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Surveillance in Stage I Seminoma Patients:  
A Long-Term Assessment

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Abstract

Background. Following orchidectomy patients with stage I seminoma of the testis may be managed by either surveillance or by adjuvant treatment. In view of the very high cure rate it is important to analyse long term outcomes.

Objective. Provide data to advise patients on treatment burden and risk of recurrence associated with surveillance.

Design, Setting & Participants. We audited the case records of 164 stage I seminoma patients registered at The Royal Marsden Hospital managed by a surveillance policy between 1980 and 2004 and followed for 1 – 20 years (median 13.5 years) documenting all treatments received as well as patterns of relapse.

Measurements & Results. 22 of 164 (13%) patients had relapsed at a median of 15.5 months (range 6-55 months) from orchidectomy. Eighteen relapses appeared to be confined to the para-aortic nodes but six of the 13 (46%) men treated only with para-aortic radiotherapy suffered a further relapse at another site. The disease-specific mortality was 1.3%. In the complete series of 164 patients there had been administered a total of 50 cycles of chemotherapy and 26 courses of radiotherapy, representing an average of 0.46 “treatment units” per patient, or an average of 3.45 “treatment units” per relapsing patient. The total number of treatment days was 390 for radiotherapy and 133 for chemotherapy. These represent an average overall of 3.2 days per patient, or 23.8 per relapsing patient.

Limitations. This was a single centre series, extending back to the 1980s and current imaging and treatment protocols have advanced since then.

Conclusions. Surveillance post-orchidectomy is a safe practice in the long-term, and the majority of patients can avoid further treatment. However there is the risk that
those who do relapse face a higher burden of treatment than would be required if adjuvant treatment had been given.
Introduction

Testicular germ cell tumours represent only around 1% of all male cancer, but they are the most common malignancy in young adult men and the median age of presentation of seminoma is 35 years. Just over half are pure seminoma and around 75% of seminoma patients present with stage I disease, i.e., no clinical evidence of metastasis. Inguinal orchidectomy is the mainstay of treatment. The patient may then be managed by surveillance or by adjuvant therapy, either radiotherapy or chemotherapy [1,2].

Radiotherapy (RT) is usually now administered as a course of 20Gy in 10 fractions over 14 days, to the para-aortic nodes [3], though in the past higher doses and larger fields were used [4]. Radiotherapy is associated with both short and long-term morbidities, of particular import given the young age and good prognosis of this group of cancer patients [5]. Peptic ulceration, bowel disturbance, cardiovascular disease, second malignancies, fertility and quality of life changes have all been reported in the context of adjuvant therapy for stage I seminoma [6,7,8,9,10,11,12]. Adjuvant chemotherapy with carboplatin has also been assessed [2], but it is too early to be confident that long term toxicities of this approach are known.

Surveillance policies offer the opportunity to detect relapsing patients early, whilst avoiding the morbidities and risks of treatment for most [13,14]. Reports have demonstrated the feasibility of surveillance protocols particularly when aligned with effective salvage regimens. Series from the Royal Marsden Hospital, the Princess Margaret Hospital, Toronto and from a national collaboration in Denmark all concluded that surveillance is a reasonable policy, albeit with some practical
difficulties in view of the lack of sensitivity of specific serum markers [15,16,17]. An overview analysis of these series together with patients from the Royal London Hospital showed that the significant prognostic factors predicting relapse on surveillance were rete testis invasion and primary tumour size [18]; however these factors have not yet been validated in an alternative series. Consensus guidelines accept surveillance as an option which can be offered to stage 1 seminoma patients following orchidectomy [19].

This retrospective analysis is of the treatment burden and long-term outcomes seen in patients managed by surveillance for stage 1 seminoma of the testis at the Royal Marsden Hospital, the series of patients having a median follow up following orchidectomy of over 13 years.

Patients and Methods

One hundred and sixty four stage I seminoma patients registered between 1980 and 2004 had been treated with inguinal orchidectomy followed by surveillance. In all cases the pathological diagnosis was confirmed by review however details of pathological risk factors such as tumour size, rete testis invasion or vascular invasion were not consistently recorded. Patients were staged according to the Royal Marsden Hospital staging classification, with stage I disease defined as tumour confined to the testis, with no evidence of metastases. Staging was confirmed by computed tomography of chest, abdomen and pelvis, and blood tests including full blood count, biochemistry, tumour markers, namely alpha-fetoprotein, the beta subunit of human chorionic gonadotrophin, and since 1998 lactic dehydrogenase.
Surveillance involved three monthly outpatient visits for the first two years, four-monthly for year three, six monthly for years four and five and annually thereafter. At each follow-up the patients underwent physical examination, chest x-ray, and analysis of tumour markers. CT scanning of the abdomen was performed six monthly for two years and then annually till five years post-orchidectomy. In the early years of the study alternate CT scans were replaced by abdominal ultrasound. A CT scan was not repeated after five years unless relapse was suspected.

