ECRONICON OPEN ACCESS

EC CANCER
Research Article

# Single Centre Outcomes of Acute Toxicity and Efficacy of Modern Radiotherapy for Stage IIA and IIB Seminoma

**Ben Alexander Fulton[1]*, White JD[1] and Dodds D[1]**

*Department of Surgery, Beatson West of Scotland Cancer Centre, University of Glasgow, United Kingdom*

***Corresponding Author:** Ben Alexander Fulton, Department of Surgery, Beatson West of Scotland Cancer Centre, University of Glasgow, United Kingdom.

**Received:** February 25, 2016; **Published:** May 16, 2016

## Abstract

**Introduction:** Radiotherapy is advocated as an alternative to chemotherapy after orchiectomy for patients with stage IIA and IIB seminoma. We have retrospectively reviewed 12 years experience of patients who underwent contemporary staging and were treated with modern radiotherapy for stage IIA and IIB seminoma. Recent advances in radiotherapy planning and delivery may confer improvements in acute and chronic toxicity profiles. This study aims to assess whether radiotherapy planning and delivery with modern radiotherapy techniques demonstrates acceptable toxicity profiles without compromise in therapeutic efficacy.

**Methods:** Retrospective analysis permitted identification of 27 consecutive patients who underwent contemporary staging and orchiectomy prior to radiotherapy for stage IIA and IIB seminoma. The primary outcomes were 5-year recurrence-free survival (RFS), overall survival (OS), acute and late toxicity after radiotherapy. All patients were treated within a single centre between 2003 and 2015.

**Results:** We identified 27 patients (median age 34.6 years) with stage IIA (n= 16) and stage IIB (n= 11) seminoma treated with radiotherapy after orchiectomy. All patients underwent contemporary staging and were treated within a single tertiary cancer centre. Patients with stage IIA seminoma had 5-year recurrence-free survival of 89.5% (95% CI 84.2-96.1%) and 5-year overall survival of 100%. Patients with stage IIB seminoma had 5-year recurrence-free survival of 82.7% (95%CI 78.2-87.2%) and 5-year overall survival of 91% (95% CI 86.1-100%). The 5-year recurrence-free survival for patients of both stage IIA and IIB seminoma treated with VMAT (volumetric modified arc therapy) was 83.3% (95% CI 80.2-86.4%) and conformal radiotherapy was 87.5% (95% CI 83.6-93.3%). Overall survival at 5-years for patients treated with VMAT was 100% and was 94.4% (95%CI 92.8-100%) for those treated with conformal radiotherapy.

No patients within the study suffered grade III or IV acute toxicity due to radiotherapy. Of the patients treated with VMAT radiotherapy, 37% suffered grade ≥ 1 nausea and 13% suffered grade I diarrhoea. No patients treated with VMAT developed grade ≥ 2 diarrhoea. The patient group treated with conformal radiotherapy showed 56% suffered grade ≥ 1 nausea and 32% suffered grade ≥ 1 diarrhoea. There was one patient in the conformal radiotherapy group, who suffered grade I late gastrointestinal toxicity and no radiotherapy-induced cancers within the follow-up period. Median follow-up in the study was 68.2 months (range 8-82 months).

**Discussion:** This retrospective analysis is in keeping with current treatment paradigms emphasizing the efficacy and safety of radiotherapy after orchiectomy for stage IIA and IIB seminoma. The data from this small series, although retrospective, does suggest there may be potential for reduction in acute toxicity using VMAT radiotherapy planning and delivery. This would need to be the subject of a larger prospective study to more precisely delineate the role of VMAT in this setting.

