Long-term outcomes following post-operative radiotherapy for Stage I/II testicular seminoma – an Australasian single-institution experience

Wee Loon Ong, BMedSci, MBBS, MPhil (Epi), 1, 2 Lester Nazareth, MBBS, 1 Benjamin Hindson, MBChB, FRANZCR, 1 Bronwyn Matheson, MBBS, FRANZCR, 1 & Jeremy L Millar, MBChB, FRANZCR 1, 2

1 Alfred Health Radiation Oncology Service, Prahran, Victoria, Australia
2 Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Victoria, Australia

Keywords
Outcomes, post-operative radiotherapy, second malignancies, seminoma

Introduction
Testicular seminoma is the most common germ cell cancer diagnosed in men. In Australia, the age-standardised incidence rate of seminoma was 3.79 cases/100,000 men, with the peak incidence in men age 30–34. 1 The primary treatment for testicular seminoma involves radical transinguinal orchidectomy with ligation of the spermatic cord.

For patients with Stage I seminoma, the options post-operatively include close surveillance, radiotherapy or chemotherapy. Given that seminoma cells are extremely radiosensitive, historically radiotherapy to the para-aortic (PA) and iliac lymph nodes are the standard post-operative treatment for Stage I seminoma patients. Post-operative radiotherapy (PORT) is associated with excellent oncological outcomes, reducing the risk of disease relapse from approximately 15% 2 to less than 5%. 3 However, long-term studies have raised concerns about the late effects of radiation treatment, including the increased risk of second malignancies (SM) 4–6 and cardiovascular diseases. 5–7

This has resulted in a shift to alternative approaches for Stage I seminoma patients, such as surveillance or single-agent chemotherapy. Single-agent post-operative...
chemotherapy has emerged as a treatment option for patients, following findings from randomised trials showing non-inferiority of post-operative chemotherapy compared to radiotherapy. However, there is a lack of long-term toxicity data on post-operative single-agent chemotherapy for Stage I seminoma. The other approach is surveillance, particularly for patients who are likely to adhere to a rigorous follow-up protocol for at least 5 years with reservation of radiation treatment for disease relapse.

For Stage IIA and IIB seminoma, PORT remains the current standard of care, with approximately 90% relapse-free survival (RFS) and almost 100% overall survival (OS), although chemotherapy, using four cycles of etoposide and cisplatin (EP) or three cycles of bleomycin, etoposide and cisplatin (BEP), is an alternative to radiotherapy. A very recent meta-analysis of 13 studies by Giannatempo et al. suggested a trend in favour of chemotherapy for management of Stage IIB seminoma given the lower incidence of side effects and relapse rate. For stage IIC disease, chemotherapy is the treatment of choice.

We aim to provide additional data to the current literature on the long-term outcomes following postoperative radiotherapy (PORT) for Stage I-II seminoma patients, based on our experience in an Australian radiation treatment centre.

### Methods

This is a retrospective study of all patients with histologically confirmed Stage I/II testicular seminoma, who were referred to and subsequently treated with PORT, at the Alfred Health Radiation Oncology Service since its establishment in 1992 through to 2013. Following PORT, all patients were followed up according to the institutional policy, which included 3–6 monthly outpatient follow-up for the first 2 years, with serum marker monitoring, chest X-ray and CT imaging of the abdomen and pelvis, and annual follow-up thereafter for at least 8–10 years. The Alfred Health Radiation Oncology Service maintained a comprehensive departmental database. For patients who had been discharged from the care of the department, patients’ most recent disease status (including any recent major medical events such as major surgeries or myocardial infarction) was obtained through contact with the primary care physicians or the medical oncologists on an annual basis.

