool (10) was used by two independent raters to evaluate the quality of all the identified practice guidelines. While all the domains were considered in evaluation of the guidelines, the rigour of development domain along with the overall rating were considered to be most relevant.

**Synthesizing the Evidence**

Due to the clinically heterogeneous sources of evidence in this report, no pooling was planned.

**RESULTS**

**Literature Search Results**

A total of 50 eligible reports were identified, including seven clinical practice guidelines, one systematic review, three RCTs focused on treatment options, 24 non-randomized studies of treatment options, and 15 non-randomized long-term toxicity studies.

**Table 1: Results of literature search.**

<b>Study Type</b>	<b>Number (Reference)</b>
<b>Clinical Practice Guideline</b>	7 (11-19)
<b>Systematic Reviews</b>	
Management of Testicular Cancer	1 (20)
<b>RCTs</b>	3 (21-23)
<b>Non-randomized Studies of Treatment</b>	
Radiotherapy	8 (24-31)
Chemotherapy	4 (32-35)
Surveillance	4 (36-39)
Comparisons	6 (40-45)
Risk-adapted treatment	2 (46,47)
<b>Non-randomized Long Term Toxicity Studies</b>	
Second Malignancy	12 (1,48-58)
Cardiac	2 (2,59)
Sexual Function	0
Quality of Life	1 (60)

**Guidelines**

Seven guidelines concerning the management of stage I seminoma were identified and evaluated using the AGREE tool. The quality of the guidelines was modest, with AGREE scores for the rigour quality domain ranging between 19% and 45.2%, and with no guidelines being recommended without provisos by either reviewer. (See Appendix A for the complete evaluation.)

**Guideline Recommendation Summary**

All guidelines recognized both surveillance and RT as primary treatment options. All guidelines but one includes details of follow-up regimes. The recommendations are summarized in Table 2 below.

After this evaluation, none of the guidelines were deemed suitable for adaptation or endorsement, owing to the variability in recommendations, the publication of new randomized and non-randomized trials, and the differing philosophies of treatment.

**Table 2: Guideline recommendations.**

Guideline	Recommendations							
	RT is an option for treatment.	Para-aortic RT field is an option for treatment.	Surveillance is an option for treatment.	Chemotherapy is an option for treatment.	Recommends risk-adapted treatment.	Suggests treatment in an order of preference.	Suggests treating all patients the same regardless of risk factors.	Give details concerning follow-up regime.
<b>Interdisciplinary Consensus on Diagnosis and Treatment of Testicular GCT (12)</b>	X		X				X	X
<b>NICE Guidance (16,17)</b>	X	X	X	X		X		
<b>EGCCCG (18)</b>	X	X	X	X		X		X
<b>EAU (11)</b>	X	X	X	X		X		X
<b>CCNS (19)</b>	X	X	X		X			X
<b>NCCN (15)</b>	X	X	X	X	X			X
<b>Martin paper (14)</b>	X	X	X	X				X

**Abbreviations:** CCNS – Cancer Care, Nova Scotia; EAU – European Association of Urology; EGCCCG – European Germ Cell Cancer Consensus Group; GCT – germ cell tumour; NCCN – National Comprehensive Cancer Network; NICE – National Institute for Clinical Excellence; RT – radiation therapy.

**Systematic Reviews**

One systematic review was identified. A Cochrane review by Shelley et al addressed management of all stages and types of testicular germ cell cancer (20); however, the majority of studies in the review either did not meet our selection criteria or had more recent data available, and so this review is not considered further.

**Randomized Controlled Trials**

Three RCTs that met our selection criteria were identified: one studying 20 versus 30Gy RT dosage (22), one studying para-aortic versus extended-field (“dogleg”) RT (21), and one that compared adjuvant RT with one cycle of adjuvant carboplatin (23). There were no studies examining surveillance or more than one cycle of adjuvant carboplatin. Study quality elements are summarized in Table 3. Given the nature of the treatment options studied, blinding of treatment allocation was not feasible in any of these trials.

**Table 3. Quality of eligible trials.**

<b>Trial Characteristic</b>	<b>Jones (2005) (22)</b>	<b>Oliver (2005) (23)</b>	<b>Fosså (1999) (21)</b>
<b>Description of random allocation</b>	Met	Unclear	Not met
<b>Design</b>	Non-inferiority	Non-inferiority	Non-inferiority
<b>Non-inferiority margin</b>	4%	3%	3%
<b>Power</b>	90% 5% significance Two-sided	90% 5% significance One-sided	90% 5% significance
<b>Planned sample size</b>	600	800	400
<b>Sample size met?</b>	Met	Met	Met
<b>Intention-to-treat analysis</b>	Yes	Yes	Some
<b>Per protocol analysis?</b>	Yes	Yes	Unclear
<b>Details of withdrawals and exclusions</b>	Unclear	Unclear	Unclear

Jones et al investigated whether the dose of RT could be reduced to 20 Gy from the usual 30 Gy treatment (22). With irradiated patients facing an increased risk of a second primary tumour and other adverse effects, it was theorized that reducing the RT dose and/or field might decrease the risk of side effects. A total of 625 patients were randomized. Although RT volume was stratified for para-aortic or extended-field (“dogleg”), over 85% of patients were treated with para-aortic RT. After a median follow-up of 61 months, 21 relapses were reported. The intent-to-treat 20 Gy-30 Gy hazard ratio (HR) for relapse was 1.11 (90% CI, 0.54-2.28; log-rank, p=.81), and the per protocol analysis results were almost identical (HR, 1.10; p=.83). There was a reduction in rates of acute toxicity in the 20 Gy arm. Details concerning recurrences and survival are available in Table 4.

Fosså et al studied the relapse rates and toxicity associated with para-aortic and ipsilateral iliac lymph node RT (21). 478 patients were randomized to receive a 30 Gy dose in 15 fractions over three weeks in either a “dogleg” (242 patients) or para-aortic (236 patients) field. After a median follow-up time of 4.5 years, a total of 18 relapses had occurred, nine in each arm of the study. All but one patient (from the para-aortic field group) were salvaged; the three-year survival rate is therefore 100% in the “dogleg” group and 99.3% (95% CI, 97.5%-99.9%) in the para-aortic group. Patients in the para-aortic group had significantly higher sperm counts after RT, but by three years this difference was no longer apparent. Details concerning recurrences and survival are available in Table 4.

