Evidence-Based Series 3-18: Version 2

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

Management of Stage I Seminoma

Members of the Genitourinary Cancer Disease Site Group

An assessment conducted in November 2016 deferred the review of Evidence-based Series (EBS) 3-18 Version 2. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

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PEBC Genitourinary Cancer DSG page at:
http://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/genitoebs/

Section 1: Guideline Recommendations
Section 2: Evidentiary Base
Section 3: EBS Development Methods and External Review Process
Section 4: Document Review and Summary tool

Release Date: March 5, 2014

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Guideline Report History

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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)

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 \([\text{AUC}]\)=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


Appendix A.

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

<table>
<thead>
<tr>
<th>Management Option</th>
<th>Benefits</th>
<th>Drawbacks</th>
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| **Surveillance**   | • Excellent cancer cure rate  
                    • No treatment-related toxicity  
                    • Excellent salvage rate  
                    • Avoids overtreatment for the majority of patients | • Requires frequent follow-up CT scans, with associated long-term risks  
                                                                 • Some patients may experience anxiety related to risk of recurrence |
| **Dogleg RT**      | • Excellent cancer cure rate  
                    • Eliminates need for routine CT scans  
                    • Reduces recurrence rates compared to patients managed by surveillance | • Long-term second cancer risk  
                                                                 • Long-term cardiac risk  
                                                                 • A large majority of patients are overtreated |
| **Para-aortic RT** | • Excellent cancer cure rate  
                    • Lower recurrence rate than for patients managed by surveillance | • Requires frequent follow-up CT scans, with associated long-term risks  
                                                                 • Long-term second cancer risk  
                                                                 • Long-term cardiac risk  
                                                                 • A large majority of patients are overtreated |
| **Chemotherapy**   | • Excellent cancer cure rate  
                    • Acute toxicity better than RT | • Long-term survival unknown  
                                                                 • Long-term toxicity unknown  
                                                                 • Requires frequent follow-up CT scans, with associated long-term risks  
                                                                 • A large majority of patients are overtreated |