The primary oncological outcomes of interest are the relapse free survival (RFS), testicular cancer specific survival (TCSS) and overall survival (OS). For TCSS, an event was defined as any death secondary to testicular seminoma due to progressive metastatic disease or acute treatment-related complications, whereas for OS, an event included any reported deaths. The long-term treatment-related side effects of interest are the cardiovascular toxicities (CV), gastrointestinal toxicities (GIT) and second malignancies (SM). The CV events were defined as any documented acute myocardial infarctions, coronary artery bypass grafts, angioplasties, coronary stent insertions, valve replacements or cerebrovascular accidents. GIT events were defined as any endoscopically confirmed peptic ulcer disease or any documented hospital admission with small bowel obstruction following radiation treatment. SM was defined as any biopsy-confirmed malignancies, irrespective of the relation to the field of radiation treatment.

All patient-, tumour-, treatment- and outcome-related data were obtained from the Alfred Health Radiation Oncology Service electronic medical records and database, including a word search for all possible terms that might refer to the outcomes of interest. To ensure consistency and accuracy in data collection, two authors (WLO and LN) reviewed and crosschecked all medical records. In addition, patient identifiers were used to access linked data from the Victorian Cancer Registry (VCR), to enable confirmation of survival data and diagnosis of SM. The VCR links to the Australian Institute of Health and Welfare National Death Index, so patients who had emigrated from Victoria would not be missed as a death if it occurred in Australia. The study was approved by the Alfred Health Ethics Committee (Project No 19/14).

### Statistical analyses

The differences in characteristic between Stage I/II seminoma patients were analysed using the Student’s t-test (or Mann–Whitney U test as appropriate) for continuous variables and the Pearson’s chi-squared test for categorical variables. A $P < 0.05$ on a two-sided statistical test is considered statistically significant. The RFS, TCSS, OS and SM free survival (SMFS) were estimated using the Kaplan–Meier methods. The time to event was defined from the date of completion of PORT to the date of outcomes of interest. Patients were censored on the date of last follow-up if they did not experience the outcomes of interest. All statistical analyses were performed using STATA/IC 13 (STATA Corp, College Station, TX).

### Results

In all, 169 patients with Stage I/II seminoma were referred to the Alfred Health Radiation Oncology Service and 125 proceeded to have treatment with external beam radiotherapy (EBRT) to the PA nodes or PA nodes and ipsilateral or bilateral iliac lymph nodes. Seventeen patients had chemotherapy and no radiation, four had treatment elsewhere and 23 were put on surveillance and
never received PORT. Of the 125 patients included in our study, 106 (85%) had Stage I seminoma, while the remaining (n = 19, 15%) had Stage II seminoma.

**Baseline characteristics**

The median age at diagnosis of seminoma was 36 (range = 20–62). Only nine patients (7%) reported a history of undescended testis. Fifty-eight patients (46%) had seminoma involving the right testis. The median tumour size was 40 mm (range: 4–105 mm). Stage II seminoma patients had significantly larger tumour size (median: 53; range: 22–90 mm) compared to Stage I seminoma patients (median: 36; range: 4–105 mm, \( P = 0.02 \)), and were more likely to have the primary tumour extending beyond the tunica albuginea (i.e. pT2 and above) – 37% in Stage II and 10% in Stage I respectively (\( P = 0.008 \)) (Table 1).

Two patients had disease relapse on referral for radiotherapy, of which one relapse occurred after 2 years of surveillance, while the other occurred approximately 3 years after adjuvant chemotherapy and was treated with retroperitoneal lymph node dissection before radiation treatment. Two Stage II seminoma patients were referred for radiotherapy due to persistent lymphadenopathy and elevated tumour markers despite post-operative chemotherapy.