In the final RCT, adjuvant RT was compared with single-dose adjuvant carboplatin for stage I seminoma (23). Patients were randomized to receive either adjuvant RT or 1 dose of carboplatin (AUC=7), with some of the patients subrandomized to receive either 20 or 30 Gy. RT was delivered using either a para-aortic strip or “dogleg” field at either 20Gy or 30Gy. Patients were also stratified to receive either “dogleg” or para-aortic radiation according to treatment centre and previous medical history. A total of 1477 patients were randomized. An RT-chemotherapy HR of 1.28 (90% CI, 0.85-1.93; p=0.32) on an intent-to-treat basis was found. These findings lead the investigators to suggest that adjuvant treatment with carboplatin was not inferior to RT. The acute toxicity of carboplatin was better than that of RT. Details concerning relapses and survival are available in Table 4.

**Table 4: Relapses and survival.**

Trial	Treatment	Total Relapses	Number of Pelvic Relapses	Relapse-free Survival	Other
<b>Jones 2005 (22)</b> N=625	20 Gy RT N=313	11	3	At 2 years: 97.0% (95% CI 94.4-98.4%)  At 5 years: 96.4% (95% CI 93.5-98.%)	8 of 9 pelvic relapses occurred in para-aortic RT field group.  The size of the nodes at relapse indicates that the patients probably did not receive routine CT scans in follow-up.
	30 Gy RT N=312	10	6	At 2 years: 97.7% (95% CI 95.2-98.9%)  At 5 years: 96.4% (95% CI 93.5-98%)	
<b>Fossa 1999 (21)</b> N=478	Dogleg RT N=242	9	0	At 3 years: 96.6% (95% CI 94.2-98.9%)	Overall survival at 3 years: 100%
	Para-aortic RT N=236	9	4	At 3 years: 96% (95% CI 93.5-98.5%)	Overall survival at 3 years: 99.3% (95% CI 97.5-99.9%)
<b>Oliver 2005 (23)</b> N=1477	RT: P or D, 20Gy or 30Gy N=904	36	10	At 3 years: 95.9% (95% CI 94.4-97.1%)	RT to Carboplatin: HR=1.28 (90%CI 0.85-1.93, p=0.32)  All pelvic relapses occurred in P RT group
	1 cycle carboplatin N=573	29	0	At 3 years: 94.8% (95% CI 92.5-96.4%)	74% of relapses in the carboplatin group occurred in the para-aortic nodes.

Abbreviations: C – carboplatin; CI – confidence interval; D – dogleg radiotherapy field; HR – Hazard Ratio; N/A – not available; P – para-aortic radiotherapy field; RT – radiotherapy; S – surveillance.

**Non-Randomized Studies**

A total of 24 non-randomized studies were located that examined different aspects of management of stage I seminoma (24-47). These data were included as they inform the results of surveillance, and much of the evidence for its use is from prospective longitudinal studies. In addition, mature results from RT studies are included as results from the randomized studies have relatively short follow-up. These studies found that overall survival for patients managed by surveillance (ranging from 97-100% at five years) did not differ greatly from that of patients managed by RT (ranging from 95-100% at five years). Overall survival of patients in a small number of non-randomized studies managed by adjuvant carboplatin was also similar (range

94-100% at five years). Relapse patterns in those studies that reported overall survival were different for the different management strategies. In both surveillance patients and those treated with adjuvant carboplatin, the majority of patients had para-aortic nodal relapse. RT patients who had extended-field RT relapsed outside the field, with relapse in the para-aortic or pelvic lymph nodes being a rare event. However, in those treated with para-aortic RT alone, pelvic nodal relapse was more notable and occurred in 2-3%. Details on these studies are provided in Appendix C.

### **Late Effects**

A total of 15 non-randomized studies of long-term toxicity were identified (1,2,48-60). These studies are discussed below in four categories: second malignancy, cardiac toxicity, sexual function changes, and quality of life.

### **Second Malignancy**

A total of 12 non-randomized studies were located that examined the risk of a second malignancy after diagnosis with seminoma (1,48-58). As two of the papers were updates of previous publications, only the most recent data have been used. There is also considerable overlap between the patients reported in the studies; as at least eight of the studies (1,50-54,57,58) overlap with a ninth (56), results from the first eight papers are not reported here. The exception to this is the study by Vudarla et al (1), which is the only study to report results for stage I seminoma patients specifically.

The largest of these studies (55,56) included 40,576 testicular cancer survivors of whom 22,424 were seminoma patients, and 10,534 received RT alone. The majority of patients treated with RT for seminoma likely had stage I, as this represents the largest proportion of seminoma patients. Among 10-year survivors of testicular cancer diagnosed at age 35 years, the relative risk (RR) of developing a second solid cancer was 1.9. The risk remained elevated for 35 years after diagnosis (RR=1.7). The RR of a second tumour within the radiation field was 2.0 (95% CI, 1.6 to 2.7) for those treated between 1943 and 1974, and 3.4 (95% CI, 2.5-4.6) for those treated in 1975 or later. In a 2007 ASCO abstract, Vudarla et al examined the risk of second cancers in 6,764 stage I seminoma patients. This study compared rates in adjuvant RT patients to expected population rates and to rates in surveillance patients. At a median follow-up of 7.6 years, 312 RT patients developed second malignancies, which was at a higher rate than expected from the endemic rate (Observed/Expected, 1.43;  $p < 0.05$ ) or from the surveillance group (O/E, 1.93;  $p < 0.05$ ) (1).

### **Cardiac**

We identified two papers that studied the long-term cardiac effects of treatment for testicular cancer (2,59). Huddart et al (2003) examined cardiac disease as a long-term complication of testicular cancer treatment (2). With respect to the patients who received RT treatment alone, 218 of the 230 patients had a diagnosis of seminoma, with 183 having a stage I diagnosis and 37 having a stage II diagnosis. As the RT treatment for stage I and stage II seminoma are very similar, the data on the RT-alone patients were accepted as representing the risks for stage I seminoma patients. Cardiac events were reported in 3.72% of the surveillance group and 9.57% of the RT-alone group. Patients treated with RT had a RR of a cardiac event of 2.74 (95% CI, 1.23-6.08;  $p = 0.013$ ) when compared to those managed by surveillance. The data suggested that the risks of cardiac events started to increase five to eight years after therapy. While chemotherapy patients also showed an increased risk of cardiac events, conclusions could not be drawn concerning the risks associated with adjuvant chemotherapy treatment in stage I seminoma patients as these data are not distinguished by stage and type of disease.