Retrospectively reviewed data included age, date of first presentation, pathological features of the tumour, date of developing relapsed disease, site(s) of relapse, tumour markers and radiological investigations at time of relapse, salvage treatment for relapsed disease, subsequent clinical course and survival status.

**Results**

After a median follow-up of 13.5 years (range 1-20 years), 22 of 164 (13%) clinical stage I seminoma patients on surveillance were found to have relapsed (see Figure 1 and Table 1). The median time from primary presentation of seminoma to first relapse was 15.5 months (6 to 55 months). Clinically, only four (18%) patients were symptomatic at time of relapse. Abnormal physical examination findings were detected in two (9%) patients. CT scans confirmed the diagnosis of relapsed disease in all 22 patients (100%). Eighteen of 22 patients had isolated relapses in the para-aortic lymph nodes (PAN). Four patients had relapses also in additional sites, one in the lung, two in the external iliac nodes, and one (with previous inguinal surgery) in the orchidectomy scar.
Treatment of relapse is detailed in Table 2. Thirteen patients with small volume abdominal lymphadenopathy at relapse were treated with local RT to retroperitoneum to a dose of 35Gy in 18-20 fractions. However six of these patients relapsed again (four just in the mediastinum) and were treated with chemotherapy. Five initial recurrences were treated with a single dose of carboplatin followed by local RT [20], and none relapsed. The other four initial recurrences were treated with four cycles of chemotherapy and the relapse rates were 1/2 for single agent carboplatin, 1/1 for EP (etoposide and cisplatin) and 0/1 for BEP (bleomycin, etoposide and cisplatin).

All 22 patients had a good initial response to salvage treatment, though only 14 remaining continuously disease free; eight second relapses occurred from four to 48 months from first relapse and two ultimately died of biopsy-proven recurrent seminoma. The first of these was a 33 year old man, who relapsed on surveillance in the left para-aortic and external iliac lymph nodes. He received four cycles of EP followed by involved field RT. He then relapsed in the peritoneal cavity and despite responding initially to further chemotherapy he eventually died following surgery for persisting intra-abdominal disease. The second was a 27 year old man who received local radiotherapy for a relapse in the para-aortic lymph nodes. He developed further bulky para-aortic disease two years later, and died of abdominal progression despite further salvage chemotherapy. The other four deaths in the series were from unrelated causes. Three died from other solid tumours, follicular lymphoma, metastatic small cell carcinoma of the tonsil and bladder cancer (not an irradiated site); one patient died of an abdominal aortic aneurysm. These results give a disease specific mortality of 1.3% in this series.
To estimate the overall burden of treatment for germ cell cancer following orchidectomy (excluding treatment of other conditions and palliative care), the individual case records were reviewed and “units of treatment”, either a cycle of chemotherapy or a course of radiotherapy, were recorded, as were number of treatment days. In the total series of 164 patients there had been a total of 50 cycles of chemotherapy and 26 courses of radiotherapy, representing an average of 0.46 “treatment units” per patient, or an average of 3.45 “treatment units” per relapsing patient. The figures for an analysis of number of treatment days were a total of 390 for radiotherapy and 133 for chemotherapy. These represent an average per patient overall of 3.2 days per patient, or 23.8 per relapsing patient.

Discussion

This study updates our previous reports [14,15, 21] on surveillance for stage I testicular seminoma patients at RMH. Since the majority were registered in the 1980s and early 1990s, there is now mature data on long term safety of this policy. After a median follow-up period of 13 years, the recurrence rate and disease-specific mortality were 13% and 1.3% respectively. This recurrence rate is lower than our previously reported result of 18% [15], as well as results reported from other groups (18-20%) [16, 17, 22], possibly because of selective use of adjuvant treatment.

In our series, of the 22 treated for relapse, 8 (36 %) suffered a second relapse. With the caveat that the patient numbers in this situation in our series are small, it appears that the recurrences treated with radiotherapy alone behaved more aggressively than the typical stage 2 seminoma, where high control rates are reported [23, 24]. There were no second relapses in the five patients whose first recurrence was treated with
carboplatin and radiotherapy however experience with this practice is largely limited to our centre and it is not a standard approach to small volume stage 2 seminoma. There was 1 relapse in the 2 patients treated with carboplatin monotherapy, and this approach is no longer recommended [25].