**Treatment**

More than half of the patients (59%) had radiation to the PA plus ipsilateral common iliac lymph nodes (the classic

| Table 1. Patient-, tumour- and treatment-related characteristics. |
|-----------------------------------------------------------------|
| **Stage**          | Stage I (n = 106; 85%) | Stage II (n = 19; 15%) | All (n = 125) |
|--------------------|------------------------|------------------------|---------------|
| **Patient characteristics** |                        |                        |               |
| Age at diagnosis, year – median (range) | 35 (20–61)            | 41 (29–62)            | 36 (20–62)    |
| History of undescended testis – n (%) |                        |                        |               |
| No                 | 100 (94)               | 16 (84)                | 116 (93)      |
| Yes                | 6 (6)                  | 3 (16)                 | 9 (7)         |
| **Tumour characteristics** |                        |                        |               |
| Laterality – n (%) |                        |                        |               |
| Right              | 47 (44)                | 11 (58)                | 58 (46)       |
| Left               | 59 (56)                | 8 (42)                 | 67 (54)       |
| Tumour size – median (range) | 36 (4–105)            | 53 (22–90)            | 40 (4–105)    |
| Primary tumour – n (%) |                        |                        |               |
| pT1                | 95 (90)                | 12 (63)                | 107 (86)      |
| pT2 (tunica vaginalis involvement) | 9 (8)                 | 5 (26)                 | 14 (11)       |
| pT3 (spermatic cord involvement) | 2 (2)                 | 2 (11)                 | 4 (3)         |
| Regional lymph nodes – n (%) |                        |                        |               |
| N0                 | 106 (100)              | 0 (0)                  | 106 (85)      |
| N1                 | 0 (0)                  | 13 (68)                | 13 (10)       |
| N2                 | 0 (0)                  | 6 (32)                 | 6 (5)         |
| Disease relapse on presentation – n (%) |                        |                        |               |
| No                 | 106 (100)              | 17 (89)                | 123 (98)      |
| Yes                | 0 (0)                  | 2 (11)                 | 2 (1.5)       |
| **Treatment details** |                        |                        |               |
| Treatment modalities – n (%) |                        |                        |               |
| Orchidectomy + RTx | 106 (100)              | 16 (84)                | 122 (98)      |
| Orchidectomy + CTx + RTx | 0 (0)                | 2 (11)                 | 2 (1)         |
| Orchidectomy + CTx + RPLND + RTx | 0 (0)               | 1 (5)                  | 1 (1)         |
| Interval between diagnosis (i.e. orchidectomy) and RTx, month – median (range) | 1.6 (0.5–9.2) | 1.5 (0.7–45) | 1.6 (0.5–45) |
| Treatment field – n (%) |                        |                        |               |
| PA lymph nodes only | 43 (41)                | 7 (37)                 | 50 (40)       |
| PA and ipsilateral common iliac nodes ‘hockey-stick’ | 54 (51)            | 8 (42)                 | 62 (50)       |
| PA and ipsilateral iliac ‘dog-leg’ | 9 (8)                | 3 (16)                 | 12 (9)        |
| PA and bilateral iliac nodes | 0 (0)                | 1 (5)                  | 1 (1)         |
| Radiation dose, Gy – median (range) | 25 (20–35)           | 35 (25–40)            | 25 (20–40)    |
| Number of fractions – median (range) | 20 (10–30)          | 25 (20–28)            | 20 (10–30)    |
| Follow-up, year – median (range) | 8.2 (0.1–19.1)       | 4.6 (0.9–14.1)        | 7.8 (0.1–19.1) |

RTx, radiotherapy; CTx, chemotherapy; RPLND, retroperitoneal lymph node dissection; PA, para-aortic; Gy, Gray.
‘hockey-stick’ or ‘modified dog-leg’ field, with the caudal edge of the field typically at the superior extent of the acetabulum), while one Stage II patient had radiation to bilateral iliac lymph nodes. The remainder of the patients (40%) had radiation administered to the PA target alone. Stage I patients were treated with a median of 25 Gy (range: 20–35 Gy) over a median of 20 fractions (range: 10–30), while Stage II patients were treated to a total median dose of 35 Gy (range: 25–40 Gy) over 25 fractions (range: 20–28). There was no acute adverse reaction requiring hospital admission following radiation treatment.

