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Changing practice evaluation - Stage 1 Seminoma: Outcomes with Adjuvant Treatment versus Surveillance, Risk Factors for Recurrence and Optimising Follow-up Protocols – experience from a Supra-regional centre

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MicroAbstract

Stage 1 seminomas treated by orchidectomy (501 cases) were analysed to identify risk factors for recurrence and methods of relapse detection. Rete testis invasion, and more strongly stromal rete testis invasion, increased the risk of relapse. Most recurrences were identified within 2 years of surgery by routine surveillance CT scans.

Abstract

Purpose: Stage 1 seminoma is frequently cured by radical orchidectomy, but management strategies following this diagnosis vary, in terms of whether adjuvant treatment is given and the nature of follow-up. We analysed stage 1 seminomas treated in the Thames Valley Cancer Network for outcomes to see if any factors are predictive for recurrence. We also studied relapses, to determine the optimal follow-up schedule.

Methods: Data was obtained from centres within the Thames Valley Cancer Network over a 12 year period from 2004-2016. We identified 501 patients with stage 1 seminoma.

Results: Relapses occurred in 6.2% of patients receiving adjuvant treatment and 6.1% without. The only statistically significant predictive factor identified for relapse was rete testis invasion, and the risk was higher when only stromal rete invasion was included, rather than pagetoid as well. There was a trend towards increased risk with increased tumour size, but this was not statistically significant. Recurrences occurred within the first 2 years following surgery in nearly 75% of cases and were identified through surveillance CT scans in 54.8% of patients. All relapses were treated curatively.

Conclusion: Active surveillance leads to excellent outcomes in stage 1 seminoma, but adjuvant treatment is an option for individual patients for those with high risk disease. Follow-up schedules should include imaging in the first 3 years, long term measurement of tumour markers, and mechanisms for patients to be seen promptly should symptoms of tumour recurrence occur.

Keywords

Testicular cancer
Adjuvant chemotherapy
Carboplatin
Adjuvant radiotherapy
Relapse rates

Introduction

Seminoma is a subtype of germ cell tumour that resembles primordial germ cells[1] and accounts for 45% of all testicular tumours.[2] Seminoma usually occurs in men aged between 30 and 40 years, and the incidence of all testicular tumours is rising, having doubled in northern Europe over the last 30 years.[1,3]

Around 70-80% of seminomas are diagnosed as stage 1, which is defined as when the tumour is confined to the testis.[2] A diagnosis of testicular cancer is usually suggested after a clinical examination, ultrasound of the testicle and blood tests. Radical orchidectomy via the inguinal approach is then performed which is both therapeutic, resulting in cure of the majority of stage 1 seminomas, and also diagnostic, providing histology, T-staging and prognostic information.[4]

While the majority of stage 1 seminomas are cured by surgery, recurrences occur due to the presence of microscopic metastatic disease[2]. Adjuvant treatment arose out of practices from the 1960's when the cure rate for metastatic disease outside the retroperitoneum was dismal, with 90% of patients with metastatic disease dying within 1 year[2,4]. Radiotherapy to the para-aortic lymph nodes used to be the standard of care, as this targeted the most common site of occult metastases and therefore the most frequent site of relapse. Later, carboplatin chemotherapy became more frequently prescribed, as it was found to be non-inferior to radiotherapy and to carry a lower risk of subsequent development of radiation induced late onset intra-abdominal malignancy.[5]

Recently surveillance has become the preferred option for stage 1 seminoma patients[6], as cure rates approach 100% whether adjuvant treatment is given or not; minimising treatment related morbidity has therefore become of greater concern[4,7]. A recent meta-analysis studying 12,075 patients with stage 1 seminoma found that although adjuvant treatment significantly reduced 5 year relapse rates from 14.8% to 3.9% compared with surveillance, this did not correspond to a significant increase in 5 year overall survival[8]. Another study evaluating active surveillance found a relapse rate of 13% in 1,344 stage 1 seminoma patients, but no deaths from disease after a median follow-up of 52 months[7].