Zagars et al studied long-term effects in 453 stage I and II seminoma patients treated between 1951 and 1999 with RT for seminoma (59). Again, as the RT treatment for stage I and stage II seminoma are similar, the data on the RT-alone patients were accepted as representing the risks for stage I seminoma patients. Overall mortality was significantly greater than expected with a standardized mortality ratio (SMR) of 1.59, with mortality after 15 years being 1.85 times the expected rate (99% CI, 1.30-2.55). Overall survival rates at 10, 20, and 30 years were 93% (95% CI, 90-95%), 79% (95% CI, 74-84%), and 59% (95% CI, 50-67%), respectively. Fifteen years after treatment, cardiac mortality was 1.95 times the expected rate (99% CI, 1.07-3.28).

### **Sexual Function**

No studies were identified that addressed sexual function in stage I seminoma patients. While data concerning sexual function are important, it is unclear what can be learned about stage I seminoma patients from the existing data, and so these articles have not been included.

### **Quality of Life**

One study was identified that addressed quality of life issues in stage I seminoma patients. In 2007, Schoffski et al released information concerning quality of life data from an RCT of seminoma patients in an ASCO abstract (60). Eight hundred seven patients who received either RT or carboplatin completed the Quality of Life Questionnaire-Cancer (QLQ-C) 30 Version 2.0 (15 quality of life dimensions) and the Testicular Tumour Questionnaire (TTQ, 16 domains) at randomization, and at one, four, and 12 months after trial entry. There was significant variation ( $p < 0.05$ ) in quality of life over time in both treatment arms. The chemotherapy group reported a better quality of life at month 1 in 11 domains, at month 4 in two domains, and at month 12 in five domains on the QLQ-C questionnaires. For the TTQ, the chemotherapy group reported a better quality of life in three domains at month 1, and in two domains at month 12.

## **DISCUSSION**

There are no randomized studies of surveillance alone compared to adjuvant therapy. This creates a challenge in articulating the options that optimize cure, expeditiously allow all patients to return to their lives, and avoid patient exposure to interventions that may lead to permanent long-term adverse events. The other challenge to recommending a management option for stage I seminoma is that the available long-term toxicity/survival data are retrospective, with all the inherent problems associated with retrospective data, and yet these data show a clear pattern of treatment-related deaths that cannot be ignored.

The data that exist suggest that virtually all patients with stage I testicular seminoma are cured regardless of the post-orchidectomy management. The five-year survival reported in all the studies identified in this systematic review was over 95%, regardless of management strategy, including surveillance alone with no adjuvant therapy. In non-randomized studies of surveillance alone, the five-year relapse-free rate was consistently reported as over 80%, with no reduction in cause-specific or overall survival. Therefore, it appears that the majority of patients are cured by orchidectomy alone, and those that are not, rarely die from their disease. The available data therefore support the conclusion that surveillance as a management option does not compromise survival. Given this fact, and the acute and long-term toxicity of adjuvant treatment, especially in terms of second malignancies, the use of any form of adjuvant therapy must be given careful consideration. Any adjuvant treatment regime would expose the 80% of patients who would never have a relapse and would be cured by orchidectomy alone to the risk of treatment-related toxicity, a serious consideration given the retrospective data concerning second malignancies and cardiac effects.

The studies that have evaluated RT in testicular cancer all report clinically important increases in second malignancy (1,56), and treatment is associated with other significant toxicities such as cardiac toxicity (2). Although changes in the field size and RT dose did occur during the time period examined in these studies, such changes are unlikely to have a large effect on the estimation of risk, as any RT given (regardless of the dose/field delivered) is associated with increase in second malignancy, and it is the absolute size of the risk that may be affected by dose and field size issues. Although the RT treatment given today is not exactly the same as that given to the patients in these long-term toxicity studies, it is sufficiently similar that these issues cannot be ignored or dismissed as being irrelevant to current treatment practices. While further prospective study of these issues would in many ways be ideal, the large numbers of patients needed, and also the long periods of time over which such data needs to be collected, limits the ways in which this information can be obtained. Further clarification of the issue will always be hampered by the inherent difficulties associated with retrospective and non-randomized studies. Further, only a small minority, if any, of patients in the long-term toxicity studies, are likely to have received single-agent carboplatin; thus it is not currently possible to comment definitively on any associated long-term toxicity associated with that treatment.

Surveillance may have an advantage over adjuvant therapy in that both acute and long-term toxicity may potentially be avoided; however, surveillance requires a commitment to more intense and prolonged follow-up from both patients and clinicians. Patient compliance is essential, as the failure to detect relapse at an early stage may compromise survival. In addition, it must be noted that repeated exposure to serial CT scans poses some potential risk of second malignancy, albeit less significant than that posed by adjuvant RT. Therefore, the disadvantage of surveillance as a management strategy is that follow-up for surveillance requires more frequent visits and imaging to detect relapse when compared to patients who have received adjuvant therapy. Despite these drawbacks, all the guidelines found and evaluated included surveillance as a treatment option for stage I seminoma, and where the treatments were ranked in order of preference, surveillance was the primary option. Surveillance has become a well-established management option worldwide. It seems that all men with stage I seminoma should be suitable candidates for surveillance as long as they are able to undergo the follow-up and CT scan procedures. More importantly, these men should have full commitment to be compliant with the designated surveillance schedule. Non-compliance may lead to more advanced disease when relapse is detected clinically, potentially requiring more aggressive treatment for a cure.

There will still be many patients who may choose to receive adjuvant therapy. When adjuvant therapy is chosen, RT remains an option for patients. In the randomized trial reported by Jones et al (22), 20 Gy (2 Gy/day) was shown to be equivalent to 30 Gy in terms of disease control. One of the rationales for using 20 Gy was to reduce toxicity. While acute toxicity was improved, the follow-up in this trial is insufficient, and it may be underpowered to identify if there is a benefit with respect to long-term toxicity or second malignancy; however, 20 Gy has the advantage of an overall shorter treatment time with good disease control. There is some variation as to what is considered to be the standard radiation dose for stage I seminoma. Consideration should be given not only to the total dose but also to the dose per fraction. In some non-randomized studies (43,44), a total dose of 25 Gy given in 1.25 Gy per fraction has provided good in-field local control with low rates of acute toxicity.