Outcomes

The patients were followed up for a median of 7.8 years (range = 0.1–19.1). Two patients experienced disease relapse, within 1 year of completion of PORT (Table 2), giving an estimated 10-year RFS of 98.4% (Fig. 1). One Stage II seminoma patient had disease relapse noted on the left superior pubic ramus and ischial tuberosity on CT imaging and bone scan approximately 4 months post-completion of 35 Gy radiotherapy to the PA and ipsilateral iliac lymph nodes. He was subsequently treated with three-cycle BEP chemotherapy and a further 24 Gy radiotherapy to the left ischial and ipsilateral pelvis for the relapse. Six months later, he had another relapse involving the right pulmonary and mediastinal region. He was then treated with second-line salvage chemotherapy (four-cycle paclitaxel, ifosfamide and cisplatin), and has remained disease-free for more than 10 years at last follow-up.

The second relapsed patient presented with Stage I seminoma and was treated with PORT to the PA fields, T11 to L5 inclusive, to a dose of 25 Gy in 15 fractions. At routine follow-up 6 months later, he was noted to have a palpable left iliac fossa mass. This was confirmed radiologically as an 8-cm left iliac nodal mass, extending superiorly to the level of the acetabular roof, outside the treatment field, as well as another PA nodal mass extending inferiorly from the level of left renal hilum, crossing the midline, in or close to the edge of the treatment field. This was proven to be seminoma recurrence on biopsy, and the patient was treated with first-line salvage chemotherapy with three cycles of BEP, with complete radiological response. Three months later, he presented with leg oedema and renal impairment with left hydronephrosis due to an 8-cm nodal recurrence.

Table 2. Characteristics and outcomes of patients with disease relapse and second malignancy after postoperative radiotherapy (PORT).

| Patient | Date of diagnosis | Tumour characteristics | Treatment details | Site of relapse | Date of relapse | Salvage treatment details | SM | Date of SM diagnosis |
|---------|-------------------|------------------------|------------------|----------------|---------------|--------------------------|----|---------------------|
| 1       | September 1998    | Stage I, pT1, N0       | PA + ipsilateral nodes (25 Gy/20#) | –              | –             | –                       | Right upper shoulder melanoma | April 2000 |
| 2       | January 2001      | Stage I, pT2, N0       | PA only (25 Gy/15#) Ipsilateral pelvic lymph nodes Ipsilateral pelvic lymph nodes + mediastinal/right hilar lymph nodes | –              | October 2001 | CTx (3xBEP)              | Prostate cancer AML | June 2009 February 2010 |
| 3       | August 2001       | Stage II, pT1, N1      | PA + ipsilateral iliac nodes (35 Gy/28#) Left superior pubic ramus and ischial tuberosity Right hilar pulmonary metastasis | –              | February 2002 | CTx (3xBEP) + RTx (ipsilateral pelvic; 24 Gy/12#) | – | – |
| 4       | February 2002     | Stage I, pT1, N0       | PA + ipsilateral nodes (25 Gy/20#) | –              | December 2002 | CTx (4xTIP)              | Lower lip cancer | March 2003 |
| 5       | March 2002        | Stage I, pT1, N0       | PA + ipsilateral nodes (25 Gy/20#) | –              | –             | –                       | Prostate cancer | October 2009 |
| 6       | July 2002         | Stage I, pT1, N0       | PA only (25 Gy 20#) | –              | –             | –                       | Stage I contralateral seminoma | December 2008 |
| 7       | October 2005      | Stage II, pT2, N2      | PA + bilateral iliac nodes (35 Gy/28#) | –              | –             | –                       | Mesothelioma | October 2008 |

CTx, chemotherapy; RTx, radiotherapy; BMT, bone marrow transplant; PA, para-aortic lymph nodes; Gy, Gray; BEP, bleomycin, etoposide, and cisplatin; TIP, paclitaxel, ifosfamide, and cisplatin; HDCT, high-dose chemotherapy; SM, second malignancy; AML, acute myeloid leukaemia.