***Keywords:*** *Radiotherapy; Seminoma*

## Introduction

Testicular cancer is the 16th most common cancer among males in the UK, accounting for 1% of all new cases of cancer. In 2013, there were 2,296 new cases of testicular cancer diagnosed in the UK [1]. In the UK and Europe, cure rates of up to 97% have been achieved [2]. In the majority of patients with low-stage testicular cancer, the main goal of therapy is reduction in toxicity, including risks of secondary cancers, whilst maintaining therapeutic efficacy. Previous series demonstrate 45-50% of patients with testicular cancer are diagnosed as pure seminoma. Only 10-15% of these patients are diagnosed with clinical stage IIA or IIB seminoma and only 5% have more advanced disease [3]. The majority of cases have early stage I disease. Radiotherapy has previously been the standard of care after orchiectomy for patients with stage II seminoma and limited lymph node involvement. The highly predictive nature of seminoma tumour spread provides the basis for the limited target volume delineation for radiotherapy.

Recent studies have assessed the role of radiotherapy with limited portals to reduce toxicity. Extended field irradiation for seminoma conflicts with the risk of late morbidity on the cardiovascular and haematopoietic systems as well as increasing concern over risk of radiation-induced second malignancies. The increasing availability of potent salvage chemotherapeutic regimens has led to reduction in use of prophylactic mediastinal or supraclavicular radiotherapy. In recent years, contralateral iliac nodal irradiation has omitted in many centres in order to reduce therapeutic toxicity. The principle radiotherapy target volume in modern series covers para-aortic, para-caval and ipsilateral high iliac lymph nodes. The radiation dose delivered for stage IIA and IIB seminoma is approximately 30 and 36Gy respectively. This treatment yields relapse-free survival of 92% for stage IIA and 90% for stage IIB with OS of almost 100% [3-8].

Concerns about the toxicity of radiotherapy have led to increased scrutiny of the role of systemic cytotoxic chemotherapy in this setting. For patients with stage IIA/IIB seminoma, 3 cycles of BEP (bleomycin, etopside and cisplatin) or 4 cycles of EP (etopside and cisplatin) are advocated as an alternative to radiotherapy. There are currently no randomised studies comparing radiotherapy and chemotherapy in this setting. Although data suggests increased short-term toxicity with 3 cycles of BEP or 4 cycles of EP compared to radiotherapy, similar disease control rates are achieved with both modalities.

Single-agent carboplatin is not an alternative to radiotherapy, BEP or EP for stage IIA or IIB seminoma. There has been interest in the role of sequential radio-chemotherapy in the treatment of stage IIA and IIB seminoma, with the theoretical principle of radiotherapy to treat macroscopic disease and carboplatin to rates of reduce systemic recurrence. The combination of 2 cycles of single-agent carboplatin followed by infra-diaphragmatic radiotherapy in a small series demonstrated relapse rates of 7.1% and 5.3% for stage IIA and IIB seminoma respectively [9]. This data is comparable to that obtained by other modern radiotherapy series and must be interpreted with caution due to the limited size of the series involved. This does remain, though, an area of academic interest and further studies are on-going investigating the role of multimodality therapy.

The role of radiotherapy in stage IIA and stage IIB seminoma remains a source of debate. This has been magnified by recent improvements in delivery and toxicity management of systemic cytotoxic chemotherapy. Advances in the planning and delivery of megavoltate radiotherapy in recent years may allow further gains in the toxicity profile offered by radiotherapy in this patient group. The aim of this retrospective series is to determine the efficacy and toxicity profile of radiotherapy for patients with stage IIA and IIB seminoma that underwent radiotherapy with both static field and volumetric modified arc therapy (VMAT) with curative intent.

## Materials and Methods

### Study Design

This retrospective study identified 27 consecutive patients diagnosed with stage IIA or stage IIB testicular seminoma who underwent orchiectomy followed by adjuvant radiotherapy between 1st January 2003 and 31st December 2015. No patients underwent planned sequential chemo-radiotherapy. All patients were assessed by a regional multi-disciplinary team serving a population of 3.4 million and received treatment at the Beatson West of Scotland Cancer Centre.