A challenge in the management of stage 1 seminoma is therefore identifying the patients that do have a higher risk of relapse, so that the risks and benefits of adjuvant treatment versus surveillance can be discussed with the patient appropriately. An analysis of 638 patients managed conservatively across 4 cancer centres aimed to identify and quantify the factors that predicted relapse[2]**.** On multivariate analysis it was found that larger tumour size, defined as greater than 4 cm, and rete testis invasion, were both independent risk factors for

recurrence. In this study patients with neither of these adverse prognostic factors had a 5 year relapse rate of 12.2%, those with one had a 5 year relapse rate of 15.9%, and the 5 year relapse rate was 31.5% in those with both[2]. This allows identification of a subset of patients who do warrant discussion about adjuvant treatment.

In our analysis we have audited the outcomes of patients diagnosed with testicular seminoma in the Thames Valley Cancer Network between 2004 and 2016. We present an analysis of risk factors and relapse rates for this cohort of patients together with analysis of how recurrences were identified and managed.

Methods

Stage 1 classical seminoma cases were identified from a prospective database of all testicular tumours reviewed by the TVCN MDT between 2004 and 2016. We identified a total of 501 patients with stage I seminoma. The study was registered and approved by the trust's audit department: audit number 3728. Ethical approval was not required for this service evaluation audit; Caldicott principles have been adhered to.

Results

In our data, seminoma accounted for 54.1% of testicular tumours and the peak incidence was 36 years of age. Over the entire study period 175 out of the 501 patients (34.9%) were given adjuvant treatment. The proportion of patients being prescribed adjuvant treatment reduced gradually over time, with 115 out of 178 (64.6%) having adjuvant treatment up to 2010, but only 60 out of 323 (18.6%) having adjuvant treatment from 2010 onwards. The overall recurrence rate was 31 out of 501 patients (6.2%). Of the patients having adjuvant treatment 11 out of 175 (6.2%) recurred, and 20 out of 326 (6.1%) of those that did not receive adjuvant treatment had a recurrence (Fig 1).

Tumour size and risk of cancer recurrence was studied, using 4 cm as a cut off. A higher proportion of those with larger tumours were given adjuvant treatment compared to those with smaller tumours. Amongst patients with tumours less than 4 cm, 107 out of 345 (31.0%) had adjuvant treatment, compared with 68 out of 156 patients (43.6%) who had tumours of 4 cm or larger. Looking at all patients, the hazard ratio for recurrence with tumours >4cm compared with those of 4cm or less was 1.219 (CI 0.58-2.55; p=0.598). Of those who were not given adjuvant treatment, this hazard ratio was 1.316 (CI 0.51-3.43;

p=0.574). Tumour size is therefore likely to be predictive of recurrence, though this did not reach statistical significance in our small dataset (Fig 2).

The risk of seminoma recurrence depending on the presence or absence of rete testis invasion was calculated. Amongst all patients the hazard ratio for recurrence with any rete invasion was 2.26 (CI 1.11-4.61; p=0.025). When only true, stromal rete invasion was analysed this affect was stronger with the hazard ratio for recurrence increasing to 3.00 (CI 1.47 – 6.14; p=0.003). This increased risk of recurrence with stromal rete invasion was greater when looking at only those patients who had not received adjuvant treatment, hazard ratio 3.35 (CI 1.38-8.11). The hazard ratio for recurrence with stromal rete invasion was also significant on multivariate analysis adjusting for age, T-size and adjuvant treatment, hazard ratio 3.19 (CI 1.50-6.77; p=0.002). Comparing the hazard ratio for recurrence with stromal rete invasion and all rete invasion, on multivariate analysis, Harrell's C index was higher with stromal rete invasion (0.7255 compared to 0.7069) meaning stromal rete invasion is a better predictor of recurrence (Fig 3).