In the randomized trial reported by Fossa et al (21), a reduced para-aortic field size was compared to standard extended-field (“dog-leg”) RT, with the hypothesis that a reduced field size would lead to reduced toxicity and second malignancy. While the trial demonstrated equivalence between the field sizes in terms of overall prevention of relapse, and also showed reduced acute toxicity, the follow-up is not sufficient to judge any reduction in long-term toxicity or second malignancy. One issue that does arise from this trial and the one reported by Jones

et al (22) was that the pattern of relapse was altered. While there was no difference in the overall number of recurrences, in both RCTs the pelvis was the most common site of relapse in patients treated with para-aortic RT, while pelvic relapse was rare for patients treated with extended-field RT. This is supported by an examination of patterns of relapse in patients in the non-randomized studies (25,27,30,43,44). Although only a small proportion of patients ultimately relapse in the pelvis, a pelvic recurrence is a serious event that is not easily detected at an early stage unless a CT scan is used. Therefore, all patients treated with para-aortic RT still require follow-up CT scans of the pelvis, an investigation that is not needed in patients treated with extended-field RT.

Neither of these modified treatments is likely to completely eliminate the risk of second malignancy, and any associated risk reduction remains unknown at this time. Thus, while para-aortic RT to a minimum dose of 20 Gy in 2 Gy fractions is the RT option that may best reduce acute toxicity, owing to concerns about the additional follow-up needed and pelvic relapses, extended-field RT may still be appropriate.

Data regarding the effects of adjuvant carboplatin therapy are limited, and the duration of follow-up is relatively short; thus, in contrast to RT, more questions remain regarding its use. The conclusion of the randomized trial reported by Oliver et al (23) was that carboplatin was equivalent to RT for prevention of short-term relapse, with improved acute toxicity. However, similar to the reduced-field RT trial discussed above, the pattern of relapse in patients treated with carboplatin was altered such that the majority of the relapses occurred in the retroperitoneal/para-aortic lymph nodes. Given these findings, continued CT monitoring for relapse cannot be eliminated from the follow-up schedule: indeed it should mirror that recommended for surveillance. This trial also has insufficient follow-up to evaluate the durability of disease control and the long-term toxicity of carboplatin in this patient population, as compared to RT. In a meta-analysis of sarcoma patients performed by Tierney et al (61), adjuvant chemotherapy showed a short-term benefit in the recurrence rate; however, overall survival did not appear to be affected, implying that recurrences may have been delayed as opposed to prevented. Without long-term survival data for chemotherapy in the treatment of seminoma, there is the possibility that recurrences have just been delayed and that late recurrences may still occur. In light of these issues, the use of carboplatin might be best restricted to situations in which there is a contraindication to RT or within a clinical trial.

Given that there are several management options, none of which have proven to have absolute superiority for patients with stage I testicular seminoma, men should be counselled concerning their treatment and the trade-offs associated with the different options after orchidectomy. While physicians may view one management approach as preferable, individual patient preferences must be considered. An individual treatment plan that takes into account the patient's wishes and is developed in consultation with an expert in the treatment of stage I seminoma should be developed for each patient. A summary of the benefits and risks of the different management strategies that physicians may wish to share with their patients appears in Table 5.

**Table 5: Benefits and risks of different management strategies in the treatment of stage I seminoma.**

<b>Management Option</b>	<b>Benefits</b>	<b>Drawbacks</b>
<b>Surveillance</b>	<ul style="list-style-type: none"> <li>• Excellent cancer cure rate</li> <li>• No Treatment related toxicity</li> <li>• Excellent salvage rate</li> <li>• Avoids overtreatment for the majority of patients</li> </ul>	<ul style="list-style-type: none"> <li>• Requires frequent follow-up CT scans, with associated long term risks</li> <li>• Some patients may experience anxiety related to risk of recurrence</li> </ul>
<b>Dogleg RT</b>	<ul style="list-style-type: none"> <li>• Excellent cancer cure rate</li> <li>• Eliminates need for routine CT scans</li> <li>• Reduces recurrence rates compared to patients managed by surveillance</li> </ul>	<ul style="list-style-type: none"> <li>• Long term second cancer risk</li> <li>• Long term cardiac risk</li> <li>• A large majority of patients are overtreated</li> </ul>
<b>Para-aortic RT</b>	<ul style="list-style-type: none"> <li>• Excellent cancer cure rate</li> <li>• Lower recurrence rate than patients managed by surveillance</li> </ul>	<ul style="list-style-type: none"> <li>• Requires frequent follow-up CT scans, with associated long term risks</li> <li>• Long term second cancer risk</li> <li>• Long term cardiac risk</li> <li>• A large majority of patients are overtreated</li> </ul>
<b>Chemotherapy</b>	<ul style="list-style-type: none"> <li>• Excellent cancer cure rate</li> <li>• Acute toxicity better than RT</li> </ul>	<ul style="list-style-type: none"> <li>• Long term survival unknown</li> <li>• Long term toxicity unknown</li> <li>• Requires frequent follow-up CT scans, with associated long term risks</li> <li>• A large majority of patients are overtreated</li> </ul>

Follow-up and imaging are recommended for all patients, even for those who receive adjuvant therapy. The ideal follow-up schedule has not been defined either in patients who have been managed with surveillance or in those who receive adjuvant therapy. Most guidelines have suggested more frequent follow-up (every three to four months) in the first three years, decreasing thereafter. A risk-based follow-up schedule with imaging of sites at risk of relapse as recommended by Martin et al may be appropriate (14) and is recommended by the DSG. While this guideline cannot be recommended without provisos as an overall guideline for managing stage I seminoma, owing to its limited scope, the DSG fully supports the follow-up recommendations given in this document

**CONCLUSIONS**

The optimal management of stage I seminoma remains to be defined. Surveillance appears to be the preferable option as this strategy minimizes the toxicity that might be associated with adjuvant treatment, while preserving high cure rates. The currently available evidence should be presented to patients in order select the most appropriate option for the individual.

**CONFLICT OF INTEREST**

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

## JOURNAL REFERENCE

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- Chung P, Mayhew LA, Warde P, Winqvist E, Lukka H; Genitourinary Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care. Management of stage I seminomatous testicular cancer: a systematic review. *Clin Oncol (R Coll Radiol)*. 2010;22:6-16. Epub 2009 Sep 22. doi:10.1016/j.clon.2009.08.006.