All patients underwent standard staging including serum tumour markers (α-Fetoprotein, HCG (human chorionic gonadotropin), lactate dehydrogenase), thoraco-abdomino-pelvic CT scan and testicular ultrasound. Some patients underwent further MRI or CT imaging as clinically indicated. All staging was in accordance with International Germ Cell Cancer Collaborative Group (IGCCCG) classification.

Data collected included patient age, gender, histological diagnosis, clinical staging, baseline tumour marker values, radiotherapy dose and fractionation, acute and late toxicity, relapse date, overall survival.

**Radiotherapy Planning and Setup**

27 patients were treated with adjuvant radiotherapy after orchiectomy for stage IIA or IIB seminoma. 19 patients were treated with conformal 2-field radiotherapy and 8 patients were treated with volumetric modified arc therapy (VMAT). All patients were planned and treated in the supine position and had tattoos placed at the level of the isocentre in the anterior and lateral planes.

**Conformal Radiotherapy**

Conformal radiotherapy (n=19) was delivered using 2-field dorsal-ventral beam arrangement using a modified dog-leg field with the superior border at the top of the T11 vertebral body and the inferior border was placed at the superior edge of the acetabulum. The lateral field borders for the lower part of the dog-leg fields was a line from the tip of the ipsilateral transverse process of the fifth lumbar vertebra to the supero-lateral border of the ipsilateral acetabulum. Prophylactic irradiation of the contralateral iliac, inguinal or scrotal region was not performed in any of the cases.

**VMAT Radiotherapy**

Patients (n=8) treated with volumetric modified arc therapy (VMAT) underwent radiotherapy mapping and contouring based on vascular anatomy. This involved a CTV incorporating the paracaval, precaval and interaortocaval lymph nodes. The inferior vena cava and aorta were contoured from 2cm below the top of the kidneys down to the point where both vessels end. A 2cm margin was then added to the nodal CTV, contoured to exclude bone, kidney and bowel. A further 0.5 cm was then added to create a planning target volume (PTV) that accounts for setup errors.

**Dose and Fractionation**

All patients with stage IIA seminoma were treated with 20Gy in 10 fractions to the whole PTV over 2 weeks followed by a boost to sites of radiological adenopathy of 10Gy in 5 fractions. In the patients with stage IIB seminoma, 14 patients received an initial 20Gy in 10 fractions to whole PTV followed by a further boost of 16Gy in 8 fractions to sites of adenopathy. A total of 5 patients received a 30Gy in 15 fractions to the whole PTV.

**Follow-up and Disease Assessment**

After completion of radiotherapy, planned follow-up was according to national guidelines. Patients were seen at 3-monthly clinic visits for the first two years after completion of therapy, 6-monthly for years 3-5 then annually from year 6-10. All patients underwent CT or MRI scan of the abdomen and pelvis with paired baseline tumour markers on completion of radiotherapy. Patients then had repeat CT/MRI only if the post-treatment scan demonstrated radiological abnormality or there was clinical/biochemical cause for repeat imaging.

Disease recurrence patterns were described as within the radiotherapy field, systemic relapse or both. The time to recurrence was taken from the time of confirmatory investigation. The patient cohort was analysed in January 2016, at which time the median follow-up was 68.2 months (range 8-82 months).

**Statistical Analysis**

Analysis intention is to treat, based on those receiving radiotherapy with conformal versus VMAT planning and delivery. The primary end-points were recurrence-free (RFS) and overall survival (OS). Secondary endpoints included acute and late toxicity for patients treated with VMAT versus conformal radiotherapy. Estimates of survival rates were expressed as percentages using the life-table Kaplan-Meier

method with differences between groups analysed using Log Rank testing. Grouped data were expressed as a median and non-parametric testing was used. Recurrence-free and overall survival was measured from the completion of radiotherapy treatment to the date of recurrence. Final multivariate analysis included disease staging to correct for baseline differences between the two groups.

All statistical analysis was done using IM SPSS version 22.0.