The tumour markers AFP, βHCG and LDH are routinely measured before and after surgery and at follow-up visits to monitor patients for recurrence. There is a non-statistically significant increased risk of recurrence with positive tumour markers (Fig 4).

The mode of detecting the 31 cases of relapse and the timing of recurrence after surgery was evaluated. Recurrence was identified on routine, surveillance CT imaging in 17 patients; in 8 cases this was at their first surveillance scan 2-4 months following orchidectomy, and in another 8 cases at the one year scan, 1 patient had a routine scan prior to discharge. Three patients presented symptomatically, one with loin pain, another with abdominal pain and a change in bowel habit, and another with discomfort in the contralateral testis. These all recurred between 1 and 2 years following surgery. Seven patients who recurred were noticed to have elevated tumour markers. These were identified later, five patients 1-5 years after orchidectomy, and two patients over 5 years later. In 4 patients we do not know how relapse was initially identified. Twenty-three of the thirty-one (74.2%) were identified within 2 years of diagnosis, and three were identified over 5 years following diagnosis.

Of the 31 first recurrences 28 were exclusively in the lymph nodes, and in 22 of those the recurrence was below the diaphragm only. One patient had lung metastases at first recurrence and for 2 patients we do not have information. Of the 31 recurrences, 13 first recurrences were treated with chemotherapy alone, 14 just with radiotherapy to the para-aortic nodes, one with chemotherapy and radiotherapy, one patient was treated with

resection followed by chemotherapy, one patient we have no information on treatment, and the final case, whose late recurrence was actually found to be a mixed seminoma and yolk sac tumour despite the initial histology indicative of pure seminoma, was treated with chemotherapy, then surgery and thirdly with radiotherapy. Of the thirty-one initial recurrences, two patients subsequently had a second relapse. The aforementioned patient with mixed pathology on first relapse had a further recurrence with liver metastases and peri-hepatic nodules and was successfully treated with high dose chemotherapy followed by stem cell transplant. The other had a second relapse of seminoma in the mediastinal and supraclavicular nodes and was treated with chemotherapy.

Of the 501 patients identified with stage 1 seminoma in this study none have died from their disease.

Discussion

Our recurrence rates for stage 1 seminomas of about 6% whether adjuvant treatment is given or not, is very different to some earlier previous studies which show a decrease in recurrences with adjuvant therapy, such as the meta-analysis by Petrelli *et al* in 2015 which had recurrence rates of 3.9% with adjuvant treatment and 14.8% without (OR, 0.17)[8]. However, it is similar to the results reported by Tandstad *et al* in 2016, who found relapse rates of 7.5% with surveillance only and 6.2% with adjuvant carboplatin[9]. In this study patients were given the choice of whether to have adjuvant treatment, but those with risk factors, size >4cm or stromal rete invasion, were recommended to have carboplatin, whereas those without risk factors were discouraged[9]. In our dataset more patients with risk factors were given adjuvant treatment too, and this probably explains the lack of difference in recurrence rates between the two groups in our study.

On identification of risk factors for recurrence we found that both large size (≥ 4cm) and rete testis invasion were predictive of relapse, but this only reached statistical significance for rete invasion. The effect was stronger when stromal rete invasion only was included. This was in keeping with the findings of Warde *et al* in 2002, who also identified these as independent risk factors.[2] They found that with tumour size below 4 cm, 5-year recurrence was 13% and with tumour size above 4 cm it was 24%, and without and with rete invasion recurrence rates of 14% and 23% respectively. We also identified raised tumour markers as a potential risk factor for recurrence, though this did not reach statistical significance.

The identification of risk factors that make individual patients at higher risk of recurrence is important for counselling patients appropriately about the benefits and risks of adjuvant treatment. For patients with no adverse risk factors who have a low risk of relapse without adjuvant treatment, the risks associated with adjuvant treatment, such as the incidence of second cancers[9] in our opinion outweigh the potential benefits, considering that almost all patients will be cured of their disease regardless of adjuvant treatment. However, for those with adverse prognostic factors this needs to be weighed up on an individual patient basis, taking into account their preferences and ability and willingness to attend regular follow-up.