© 2016 The Authors. Journal of Medical Radiation Sciences published by John Wiley & Sons Australia, Ltd on behalf of Australian Institute of Radiography and New Zealand Institute of Medical Radiation Technology.
overlying the psoas muscle as well as new mediastinal nodal involvement. He was treated then with high-dose chemotherapy with autologous bone marrow transplant (BMT) support, again, with complete radiological response. Consolidative radiotherapy was then given to the site of the left iliac node mass (previously radiotherapy naïve) and the left PA mass, L1 to L3 inclusive (overlapping with the original PA strip field); both fields treated to 25 Gy in 15 fractions. There has been no further disease relapse at 13-year follow-up.

At last follow-up, there were five deaths in our cohort, none of which were testicular cancer related, giving an estimated 10-year TCSS of 100% and OS of 97.3% respectively. The excellent oncological outcomes reported in our study are consistent with those reported in the international literature. There is a worldwide trend towards decreased utilisation of PORT for Stage I seminoma. Data from the US National Cancer Database showed that the utilisation of PORT for Stage I seminoma dropped from 71% in 2000 to 47% in 2008, with a corresponding rise in the proportion of patients being put on surveillance from 30% in 2000 to 40% in 2008. The most recent European Association of Urology guidelines also do not recommend PORT for Stage I seminoma. However, PORT still has an important role for management of Stage II seminoma. Our reported 98.4% 10-year RFS and 100% TCSS confirms an excellent long-term oncological outcome among patients with Stage I/II seminoma treated with PORT, to limited infra-diaphragmatic fields, and our patients had minimal

patients at a median of 5.6 years after completion of PORT (range: 0.3–8.9 years) (Table 2), with an estimated 10-year SMFS of 92.9% (Fig. 3). We observed one CV event – a cerebrovascular accident 18 months following completion of PORT in a patient with known ischaemic heart disease and a history of myocardial infarction 10 years prior to PORT. There was also one patient with GIT toxicity (gastroscopy-confirmed peptic ulcer disease) reported during the follow-up period.

Discussion

We report the long-term outcomes of patients with Stage I/II seminoma, treated with PORT in an Australian radiation oncology centre. In our cohort of patients, the 10-year RFS, TCSS and OS were 98.4%, 100% and 97.3% respectively. The excellent oncological outcomes reported in our study are consistent with those reported in the international and Australian literature. There is a worldwide trend towards decreased utilisation of PORT for Stage I seminoma. Data from the US National Cancer Database showed that the utilisation of PORT for Stage I seminoma dropped from 71% in 2000 to 47% in 2008, with a corresponding rise in the proportion of patients being put on surveillance from 30% in 2000 to 40% in 2008. The most recent European Association of Urology guidelines also do not recommend PORT for Stage I seminoma. However, PORT still has an important role for management of Stage II seminoma. Our reported 98.4% 10-year RFS and 100% TCSS confirms an excellent long-term oncological outcome among patients with Stage I/II seminoma treated with PORT, to limited infra-diaphragmatic fields, and our patients had minimal
PORT Outcomes for Seminoma

W. L. Ong et al.

Table 3. Summary of Australasian studies reporting outcomes of Stages I and II seminoma patients following postoperative radiotherapy (PORT).