## Results

### Patient Characteristics

A total of 27 patients were included in the study (all males) and their details related to treatment modality are shown in Table 1. The median age of patients at diagnosis was 34.6 years and median follow-up was 68.2 months (range 8-82 months).

| | Number of Patients |
|---|---|
| Males | 27 |
| Median Age (years) | 34.6 years |
| Clinical Disease Staging | |
| IIA | 16 |
| IIB | 11 |
| Pathology | |
| Seminoma | 27 |
| CT Done for Staging | |
| Yes | 27 |
| No | 0 |
| Tumour Markers Staging | |
| Yes | 27 |
| No | 0 |
| Radiotherapy Delivery | |
| Conformal | 19 |
| VMAT | 8 |
| Median follow-up | 68.2 months |

***Table 1:*** *Patient Demographics (n=27).*

### Compliance

All patients completed the planned number of fractions of radiotherapy. There were 2 patients who had delay in single radiotherapy fraction of one day, one due to non-treatment toxicity and the other due to patient non-attendance. Of the patients treated with VMAT radiotherapy planning, 50% (n= 4) were stage IIA and 50% (n= 4) were stage IIB. Of the patients treated with conformal radiotherapy, 63% (n= 12) were stage IIA and 37% (n= 7) were stage IIB.

### Recurrence-Free and Overall Survival

Patient undergoing radiotherapy with stage IIA seminoma had 5-year recurrence-free survival of 89.5% (95% CI 84.2-96.1%) and 5-year overall survival of 100%. Patient with stage IIB seminoma undergoing radiotherapy had a 5-year recurrence-free survival of 82.7% (95% CI 78.2-87.2%) and 5-year overall survival of 91.0% (95% CI 86.1-100.0%). The 5-year recurrence-free survival for patients with both stage IIA and IIB seminoma treated with VMAT was 83.3% (95% CI 80.2-86.4%) and conformal radiotherapy was 87.5% (95% CI

83.6-93.3%). Overall survival at 5-years for patients treated with VMAT was 100% and was 94.4% (95%CI 92.8-100%) for those treated with conformal radiotherapy. There was one disease-related death in the conformal radiotherapy group, in a patient treated for stage IIB seminoma. The recurrence occurred outside the radiotherapy field.

**Treatment-Related Morbidity**

The overall rate of acute toxicity in the patients treated with radiotherapy for stage IIA and IIB seminoma is shown in Table 2. There was no grade III or IV acute toxicity seen for patients treated within this study.

| | Skin (%) | | Nausea (%) | | Diarrhoea (%) | |
|---|---|---|---|---|---|---|
| RTOG grade | IIA (n=16) | IIB (n=11) | IIA (n=16) | IIB (n=11) | IIA (n=16) | IIB (n=11) |
| 0 | 88 | 100 | 56 | 37 | 81 | 64 |
| 1 | 12 | 0 | 38 | 45 | 13 | 18 |
| 2 | 0 | 0 | 6 | 18 | 6 | 18 |
| 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| 4 | 0 | 0 | 0 | 0 | 0 | 0 |

***Table 2**: Rates of Acute and Late Toxicity in Patients Undergoing Radiotherapy for Stage IIA or IIB Seminoma.*

Rates of acute toxicity in patients undergoing VMAT versus conventional radiotherapy planning (combined stage IIA and IIB) are shown in Table 3.

| | Skin (%) | | Nausea (%) | | Diarrhoea (%) | |
|---|---|---|---|---|---|---|
| RTOG grade | VMAT (n=8) | Conformal (n=19) | VMAT (n=8) | Conformal (n=19) | VMAT (n=8) | Conformal (n=19) |
| 0 | 100 | 88 | 63 | 43 | 87 | 68 |
| 1 | 0 | 12 | 25 | 47 | 13 | 16 |
| 2 | 0 | 0 | 12 | 10 | 0 | 16 |
| 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| 4 | 0 | 0 | 0 | 0 | 0 | 0 |

***Table 3:** Rates of Acute Toxicity in Patients Treated with VMAT Versus Conventional Radiotherapy, across both Stage IIA and IIB Seminoma.*

There were no radiotherapy-induced second cancers seen to date with the patients in this study. There was 1 patient with stage IIB seminoma treated with conformal who had late grade I diarrhoea beginning 12 months after radiotherapy, but no other late toxicity seen within the follow-up period of this study.