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For a complete list of the Genitourinary DSG members, please visit the CCO Web site at <http://www.cancercare.on.ca/>

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## REFERENCES

1. Vudarla N, Jawed I, Kaya H, Tward JD, Macdonald O.K, Martincic D, et al. Survival and secondary malignancy rates for adjuvant radiation therapy versus observation in stage I testicular seminoma: A Surveillance, Epidemiology, and End Results (SEER) analysis [abstract]. *J Clin Oncol*. 2007;25(18S):A5020
2. Huddart RA, Norman A, Shahidi M, Horwich A, Coward D, Nicholls J, et al. Cardiovascular disease as a long-term complication of treatment for testicular cancer. *J Clin Oncol*. 2003;21(8):1513-23.
3. National Cancer Institute of Canada. Canadian Cancer Statistics 2007. Toronto (Canada): National Cancer Institute of Canada ; 2007.
4. McGlynn KA, Devesa SS, Sigurdson AJ, Brown LM, Tsao L, Tarone RE. Trends in the incidence of testicular germ cell tumors in the United States. *Cancer*. 2003;97(1):63-70.
5. Weir HK, Marrett LD, Moravan V. Trends in the incidence of testicular germ cell cancer in Ontario by histologic subgroup, 1964-1996. *CMAJ*. 1999;160(2):201-5.
6. Warde PR, Sturgeon JFG, Gospodarowiz MK. Testicular cancer. In: Gunderson LL, Tepper JE, editors. *Clinical radiation oncology*. London (UK): Churchill Livingstone; 2007. p. 1261-85.
7. Choo R, Sandler H, Warde P, Hruby G, DeBoer G. Survey of radiation oncologists: practice patterns of the management of stage I seminoma of testis in Canada and a selected group in the United States. *Can J Urol*. 2002;9(2):1479-85.
8. Alomary I, Samant R, Genest P, Eapen L, Gallant V. The preferred treatment for stage I seminoma: a survey of Canadian radiation oncologists. *Clin Oncol (R Coll Radiol)*. 2006;18(9):696-9.
9. Browman GP, Levine MN, Mohide EA, Hayward RS, 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.
10. The AGREE Collaboration. The Appraisal of guidelines for research & evaluation (AGREE) instrument. London (UK): The AGREE Research Trust; 2001. Available from: <http://www.agreecollaboration.org/instrument/>
11. Albers P, Albrecht W, Algaba F, Bokemeyer C, Cohn-Cedermark G, Horwich A, et al. Guidelines on testicular cancer. *Eur Urol*. 2005;48(6):885-94.
12. Krege S, Souchon R, Schmoll HJ. Interdisciplinary consensus on diagnosis and treatment of testicular germ cell tumors: result of an update conference on evidence-based medicine (EBM). *Eur Urol*. 2001;40(4):372-91.
13. Laguna MP, Pizzocaro G, Klepp O, Algaba F, Kisbenedek L, Leiva O. EAU guidelines on testicular cancer. *Eur Urol*. 2001;40(2):102-10.
14. Martin JM, Panzarella T, Zwahlen DR, Chung P, Warde P. Evidence-based guidelines for following stage 1 seminoma. *Cancer*. 2007;109(11):2248-56.
15. Motzer RJ, Bahnson RR, Boston B, Carducci MA, Fishman M, Hancock SL, et al. Testicular cancer clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2007;3(1):52-76.
16. National Institute for Clinical Excellence. Guidance on cancer services. Improving outcomes in urological cancers: the manual. London (UK): National Institute for Clinical Excellence (NICE); 2002 Sep 19. Available from: [http://www.nice.org.uk/nicemedia/pdf/Urological\\_Manual.pdf](http://www.nice.org.uk/nicemedia/pdf/Urological_Manual.pdf)
17. National Institute for Clinical Excellence. Guidance for commissioning cancer services. Improving outcomes in urological cancers: the research evidence. London (UK): National Institute for Clinical Excellence (NICE); 2002 Sep 19. Available from: [http://www.nice.org.uk/nicemedia/pdf/Urological\\_Research\\_Evidence.pdf](http://www.nice.org.uk/nicemedia/pdf/Urological_Research_Evidence.pdf)

18. Schmoll HJ, Souchon R, Krege S, Albers P, Beyer J, Kollmannsberger C, et al. European consensus on diagnosis and treatment of germ cell cancer: a report of the European Germ Cell Cancer Consensus Group (EGCCCG). *Ann Oncol.* 2004;15(9):1377-99.
19. Wood L, Wilke D, Rutledge R, Rendon R, Broadfield L, Bell D, et al. Guidelines for the management of adult testicular cancer. Halifax (NS): Cancer Care Nova Scotia; revised 2005. Available from:  
<http://www.cancercare.ns.ca/media/documents/TesticularGuidelinesREV2006.pdf>
20. Shelley MD, Burgon K, Mason MD. Treatment of testicular germ-cell cancer: a Cochrane evidence-based systematic review. *Cancer Treat Rev.* 2002;28(5):237-53.
21. Fossa SD, Horwich A, Russell JM, Roberts JT, Cullen MH, Hodson NJ, et al. Optimal planning target volume for stage I testicular seminoma: A Medical Research Council randomized trial. Medical Research Council Testicular Tumor Working Group. *J Clin Oncol.* 1999;17(4):1146.
22. Jones WG, Fossa SD, Mead GM, Roberts JT, Sokal M, Horwich A, et al. Randomized trial of 30 versus 20 Gy in the adjuvant treatment of stage I testicular seminoma: a report on Medical Research Council Trial TE18, European Organisation for the Research and Treatment of Cancer Trial 30942 (ISRCTN18525328). *J Clin Oncol.* 2005;23(6):1200-8.
23. Oliver RT, Mason MD, Mead GM, von der MH, Rustin GJ, Joffe JK, et al. Radiotherapy versus single-dose carboplatin in adjuvant treatment of stage I seminoma: a randomised trial. *Lancet.* 2005;366(9482):293-300.
24. Bamberg M, Schmidberger H, Meisner C, Classen J, Souchon R, Weinknecht S, et al. Radiotherapy for stages I and IIA/B testicular seminoma. *Int J Cancer.* 1999;83(6):823-7.
25. Classen J, Schmidberger H, Meisner C, Winkler C, Dunst J, Souchon R, et al. Para-aortic irradiation for stage I testicular seminoma: results of a prospective study in 675 patients. A trial of the German testicular cancer study group (GTCSG). *Br J Cancer.* 2004;90(12):2305-11.
26. Livsey JE, Taylor B, Mobarek N, Cooper RA, Carrington B, Logue JP. Patterns of relapse following radiotherapy for stage I seminoma of the testis: implications for follow-up. *Clin Oncol (R Coll Radiol).* 2001;13(4):296-300.
27. Logue JP, Harris MA, Livsey JE, Swindell R, Mobarek N, Read G. Short course para-aortic radiation for stage I seminoma of the testis. *Int J Radiat Oncol Biol Phys.* 2003;57(5):1304-9.
28. Niewald M, Waziri A, Walter K, Nestle U, Schnabel K, Humke U. Low-dose radiotherapy for stage I seminoma: early results. *Radiother Oncol.* 1995;37(2):164-6.
29. Niewald M, Freyd J, Fleckenstein J, Wullich B, Rube C. Low-dose radiotherapy for Stage I seminoma-long-term results. *Int J Radiat Oncol Biol Phys.* 2006;66(4):1112-9.
30. Sommer K, Brockman WP, Hubener KH. Treatment results and acute and late toxicity of radiation therapy for testicular seminoma. *Cancer.* 1990;66(2):259-63.
31. Taylor MB, Carrington BM, Livsey JE, Logue JP. The effect of radiotherapy treatment changes on sites of relapse in stage I testicular seminoma. *Clin Radiol.* 2001;56(2):116-9.
32. Argirovic D. Germ cell testicular tumors in clinical stage A and normal values of serum tumor markers post-orchietomy: the experience in the management of 300 consecutive patients. *Journal of BUON.* 2005;10:195-2000.
33. Dieckmann KP, Bruggeboes B, Pichlmeier U, Kuster J, Mullerleile U, Bartels H. Adjuvant treatment of clinical stage I seminoma: is a single course of carboplatin sufficient? *Urology.* 2000;55(1):102-6.
34. Reiter WJ, Brodowicz T, Alavi S, Zielinski CC, Kozak W, Maier U, et al. Twelve-year experience with two courses of adjuvant single-agent carboplatin therapy for clinical stage I seminoma. *J Clin Oncol.* 2001;19(1):101-4.