In the 22 patients who relapsed out of the total of 164 on surveillance the actual treatment burden was 26 courses of radiotherapy and 18 courses (50 cycles) of chemotherapy. These occupied a total of 523 treatment days. However, in our series there appeared to be an excess of further recurrences after radiotherapy for small volume retroperitoneal relapse. Additionally we treated 2 relapsing patients with carboplatin monotherapy. For purposes of comparison with current adjuvant treatments, if our series were “idealised” assuming only 2/13 recurrences after radiotherapy and that the standard chemotherapy approach was BEP x 3 the treatment burden on surveillance would be much reduced to an estimated 37 cycles of chemotherapy, 14 courses of radiotherapy and a total of 156 treatment days.

These figures can be compared with an estimate of treatment burden following adjuvant radiotherapy, assuming 4-5% relapse, and 85% disease free survival of relapsing patients with combination chemotherapy; 164 courses of radiotherapy and nine of chemotherapy (29 cycles, 7 x 3cycles of 3 day BEP and 2 x 4 cycles of 5 day BEP). The estimated number of treatment days would be 1743. An approximate estimate of treatment burden after carboplatin, assuming a 5% relapse risk after a single adjuvant cycle and that further treatments would include 5 courses of radiotherapy 2x3 cycles of 3 day BEP and 1x4 cycles of five day BEP; 174 cycles of chemotherapy and five courses of radiotherapy, though of course in this setting the
majority of chemotherapy courses would be of low toxicity as they would comprise a single dose of carboplatin. These would take an estimated 277 treatment days, less even than surveillance. An estimate can also be made of treatment burden associated with a selective policy as published by the Spanish Germ Cell Cancer Cooperative Group [26]. In this study, of 314 patients with stage 1 seminoma 100 were regarded as low risk, were managed by surveillance and 6% relapsed, whereas 214 were higher risk and received 2 cycles of adjuvant carboplatin and 3.3% relapsed. The estimated treatment burden in this series is 24 chemotherapy cycles in the surveillance patients and 428 cycles of carboplatin monotherapy, 28 cycles of EP and 1 course of radiotherapy in the higher risk patients, leading to a total of about 688 treatment days in 314 patients (or an expected 360 treatment days in our 164 patients). Though the measure of treatment burden based on number of treatment cycles/courses favours surveillance in the entire population, those individuals who relapsed on surveillance had a relatively high treatment burden.

The tempo of relapse is relatively slow compared to that noted in stage I non-seminomatous germ cell tumours on surveillance with 20% of seminoma relapses more than 3 years after orchidectomy. In the Medical Research Council prospective surveillance trial [27], 75% of 396 patients with stage 1 nonseminoma were relapse-free at two years and 73% at five years. Thus for seminoma long-term follow up is important in the monitoring of stage I seminoma patients, however none of our 98 patients known to be relapse free five years after orchidectomy suffered a later relapse. Though we did not undertake routine CT scans after five years the substantial further follow-up data would suggest that late relapse is very uncommon. The combined series analysis of prognostic factors [18], reported a 3.6% difference in
relapse-free rates between five and ten years based on a median follow-up of seven years, but imaging protocols were variable and investigations after two to three years were described simply as “less frequent”. Thus if regular annual CT scans of the abdomen had been performed these relapses may have been detected earlier.

With regard to detection of relapse, it is notable that only 18% of the patients were symptomatic, with 9% demonstrating physical signs at relapse. Blood tests were of limited value; beta HCG was elevated in one third of patients at relapse (LDH was not analysed in follow up in the majority of our patients). The incorporation of both LDH and placental alkaline phosphatase measurement [28, 29] into a surveillance programme may enhance the sensitivity of a surveillance programme though there are concerns about specificity. Chest X-ray detected recurrence in only one patient. This is similar to results found when exploring the use of routine chest x-ray in surveillance for non-seminomatous germ cell tumour [29], and suggests that there is little benefit to routine CXR in the follow up of stage I seminomas. The majority of relapses were diagnosed on CT scanning and it is likely that recent imaging improvements have increased the sensitivity of the technique compared to the early years of this series. The optimal protocol for routine surveillance CT scanning in this group of patients has yet to be defined. Positron emission tomography (PET) of 18 fluorodeoxyglucose has been assessed in high-risk stage 1 nonseminoma, but appears to lack sensitivity as 33 of 87 PET negative patients relapsed on surveillance [30].

Patients with stage I seminoma have a long life expectancy and considerations of late treatment-related toxicities are important. Our analysis supports the safety of surveillance compared to adjuvant therapy post-orchidectomy. The surveillance
programme does however come at a cost to the subset of patients who relapse, since they generally face an increased burden of treatment compared to the adjuvant setting. It also requires high levels of physician and patient motivation and compliance with medical advice is difficult to predict [31]. Non-attenders risk presenting with large volume disease recurrence and subsequent difficulties with salvage. Therefore the decision regarding surveillance or adjuvant therapy should be made in the context of both the individual and the treatment centre.
References


