Ontario
Cancer Care Ontario
Action Cancer Ontario

Evidence-Based Series 3-18 Version 2 IN REVIEW

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 December 2021 placed Guideline 3-18 Version 2 IN REVIEW. This means that it is undergoing a review for currency and relevance. It is still appropriate for this document to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

EBS 3-18 Version 2 is comprised of 4 sections. You can access the summary and full report here:

https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/441

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

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/
or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

PEBC Report Citation (Vancouver Style): Chung P, Mayhew LA, Warde P, Winquist E, Lukka H; members of the Genitourinary Cancer Disease Site Group. Management of stage I seminoma. M Lock and J Brown, reviewers. Toronto (ON): Cancer Care Ontario; 2008 Jan 30 [In Review 2021 Dec]. Program in Evidence-based Care Practice Guideline No.:3-18 Version 2. IN REVIEW.

Journal Citation (Vancouver Style): Chung P, Mayhew LA, Warde P, Winquist 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(1):6-16.

Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original January 30 2008	1981 through May 2007	Full Report	Web publication	NA
Version 2 March 2014	September 2007 to December 2013	New data found in Section 4: Document Review Summary and Tool	Updated Web publication	2008 recommendations are ENDORSED

Evidence-Based Series #3-18: Version 2: Section 1

Management of Stage I Seminoma: Guideline Recommendations

P. Chung, L.A. Mayhew, P. Warde, E. Winquist, H. Lukka,
and Members of the Genitourinary Cancer Disease Site Group

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

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 4: Document Review Summary and Tool for a summary of updated evidence published between 2007 and 2013, and for details on how this Clinical Practice Guideline was ENDORSED.

Report Date: March 5, 2014

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).

Funding

The PEBC is a provincial initiative of Cancer Care Ontario 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.

Contact Information

For further information about this report, please contact **Dr. Himu Lukka**, Chair, Genitourinary Cancer Disease Site Group, Juravinski Cancer Centre, 699 Concession Street, Hamilton, ON, L8V 5C2; TEL (905) 387-9711 ext. 67699; FAX (905) 575-6326; Email himu.lukka@hrcc.on.ca
or **Dr. Eric Winquist**, Vice-Chair, Genitourinary Cancer Disease Site Group, London Health Sciences Centre, 790 Commissioners Road East, London, Ontario, N6A 4L6 TEL (519) 685-8600 ext. 53243; FAX (519) 685-8624.

For information about the PEBC and the most current version of all reports, please visit the CCO Web site at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-525-9140, ext. 22055 Fax: 905-522-7681

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, Mellemgaard 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, Mellemgaard 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.

Management Option	Benefits	Drawbacks
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