35. Steiner H, Holth L, Wirtenberger W, Berger AP, Bartsch G, Hobisch A. Long-term experience with carboplatin monotherapy for clinical stage I seminoma: a retrospective single-center study. *Urology*. 2002;60(2):324-8.
36. Daugaard G, Petersen PM, Rorth M. Surveillance in stage I testicular cancer. *APMIS*. 2003;111(1):76-83.
37. Francis R, Bower M, Brunstrom G, Holden L, Newlands ES, Rustin GJ, et al. Surveillance for stage I testicular germ cell tumours: results and cost benefit analysis of management options. *Eur J Cancer*. 2000;36(15):1925-32.
38. Horwich A, Alsanjari N, A'Hern R, Nicholls J, Dearnaley DP, Fisher C. Surveillance following orchidectomy for stage I testicular seminoma. *Br J Cancer*. 1992;65(5):775-8.
39. Warde PR, Gospodarowicz MK, Goodman PJ, Sturgeon JF, Jewett MA, Catton CN, et al. Results of a policy of surveillance in stage I testicular seminoma. *Int J Radiat Oncol Biol Phys*. 1993;27(1):11-5.
40. Alomary I, Samant R, Gallant V. Treatment of stage I seminoma: a 15-year review. *Urol Oncol*. 2006;24(3):180-3.
41. Oliver RT, Edmonds PM, Ong JY, Ostrowski MJ, Jackson AW, Baille-Johnson H, et al. Pilot studies of 2 and 1 course carboplatin as adjuvant for stage I seminoma: should it be tested in a randomized trial against radiotherapy? *Int J Radiat Oncol Biol Phys*. 1994;29(1):3-8.
42. Powles T, Oliver T, Ostrowski M, Levay J, Shamash J, Williams M. The long term side effects of adjuvant carboplatin for stage I seminoma [abstract]. *J Clin Oncol*. 2007;25(18S):A5089.
43. Warde P, Gospodarowicz MK, Panzarella T, Catton CN, Sturgeon JF, Moore M, et al. Stage I testicular seminoma: results of adjuvant irradiation and surveillance. *J Clin Oncol*. 1995;13(9):2255-62.
44. Warde P, Gospodarowicz MK, Panzarella T, Chow E, Murphy T, Catton CN, et al. Long term outcome and cost in the management of stage I testicular seminoma. *Can J Urol*. 2000;7(2):967-72.
45. Warde P, Chung P, Sturgeon J, Panzarella T, Giuliani M, Tew-George B, et al. Should surveillance be considered the standard of care in stage I seminoma? Abstract No. [abstract]. *J Clin Oncol*. 2005;23(16S (part I of II)):A4520.
46. Aparicio J, Garcia dM, X, Maroto P, Paz-Ares L, Alba E, Saenz A, et al. Multicenter study evaluating a dual policy of postorchidectomy surveillance and selective adjuvant single-agent carboplatin for patients with clinical stage I seminoma. *Ann Oncol*. 2003;14(6):867-72.
47. Aparicio J, Germa JR, Garcia dM, X, Maroto P, Arranz JA, Saenz A, et al. Risk-adapted management for patients with clinical stage I seminoma: the Second Spanish Germ Cell Cancer Cooperative Group study. *J Clin Oncol*. 2005;23(34):8717-23.
48. Bokemeyer C, Schmoll HJ. Secondary neoplasms following treatment of malignant germ cell tumors. *J Clin Oncol*. 1993;11(9):1703-9.
49. Hay JH, Duncan W, Kerr GR. Subsequent malignancies in patients irradiated for testicular tumours. *Br J Radiol*. 1984;57(679):597-602.
50. Horwich A, Bell J. Mortality and cancer incidence following radiotherapy for seminoma of the testis. *Radiother Oncol*. 1994;30(3):193-8.
51. Jacobsen GK, Mellempgaard A, Engelholm SA, Moller H. Increased incidence of sarcoma in patients treated for testicular seminoma. *Eur J Cancer*. 1993;29A(5):664-8.
52. Moller H, Mellempgaard A, Jacobsen GK, Pedersen D, Storm HH. Incidence of second primary cancer following testicular cancer. *Eur J Cancer*. 1993;29A(5):672-6.
53. Richiardi L, Scelo G, Boffetta P, Hemminki K, Pukkala E, Olsen JH, et al. Second malignancies among survivors of germ-cell testicular cancer: a pooled analysis between 13 cancer registries. *Int J Cancer*. 2007;120(3):623-31.