## Discussion

Radiotherapy has been a long-standing therapeutic alternative to cytotoxic chemotherapy after orchiectomy for stage IIA and IIB seminoma. Historical studies have demonstrated similar efficacy between these modalities, although there remains some concern about the potential of late cardiovascular toxicity and risk of secondary radiation-induced cancers with radiotherapy. The data from this retrospective case series is in-keeping with the established literature in demonstrating the excellent tolerance and efficacy of radiotherapy in this setting. This study did not demonstrate any radiation-induced cancers, but this is out with the follow-up timeframe and scope of this study.

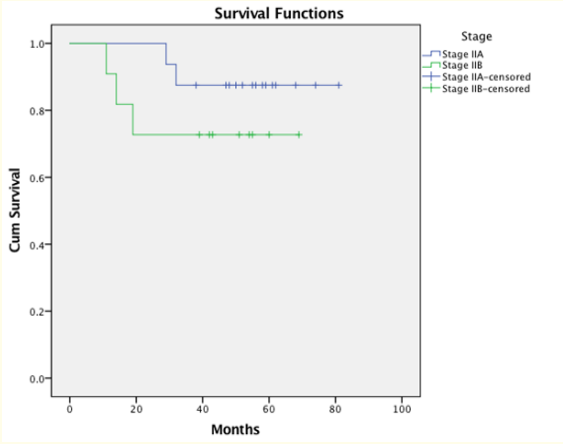


***Figure 1:*** *Kaplan-Meier Curve Showing Recurrence Free Survival (In Months) Comparing Stage IIA and IIB Seminoma.*

In 2003, Classen., *et al* prospectively evaluated the role of modern radiotherapy with reduced treatment portals for stage IIA/IIB testicular seminoma. Patients with stage IIA disease were treated with 30Gy and patients with stage IIB disease received 36Gy. Classen., *et al* showed patients treated with radiotherapy had relapse-free survival at 6 years of 95.3% (95% CI 88/9-100%) and 88.9% (95% CI 74.4-100%) for stage IIA and IIB groups respectively. This current series demonstrates 5-year relapse free survival of 89.5% (95% CI 84.2-96.1%) and 82.7% (95% CI 78.2-87.2%) for stage IIA and IIB seminoma, respectively.

The study by Classen., *et al* demonstrated maximum acute side-effects of 8% grade III nausea for stage IIA and 10% grade III nausea and diarrhoea for stage IIB patient groups undergoing radiotherapy. 12% and 14% of patients suffered grade II nausea in stage IIA and IIB groups, respectively as well as 9% and 24% of patients in stage IIA and IIB groups respectively who suffered grade II diarrhoea. There were no late toxicities demonstrated within either treatment groups. This current series demonstrates similar acute and late toxicity profiles to historical literature, also highlighting the increased toxicity profile seen in patients with stage IIB versus IIA seminoma treated with radiotherapy. In this series, 12% of patients with stage IIA seminoma suffered grade ≥ 1 skin changes, 38% had grade ≥ 1 nausea and 19% had grade ≥ 1 diarrhoea. This compares to the patients with stage IIB seminoma, in which 0% suffered grade ≥ 1 skin changes, 63% suffered grade ≥ 1 nausea and 36% suffered grade ≥ 1 diarrhoea. This is an expected finding, given that patients with stage IIB seminoma were treated with a higher dose of radiotherapy than those with stage IIA disease which would explain the increase in toxicity amongst these groups. This study reflects, as shown in recent series, that modern radiotherapy offers an acceptable acute and late toxicity profiles in patients with stage IIA and IIB seminoma.