Avoiding the use of adjuvant treatment is desirable to both reduce the morbidity from unnecessary treatments as well as minimising the costs associated with treatment, and is appropriate for patients with a low recurrence risk, most of whom are cured by orchidectomy alone. One of the concerns is that adjuvant treatment may increase the risk of second malignancies developing, and a study by Travis et al in 1997 aimed to quantify this risk[10]. Other morbidity from adjuvant treatment may include cardiovascular risk, reduced fertility and acute complications, such as neutropenia and nausea, from chemotherapy. Travis et al studied cancer registries looking for incidence of second malignancy, excluding that of the contralateral testis, for 29,000 patients who had survived at least one year after a diagnosis of testicular cancer. They compared the rates of malignancy in this cohort against rates to be expected for men of a similar age in the same geographical region to calculate an observed to expected ratio of cancer incidence. They found a significant increase in acute leukaemias in men whose primary treatment included either chemotherapy or radiotherapy. There were also increased rates of stomach, colon, rectum, pancreas, prostate, kidney, bladder, thyroid and connective tissue malignancies. The increased risk of developing these cancers augmented over time, and malignancy of the stomach and bladder was more strongly associated with radiotherapy. Though few of the patients in the study had reached 20 years following their initial treatment, the study estimated the absolute risk of developing a second malignancy was 15.7% at 25 years, compared to a 9.3% risk in the general population. These results may not be directly applicable to today's patients as this data includes cases going back to the 1930s. In more recent decades radiotherapy fields and doses have been reduced suggesting this study may overestimate the burden of second cancers, and this study did not specify cancer stage, therefore probably included patients having longer chemotherapy courses for metastatic disease than the single cycle given adjuvantly. However, the median follow-up of patients in this study was only 10.2 years. Given the excess risk of solid cancers increased with time following treatment, and patients with testicular cancer are young, continued follow-up for several decades could have been beneficial to aid true excess risk evaluation.

There is currently no agreed consensus on the optimal follow-up protocol for patients diagnosed with stage 1 seminomas. Currently our practice is to review patients in clinic with physical examination and tumour markers every 3 months for the first year and then at decreasing intervals until discharge at 5 years. A CT scan is performed at 3 months, 1 year and 3 years post diagnosis.

Since over half of our recurrences were identified by surveillance CT staging in the first year, this confirms the utility of these routine scans early in the follow-up protocol and this also concurs with data from Kollmannsberger *et al* in 2015, who found that most relapses (92%) occurred within the first 3 years and that the majority of these were found on routine CT imaging (87%)[7]. We found no recurrences on chest x-ray or physical examination, which again is in keeping with the findings by Kollmannsberger *et al*, who also detected no relapses by this method. While chest x-ray is a low cost procedure with minimal radiation exposure in comparison to a CT scan, this calls into question the benefit of surveillance by this modality, as it may provide false reassurance to patients, when most relapses occur in the abdomen and so cannot be detected in this way. We used to perform chest X-rays for appointments where CT scans were not being requested, however, given no relapses have been identified on chest x-ray in the last 12 years, we have changed practice and no longer do them.

Three of our patients had recurrence detected by reporting new symptoms and therefore it is important for patients to be able to contact their treating team if new problems develop in between appointments, especially given that all cases picked up symptomatically in our dataset were over a year after their initial treatment when follow-up frequency will be reducing. In the Thames Valley Cancer Network this is achieved by the provision of specialist nurses who the patients are able to contact if they have concerns, allowing imaging to be arranged prior to clinic review if this is required.

Given no recurrences have been identified on physical examination, the availability for patients to make contact should they have concerns is probably of greater importance than routine clinical review, and suggests that nurse led telephone appointments to ask about symptoms and relay tumour marker results may be as effective as routine clinical review. Our data showed seven cases that were picked up on measurement of LDH, AFP or βHCG and these tended to be the later recurrences, from 1 to over 5 years since diagnosis. This confirms the importance of this simple blood test not only at review over the 5 years of hospital led follow-up, but also the value of continuing this by the general practitioner.