| Author, year | Hospital | Study period | Disease status | Number of patients | Relapse (crude%) | Relapse-free survival | Mortality (crude%) | Overall survival |
|--------------|----------|--------------|----------------|--------------------|-----------------|---------------------|-------------------|------------------|
| Mason et al. (1988) | Queensland Radium Institute, QLD | 1968–1985 | Stage II | 49 | 7/49 (14%) | – | 8/49 (16%) | 5-year RFS = 82% |
| Lindemann et al. (1991) | Westmead Hospital, NSW | 1980–1987 | Stage I | 57 | 1/57 (1.8%) | – | – | – |
| Yeoh et al. (1993) | Royal Adelaide Hospital, SA | 1981–1990 | Stage II | 14 | 2/14 (14%) | – | – | – |
| Kearsley et al. (1994) | Royal Brisbane Hospital, QLD | 1960–1989 | Stage I | 8 | – | – | 3/77 (3.9%) | 10-year OS = 96% |
| Martin et al. (2010) | Royal Brisbane Hospital, QLD and Alfred Health, VIC | 1989–2007 | Stage I | 18 | 0/18 | 100% | 0/18 | 5-year OS = 100% |
| Current study (2016) | Alfred Health, VIC | 1992–2013 | Stage I | 106 | 1/106 (0.9%) | 10-year OS = 97% | 2/106 (1.9%) | 10-year OS = 97% |

*Patients with previous history of cryptochidism.

adverse effects from the radiation in the first decade, serving to remind us that PORT is a valid and effective option for men who cannot, or do not wish to be, managed with surveillance or chemotherapy. PORT has fallen into disfavour because of comparable disease control achieved with single-agent chemotherapy in Stage I disease, and the belief that this will not cause adverse effects in the way PORT did in the decades after treatment – though longer term adverse effects with single-agent chemotherapy are yet to be determined.

In our series, two patients (one Stage I and one Stage II) experienced disease relapse, both of which occurred within 1 year of completion of PORT. One of the patients had Stage I seminoma treated with PORT to the PA fields alone, and the pelvic relapse pattern observed in this case is consistent with what is known in the current literature. In the TE10 trial comparing radiation to the PA versus dog-leg field, Fossa et al. reported pelvic relapse in four patients in the PA only treatment arm, and none in the dog-leg field treatment arm.16 In another series of 199 Stage I seminoma patients treated at the Mayo Clinic with a median follow-up of 13 years, there was only one patient with disease relapse in the pelvic region, who had radiation treatment limited to the PA region only.26

We reported seven SMs – pulmonary mesothelioma, melanoma, lower lip cancer, acute myeloid leukaemia, contralateral seminoma and two prostate cancers – in six patients in our series, with a 10-year estimated SMFS of 92.9%. Seminoma patients are at increased risk of SM, particularly at greater than 10 and 20 years after treatment, consequent to the effect of radiotherapy, chemotherapy and possibly shared risk factors in the carcinogenesis pathway.4,6 In one of the largest multi-national studies of 22,424 seminoma patients with at least 10-year survival in the Nordic countries, Ontario and the US Surveillance, Epidemiology, and End Results (SEER) programme, Travis et al. reported a standardised incidence ratio (SIR) for second solid tumours of 2.0 (95% CI = 1.8–2.2) following radiotherapy alone, and SIR of 3.8 (95% CI = 2.2–6.0) following chemoradiotherapy.6 Compared to the general population, seminoma survivors have 3.4 times increased risk of pulmonary mesothelioma (95% CI = 1.7–5.9), 1.4 times risk of prostate cancer (95% CI = 1.2–1.6) and 1.8 times risk of malignant melanoma (95% CI = 1.3–2.3).

In a similar international study, comprising data from 13 cancer registries, Richiardi et al. investigated the risk of secondary non-solid tumour and reported an SIR for myeloid leukaemia of 2.4 (95% CI = 1.4–3.8) among 16,603 seminoma patients.3 In our series, we reported one incident of secondary AML. The patient was treated with high-dose chemotherapy and autologous BMT as well as PORT, adding to his risk of secondary AML. It has been reported in a recent study of the Australasian BMT Recipient Registry that BMT patients have significantly increased risk of AML compared to the general population (SIR = 20.6), and the risk is higher among male patients, those transplanted at a younger age, in the earlier BMT era, or in those with lymphoma or testicular cancer.27 Multiple earlier studies have also pointed to the introduction of etoposide, with known leukemogenic potential,28,29 as the main risk factors for development of secondary AML in testicular cancer patients.30,31 In a matched case–control study of 36 patients with leukaemia and 106 controls, sampled from the same cohort of seminoma survivors in the Nordic/Ontario/SEER study, Travis et al. reported a threefold increased risk of leukaemia with radiotherapy treatment alone, while chemotherapy, either alone or in combination with...
radiotherapy, was associated with fivefold increased risk of leukaemia.