54. Robinson D, Moller H, Horwich A. Mortality and incidence of second cancers following treatment for testicular cancer. *Br J Cancer*. 2007;96(3):529-33.
55. Travis LB, Curtis RE, Storm H, Hall P, Holowaty E, van Leeuwen FE, et al. Risk of second malignant neoplasms among long-term survivors of testicular cancer. *J Natl Cancer Inst*. 1997;89(19):1429-39.
56. Travis LB, Fossa SD, Schonfeld SJ, McMaster ML, Lynch CF, Storm H, et al. Second cancers among 40,576 testicular cancer patients: focus on long-term survivors. *J Natl Cancer Inst*. 2005;97(18):1354-65.
57. van Leeuwen FE, Stiggelbout AM, van den Belt-Dusebout AW, Noyon R, Eliel MR, van Kerkhoff EHM, et al. Second cancer risk following testicular cancer: a follow-up study of 1,909 patients. *J Clin Oncol*. 1993;11(3):415-24.
58. Wanderas EH, Fossa SD, Tretli S. Risk of a second germ cell cancer after treatment of a primary germ cell cancer in 2201 Norwegian male patients. *Eur J Cancer*. 1997;33(2):244-52.
59. Zagars GK, Ballo MT, Lee AK, Strom SS. Mortality after cure of testicular seminoma. *J Clin Oncol*. 2004;22(4):640-7.
60. Schoffski P, Hohn N, Kowalski R, Classen J, Meisner C, Fechner G, et al. Health-related quality of life (QoL) in patients with seminoma stage I treated with either adjuvant radiotherapy (RT) or two cycles of carboplatinum chemotherapy (CT): Results of a randomized phase III trial of the German Interdisciplinary Working Part on Testicular Cancer. [abstract]. *J Clin Oncol*. 2007;25(18S): A5050.
61. Tierney JF, Stewart LA, Parmar MKB. Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data. *Lancet*. 1997;350(9092):1647-54.

**Appendix A. Results of AGREE tool rating of guidelines.**

Guideline	Agree Domain Scores						Overall Rating
	Scope and Purpose	Stakeholder Involvement	Rigour of Development	Clarity and Presentation	Applicability	Editorial Independence	
<b>Interdisciplinary Consensus on Diagnosis and Treatment of Testicular GCT (2001) (12)</b>	16.7%	33.3%	33.3%	29.2%	0%	8.3%	Not recommended (2)
<b>NICE Guidance (2002) (16,17)</b>	44.4%	41.7%	45.2%	58.3%	44.4%	16.7%	Recommended with provisos or alterations (1) Not recommended (1)
<b>EGCCCG (2004) (18)</b>	44.4%	25%	42.9%	54.2%	11.1%	16.7%	Recommended with provisos or alterations (2)
<b>NCCN (2007) (15)</b>	44.4%	29.2%	19.0%	83.3%	11.1%	66.7%	Recommended with provisos or alterations (1) Not recommended (1)
<b>EAU (2001, 2005) (11,13)</b>	33.3%	25%	33.3%	58.3%	11.1%	16.7%	Recommended with provisos or alterations (2)
<b>CCNS (2005) (19)</b>	44.4%	37.5%	38.1%	50%	0%	41.7%	Recommended with provisos or alterations (2)
<b>Martin (2007) (14)</b>	55.6%	16.7%	42.9%	25%	11.1%	33.3%	Recommended with provisos or alterations (1) Not recommended (1)

**Abbreviations:** AGREE – Appraisal of Guidelines for Research & Evaluation; CCNS – Cancer Care, Nova Scotia; EAU – European Association of Urology; EGCCCG – European Germ Cell Cancer Consensus Group; GCT – germ cell tumour; NCCN – National Comprehensive Cancer Network; NICE – National Institute for Clinical Excellence.

**Appendix B. Martin (14) recommendations for frequency of follow-up and imaging.**

**Table 1. Recommendations for frequency of follow-up and imaging.**

<b>Annual Hazard Rate %</b>	<b>Frequency per year</b>	<b>Surveillance year</b>	<b>Extended-field RT year</b>	<b>Para-aortic RT year</b>	<b>Carboplatin 1 cycle year</b>	<b>Carboplatin 2 cycles year</b>
>5	3	1-2	N/A	N/A	N/A	N/A
1-5	2	3-4	1-3	1-3	1-3	1-2
0.3-1	1	5-10	4-6	4-6	Limited Data	Limited Data
<0.3	Cease	After 10	After 6	After 6	Limited Data	Limited Data

**Table 2. Recommendations for investigations required during follow-up.**

<b>Investigation</b>	<b>Surveillance</b>	<b>Extended-field RT</b>	<b>Para-aortic RT</b>	<b>Carboplatin 1 cycle</b>	<b>Carboplatin 2 cycles</b>
CT abdomen	Yes	No	No	Yes	Yes
CT pelvis	Yes	No	Yes	Yes	Yes
Chest X-ray	Yes	Yes	Yes	Yes	Yes

**Appendix C. Non-randomized trial data.**

Study	N	Treatment Arms	Overall Survival
<b>Radiotherapy</b>			
Niewald 2006 (28,29)	191	RT 30 Gy N=16	At five years: 95-100% across groups
		RT 25.5 Gy N=62	
		RT 20 Gy N=69	
Classen 2004 (24,25)	721	RT 26 Gy	At five years: 99.1%
Logue 2003 (27)	431	Para-aortic RT	At five years: 98% ( $\pm 0.72$ SE)
Livsey 2001 (26)	409	Para-aortic RT N=339	At five years: 99.5%*
		Extended-field RT N=70	
Sommer 1990 (30)	172	Para-aortic and para-iliac radiation	At five years: 98.5%
Taylor 2001 (31)	406	Extended-field RT N=68	Approaching 100%† (One death)
		Para-aortic RT N=338	
<b>Surveillance</b>			
Horwich 1992 (38)	103	Surveillance	At five years: 97.1%
Francis 2000 (37)	120	Surveillance	At five years: 100% At ten years: 94.4% (95% CI 86-100%)
Daugaard 2003 (36)	394	Surveillance	At median follow-up of 60 months: 98.6%
Warde 1993 (39)	148	Surveillance	At median follow-up of 47 months: 98.6%
<b>Carboplatin</b>			
Steiner 2002 (35)	108	2 cycles carboplatin	100%
Reiter 2001 (34)	107	2 cycles carboplatin	At five years: 94%
Dieckmann 2000 (33)	125	1 cycle carboplatin	At five years: 100%

Study	N	Treatment Arms	Overall Survival
Argirović 2005 (32)	163	2 cycles carboplatin	At four years: 99.4%
<b>Comparisons</b>			
Warde 1995/2000 (43,44)	471	RT N=245 Surveillance N=226	At five years: 97%*
Alomary 2006 (40)	150	RT N=107 Surveillance N=43	At five years: 100%
Warde 2005 (45)	704	Surveillance N=421 RT N=283	At five years: 99.8%
Oliver 1994 /Powles 2007 (41,42)	199	RT N=79 Surveillance N=67 1 cycle carboplatin N=25 2 cycles carboplatin N=53	At four years: 98% S: 98.3%† C: 98%† At twenty years: RT: 76%
<b>Risk-adapted Management</b>			
Aparicio 2003 (46)	203	Surveillance N=143 2 cycles carboplatin N=60	At five years: 96.7% (95% CI 92.8- 100%)
Aparicio 2005 (47)	314	Surveillance N=100 2 cycles carboplatin N=214	At five years: 100%*

**Abbreviations:** C – carboplatin; CI – confidence interval; RT – radiotherapy; S – surveillance; SE – standard error.

\* Actuarial rate

† Timeframe not specified



### **Evidence-Based Series #3-18: Section 3**

## **Management of Stage I Seminoma: EBS Development Methods and External Review Process**

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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: January 30, 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 core products developed by the PEBC are the evidence-based series (EBS) reports, including EBS clinical practice and organizational guidelines, which focus on clinical or organizational problems or questions; EBS standards, which focus on system problems or questions; and the EBS reports that combine both questions and problems.