Limitations

Since this study covers only our cancer network, it is limited by relatively small numbers in our dataset. This means that the numbers of patients with adverse risk factors and those relapsing are small, given that these make up the minority of patients. It is also limited by the fact that it was retrospective, meaning that in a small proportion of cases complete data was not available.

Conclusion

We have analysed the risk factors for recurrence of stage 1 seminoma and found similar adverse risk factors, increasing size and rete testis invasion, to other published studies[2]. How and when relapses occur was evaluated and we found that most recurrences occur early, nearly 75% within 2 years of orchidectomy, and that most recurrences are detected by routine imaging, measurement of tumour markers or present symptomatically[7].

Clinical Practice Points

This study confirmed rete testis invasion as a risk factor for stage 1 seminoma relapse, as previously identified in other studies, particularly stromal rete invasion. It also showed that adjuvant treatment did not improve overall survival in routine clinical practice. We therefore suggest that adjuvant treatment only be offered to those patients with higher risk tumours, and only after discussion with the patient about the potential risks and benefits. We found that relapses were most often identified by surveillance CT scans, though relapses also presented symptomatically or were discovered on investigation of elevated tumour markers. Most cases of relapse were below the diaphragm. No cases of relapse were found through chest X-ray or clinical examination. We therefore suggest that follow-up schedules could be altered to include more telephone appointments for assessment of symptoms and relay of tumour marker results by specialist nurses, replacing some hospital appointments for examination by a doctor and chest X-ray. This would save the cost associated with hospital appointments without compromising prompt detection of relapses and curative treatment.

Acknowledgements

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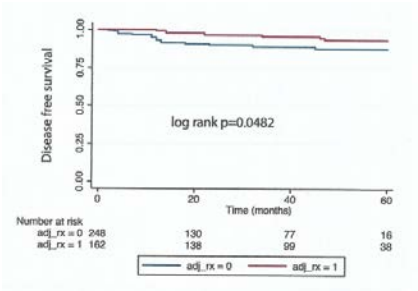

Fig 1: Recurrence over time in patients receiving (=1) and not receiving (=0) adjuvant treatment.

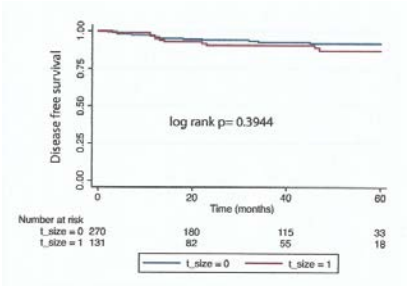

Fig 2: Recurrences over time in patients with tumours <4cm (=0) and tumours >4cm (=1)

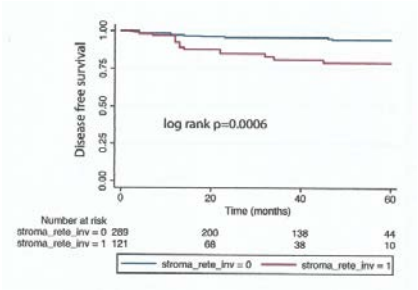

Fig 3: Recurrences over time in patients with stromal rete invasion (=1) and without stromal rete invasion (=0)

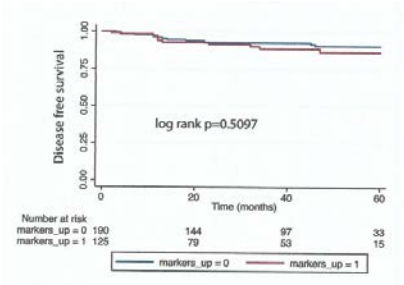

Fig 4: Recurrences over time in patients with raised tumour markers (=1) and without raised tumour markers (=0)