We also reported one incident of metachronous contralateral testicular seminoma, diagnosed approximately 6 years after the diagnosis of the first testicular seminoma. The patient had PORT to the PA nodes following the first radical orchidectomy, and was treated with two cycles of carboplatin following the contralateral radical orchidectomy. Testicular cancer patients are well recognised to be at increased risk of developing contralateral testicular seminomas. In the SEER study, Fossa et al. reported 1.9% (95% CI = 1.7–2.1%) in 15-year cumulative risk of metachronous contralateral testicular cancer, while Schaapveld et al. reported a 20-year cumulative risk of 2.2% (95% CI = 1.8–2.8%) in another population-based study in the Netherlands. The development of contralateral testicular cancer, as with undescended testis, is a component of testicular dysgenesis syndrome (TDS) as a result of disruption of embryonal programming and gonadal development. This implies a shared underlying aetiology with the primary testicular cancer, and hence a metachronous contralateral testicular cancer should not be considered as a radiotherapy-induced SM.

We observed one CV event and one GIT event. The CV event is unlikely to be secondary to PORT for seminoma given the short timeframe following PORT, and the patient’s known cardiac history. While we acknowledge the possibility of under-reporting CV toxicities given our strict definition of CV toxicities for the study purpose, there is also a lack of consistency in the literature as to what entails CV toxicities following PORT for seminoma. Most studies included coronary artery diseases as a CV toxicity, however others also included congestive heart failure, stroke, transient ischaemic attack and even peripheral vascular disease, while some only reported on CV mortality. In a large population-based study in the Netherlands involving more than 2000 testicular cancer patients, the 20-year actuarial risk of CV toxicities following PORT were reported to be as high as 18%; however, it is important to note the study included patients treated in the 1960s and 1970s – often with larger radiation field, higher radiation dose and frequent use of prophylactic mediastinal irradiation.

The men in our series are relatively young, with an average age of 36 and had a median follow-up of less than 8 years; hence, we might not be surprised by a low incidence (or lack) of CV events observed. Earlier studies have suggested that CV events following cardiac radiotherapy generally become evident beyond approximately 10–15 year follow-up. In a single-institution study in the United States, Zagar et al. reported no increased cardiac mortality in the first 15 years following infra-diaphragmatic PORT for seminoma, but significantly increased cardiac mortality beyond 15 years. Patients may also have had CV events managed at other hospitals, which were not documented in our medical records on follow-up. This is one of our limitations, due to the retrospective nature of this study.

On the other hand, one of the strengths of this study is the accuracy in the definition of survival and SM events since data linkage with the VCR ensures that we have captured all SM and deaths among our cohort of patients. While we could not discount the possibility of patients moving overseas, we believe that the VCR data linkage provides the most accurate available data on SM and deaths.

Conclusion

This study showed high rates of disease control for Stage I/II seminoma patients treated with PORT, and low incidence of SM within the first decade. While the late effects may start to accumulate in the next few decades, our results support the effectiveness and safety of PORT in selected Stage II patients, and in Stage I patients not suited for adjuvant chemotherapy or surveillance.