To accomplish its mandate, the PEBC supports a network of committees, including long-standing disease-specific panels (e.g., Lung Cancer Disease Site Group, Hematology Disease Group) and time-limited Guideline Development Groups (GDGs) and Expert Panels (e.g., Diagnostic Assessment Program Standards Expert Panel). Panel membership can include clinical experts, administrative leaders, methodologists, and community representatives from across the province. Inspired by the Practice Guidelines Development Cycle (1,2), the panel members work together to (i) identify a specific question or problem, (ii) assemble, describe, and appraise relevant evidence to address the question/problem, and (iii) draft recommendations. The resulting draft EBS then is circulated to relevant stakeholders in the province for formal external review. The results of the external review are described in the final EBS report. The PEBC has a formal standardized process to ensure the currency of each clinical practice guideline report, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information.

## The Evidence-Based Series

Each Evidence-Based Series is comprised of three sections.

- *Section 1: Guideline Recommendations.* This section contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the DSG or GDG involved and a formalized external review.
- *Section 2: Evidentiary Base.* This section presents the comprehensive systematic review of the clinical and scientific research on the topic and the conclusions reached by the DSG or GDG.
- *Section 3: EBS Development Methods and External Review Process.* This section summarizes the guideline development process and the results of the formal external review by Ontario practitioners of the draft version of the clinical practice guideline and systematic review.

## DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

### Development and Internal Review

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

### Report Approval Panel Review Prior to External Review

Prior to the submission of this evidence-based series report for external review, the draft report was reviewed by the PEBC Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues. Key issues raised by the Panel and their resolution by the DSG (*italicized*) included the following:

- RAP suggested that the benefits and risks of the different management options be made clearer. *Table 1 in Section 1 (Table 5 in Section 2) summarizing the benefits and risks of the management options was added.*
- RAP asked for more explicitness regarding the connection between evidence and recommendations. *This was clarified in the revised version.*
- RAP asked for more clarification regarding the role of randomized controlled trial (RCT) versus non-randomized study evidence. *The role of the non-randomized study evidence with respect to the RCT data was clarified in the revised version.*
- RAP suggested the issue of why the different treatment options require different follow-up regimes be more explicit. *The interpretive summary in Section 2 and the qualifying statements in Section 1 were rewritten to provide more clarity on this issue.*
- RAP questioned how the late effects data related to the current treatments in use. *Clarification regarding this issue was provided in the interpretive summary. Current radiotherapy techniques are believed to be similar enough to those used in these studies for these data to be directly relevant to current treatment.*
- RAP suggested including data on the infertility risks of carboplatin. *As this outcome was not included in our selection criteria and the literature search, there were no data to*

*report for fertility. This may be a topic for the Genitourinary DSG to explore in a separate guideline.*

### External Review

This guideline was reviewed in draft form at the 1<sup>st</sup> Canadian Germ Cell Cancer Consensus Conference, 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). Fourteen of the attendees were medical oncologists, thirteen were radiation oncologists, eleven were urologists/urological surgeons, and one was a pathologist. Also present were a nurse practitioner, a radiation therapist, a member of Cancer Care Ontario'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 guidelines, and then were given presentations on the European and American guidelines. Conference attendees were given the opportunity to discuss the different guidelines and to pose questions to the presenters. They were also given paper copies of the guidelines. The next day, attendees were asked to come to a consensus concerning recommendations for treatment.

The conference attendees offered the following feedback on the guideline and the Genitourinary DSG responses (italicized) included the following:

- Some participants thought that a risk-adapted approach should have been mentioned, while others believed that the prognostic factors had not been properly validated. *No change was made to the guideline.*
- Some participants felt there should be guidance as to who is a good candidate for surveillance. *This has been clarified in the interpretive summary.*
- Conference attendees expressed discomfort with recommending chemotherapy when only one short-term RCT provided data. The chemotherapy data are not mature enough to determine if recurrences have been prevented or merely postponed, and the quality of life measurements used have not been validated. Lack of data does not mean that there are no dangers. Carboplatin should only be the third choice, available only in exceptional circumstances. *The reasons for not recommending chemotherapy have been made clearer in this document.*
- Surveillance should be stressed as the treatment option of choice, because we harm more patients with adjuvant treatment than would otherwise die from the disease. *The benefits of surveillance have been stressed in the revised document.*

With respect to consensus concerning the treatment of stage I seminoma, the attendees all agreed that surveillance was the management option of choice. They also agreed that if adjuvant treatment was chosen, the treatment of choice should be RT.

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

### **Report Approval Panel Review After External Review**

Once the changes based on the external review process had been incorporated into the document, the draft report was again reviewed by the PEBC Report Approval Panel. Key issues raised by the Panel and the Genitourinary DSG responses (italicized) included the following:

- A reorganization of Section 1 of the document was requested. *This section was reorganized to provide greater clarity.*
- Clarification was requested about RT being the second choice and chemotherapy being the third choice for treatment. *The recommendations were reworded so that the order of recommendation was clearer.*
- A rewording of the literature search results was requested. *This section was reworded so that results were clearer.*
- A clarification as to why blinding was labelled as not relevant was requested. *A statement was added stating that blinding could not be used owing to the differences in the treatment regimes, and the blinding information was removed from the study quality table.*
- Removal of mention of guidelines found that did not distinguish stage I seminoma patients specifically was requested. *These were removed as requested.*
- Clarification of the non-randomized data was requested. *An appendix (Appendix C) was added containing basic summary data from these studies.*

### **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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## REFERENCES

1. 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;13:502-12.
2. Browman GP, Newman TE, Mohide EA, Graham ID, Levine MN, Pritchard KI, et al. Progress of clinical oncology guidelines development using the practice guidelines development cycle: the role of practitioner feedback. *J Clin Oncol.* 1998;16(3):1226-31.