The data from this series also suggests a possible reduction in acute toxicity using VMAT versus conventional radiotherapy planning and treatment delivery. Patients in this study treated with VMAT, showed 0% of suffered grade ≥ 1 skin changes, 37% had grade ≥ 1 nausea and 13% had grade ≥ 1 diarrhoea. This compares to the patient group treated with conformal radiotherapy, where 11% of patients had grade ≥ 1skin changes, 57% had grade ≥ 1 nausea and 32% of patients suffered grade ≥ 1 diarrhoea. There were no grade 3 or 4 toxicities throughout this study. The paucity of late toxicity reported within the studied patients makes it difficult to determine any difference between VMAT and conformal radiotherapy in terms of late toxicity.

This study has several potential limitations. It was conducted as a non-randomised retrospective comparative analysis and therefore potentially vulnerable to selection bias. The follow-up period means this study will not be likely to detect any patients who may suffer late radiation-induced cancers. There is theoretical suggestion that the increased monitor units used with VMAT to deliver radiotherapy may confer higher total body ionising radiation doses for patients, but there is no long-term data to strengthen or refute this theory. This

would require to be the subject of a larger, prospective study. There are, however, many strengths to this study in that it represents a series of consecutive patients over an abbreviated timeframe treated with modern radiotherapy planning and delivery techniques. There was good follow-up for patients within a well defined geographic distribution and high rates of clinical, biochemical and radiological follow-up to assess response and toxicity. This retrospective study was not designed to provide information on risks of secondary radiation induced cancers.

## Conclusion

This retrospective analysis is in-keeping with current treatment paradigms emphasizing the efficacy and safety of radiotherapy after orchiectomy for stage IIA and IIB seminoma. The data from this small series, although retrospective, does suggest there may be potential for reduction in acute toxicity using VMAT radiotherapy planning and delivery. This would need to be the subject of a larger prospective study to more precisely delineate the role of VMAT in this setting.

## Conflict of Interest

None of the authors have any conflict of interest to declare.

## Bibliography

1. Data provided by the Office for National Statistics on request (2014).
2. Hoffmann R., *et al*. "Innovations in Health Care and Mortality Trends from Five Cancers in Seven European Countries between 1970 and 2005". *International Journal of Public Health* 59.2 (2014): 341-350.
3. Classen J., *et al*. "Radiotherapy for Stages IIA/IIB Testicular Seminoma: Final Report of a Prospective Multicentre Clinical Trial". *Journal of Clinical Oncology* 21.6 (2003): 1101-1106.
4. Zagars GK and Pollack A. "Radiotherapy for Stage II Testicular Seminoma". *International Journal of Radiation Oncology* 51.3 (2001): 643-649.
5. Stein M., *et al*. "Testicular Seminoma: 20-Year Experience at the Northern Israel Oncology Center (1968-1988)". *International Urology and Nephrology* 26.4 (1994): 461-469.
6. Lederman GS., *et al*. "Radiation Therapy of Seminoma: A 17-Year Experience at the Joint Center for Radiation Therapy". *Radiotherapy and Oncology Journal* 14.3 (1989): 203-208.
7. Chung PW., *et al*. "Stage II Testicular Seminoma: Patterns of Recurrence and Outcome of Treatment". *European Urology Journal* 45.6 (2004): 754-760.
8. Horwich A., *et al*. "Neoadjuvant Carboplatin before Radiotherapy in Stage IIA and IIB Seminoma". *Annals of Oncology* 24.8 (2013): 2104-2107.
9. Patterson H., *et al*. "Combination Carboplatin and Radiotherapy in the Management of Stage II Testicular Seminoma: Comparison with Radiotherapy Treatment Alone". *Radiotherapy and Oncology* 59.1 (2001): 5-11.

**Volume 2 Issue 3 May 2016**