Acknowledgement

The authors thank Robin Smith for management of the Alfred Health Radiation Oncology Service database.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Baade P, Carriere P, Fritschi L. Trends in testicular germ cell cancer incidence in Australia. Cancer Causes Control 2008; 19: 1043–9.
2. Chung P, Warde P. Stage I seminoma: Adjuvant treatment is effective but is it necessary? J Natl Cancer Inst 2011; 103: 194–6.
3. Mead GM, Fossa SD, Oliver RT, et al. Randomized trials in 2466 patients with Stage I seminoma: Patterns of relapse and follow-up. J Natl Cancer Inst 2011; 103: 241–9.
4. Richiardi L, Scelo G, Boffetta P, et al. Second malignancies among survivors of germ-cell testicular cancer: A pooled analysis between 13 cancer registries. Int J Cancer 2007; 120: 623–31.
5. van den Belt-Dusebout AW, de Wit R, Gietema JA, et al. Treatment-specific risks of second malignancies and cardiovascular disease in 5-year survivors of testicular cancer. J Clin Oncol 2007; 25: 4370–8.
6. Travis LB, Fossa SD, Schonfeld SJ, et al. Second cancers among 40,576 testicular cancer patients: Focus on long-term survivors. J Natl Cancer Inst 2005; 97: 1354–65.

7. Huddart RA, Norman A, Shahidi M, et al. Cardiovascular disease as a long-term complication of treatment for testicular cancer. J Clin Oncol 2003; 21: 1513–23.

8. Haugnes HS, Wethal T, Aass N, et al. Cardiovascular risk factors and morbidity in long-term survivors of testicular cancer: A 20-year follow-up study. J Clin Oncol 2010; 28: 4649–57.

9. Zagars GK, Ballo MT, Lee AK, et al. Mortality after cure of testicular seminoma. J Clin Oncol 2003; 21: 1146.

10. van den Belt-Dusebout AW, Nuver J, de Wit R, et al. Local irradiation in the treatment of testicular seminoma: Final report of a prospective multicenter clinical trial. J Clin Oncol 2003; 21: 1101–6.

11. Garcia-del-Muro X, Maroto P, Guma J, et al. Chemotherapy as an alternative to radiotherapy in the treatment of Stage IIA and IIB testicular seminoma: A Spanish Germ Cell Cancer Group Study. J Clin Oncol 2008; 26: 5416–21.

12. Chung PW, Gospodorowicz MK, Panzarella T, et al. Stage II testicular seminoma: Patterns of recurrence and outcome of treatment. Eur Urol 2004; 45: 754–9; discussion 759–760.

13. Giannatempo P, Greco T, Mariani L, et al. Radiotherapy or chemotherapy for clinical Stage IIA/B testicular seminoma: Final report of a systematic review and meta-analysis of patient outcomes. Ann Oncol 2015; 26: 657–68.

14. Fossa SD, Horwich A, Russell JM, 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: 1146.

15. Jones WG, Fossa SD, Mead GM, et al. Randomized trial of 30 versus 20 Gy in the adjuvant treatment of Stage I Testicular Seminoma: A report on Medical Research Council Testicular Tumor Working Group. J Clin Oncol 2005; 23: 1200–8.

16. Oliver RT, Mead GM, Rustin GJ, et al. Randomized trial of carboplatin versus radiotherapy for Stage I seminoma: Mature results on relapse and contralateral testis cancer rates in MRC TE19/EORTC 30982 study (ISRCTN27163214). J Clin Oncol 2011; 29: 957–62.
34. Schaapveld M, van den Belt-Dusebout AW, Gietema JA, et al. Risk and prognostic significance of metachronous contralateral testicular germ cell tumours. *Br J Cancer* 2012; **107**: 1637–43.

35. Skakkebaek NE, Rajpert-De Meyts E, Main KM. Testicular dysgenesis syndrome: An increasingly common developmental disorder with environmental aspects. *Hum Reprod* 2001; **16**: 972–8.

36. Fossa SD, Oldenburg J, Dahl AA. Short- and long-term morbidity after treatment for testicular cancer. *BJU Int* 2009; **104**(9 Pt. B):1418–22.