

Surveillance in stage I testicular seminoma - risk of late relapse

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Introduction: Surveillance is an alternative to adjuvant radiotherapy for stage I testicular seminoma. We present the long-term results of seminoma surveillance, with emphasis on quantifying the risk of late relapse beyond 5 years.

Methods: From 1981 to 1993, of 431 men with stage I testicular seminoma, 203 were managed by surveillance following radical orchidectomy. The surveillance protocol comprised a combination of clinical examination, CT

scans of abdomen and pelvis, chest x-rays and serum markers, at defined intervals.

Results: At a median follow-up of 9.2 years, 35 men have relapsed. Five of the relapses occurred more than 5 years after orchidectomy (at 5.1, 6.9, 7.3, 7.3, and 9.0 years). The actuarial risk of relapse at 5 and 10 years was 15% (standard error [SE] 1.1%) and 18% (SE 1.8%) respectively. One hundred sixty one men were free of relapse at 5 years, and have been followed beyond this point for a median of 4.3 years. The actuarial risk of relapse between 5 and 10 years was 4% (SE 0.5%).

Conclusions: These results demonstrate that there is a small but clinically significant risk of relapse more than 5 years after orchidectomy for stage I seminoma. These data support the need for long term surveillance.

Key Words: seminoma, surveillance, late relapse

Introduction

In Stage I seminoma, surveillance or adjuvant radiation are both management options after orchidectomy. Given the increasing concern with

regard to radiation-induced malignancies,¹⁻³ together with the availability of curative chemotherapy for metastatic disease,^{4,5} surveillance with salvage treatment in the event of relapse, may be the preferred alternative. Four large series of seminoma surveillance have been reported with a median follow-up of between 48 and 73 months,⁶⁻⁹ each one demonstrating a relapse-free rate of approximately 80% to 85%, at 4 or 5 years after orchidectomy. Thus, there is a need to characterize long term outcome for these men. There is lack of published data on the

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outcome of seminoma surveillance beyond 5 years. Late relapse may be a feature of seminoma.

Long-term outcome data would refine the design of surveillance protocols and would further guide patients and clinicians with regard to the choice between surveillance and adjuvant treatment following orchidectomy for stage I seminoma. We have updated our previous seminoma surveillance analysis,⁸ with an emphasis on quantifying the risk of late relapse.

Methods

Between 1981 and 1993, of a total of 431 men with stage I testicular seminoma presenting at Princess Margaret Hospital, 203 were managed by surveillance following radical orchidectomy. The remaining 228 men, according to patient preference, received radiation therapy to the retroperitoneal lymph nodes. Initial staging investigations following orchidectomy included chest radiograph, computerized tomography (CT) scan of the abdomen and pelvis, and assay of serum α -fetoprotein (α FP) and β -human chorionic gonadotrophin (β HCG). Paraffin blocks of the surgical specimen were routinely obtained from the referring hospital for histopathological review.

The follow up policy has evolved and currently the surveillance protocol remains the following: for the first 3 years after orchidectomy, clinical examination, CT scan of the abdomen and pelvis and serum tumor markers (α FP and β HCG) at 4-month intervals, together with a chest radiograph at alternate visits. Between 4 and 7 years after orchidectomy, clinical examination and CT scan of the abdomen and pelvis every 6 months, together with an annual chest radiograph. From 8 years after orchidectomy onwards, clinical examination, CT scan of the abdomen and pelvis, and a chest radiograph were obtained annually.

Statistical methods

All survival and relapse-free probabilities were calculated from the date of orchidectomy using the Kaplan-Meier estimate. The calculation of the probability of relapse at 10 years from surgery among those who were alive and relapse-free at 5 years was based on the subset of patients for whom there was at least 5 years of follow up. The hazard function was used to illustrate the instantaneous relapse rate. That is, the relapse rate at a given time t , conditional on being alive and relapse free up to time t . Unlike the relapse-free probability curve, the hazard function is not a probability but a rate, so its values do not have to start at 1 and decrease towards zero; in fact the range of the hazard function is 0 to infinity. The hazard plot employed a

smoothing method produced with a SAS macro program using output from PROC LIFETEST in SAS.

Results

The patient characteristics of the 203 men with stage I seminoma managed by surveillance are shown in Table 1. At a median follow-up of 9.2 years (range 2.3 to 16.4 years), 35 men have relapsed. Of these, 14 were within 1 year, a further 11 within 2 years and 5 between 2 and 5 years after orchidectomy. The remaining 5 relapsed more than 5 years after orchidectomy (at 5.1, 6.9, 7.3, 7.3, and 9.0 years). Four of these 5 were 30 years or younger at diagnosis, 2 had small vessel invasion, none had primary tumors over 4.5 cm or rete testis involvement. The actuarial risk of relapse at 5 and 10 years was 15% (standard error [SE] 1.1%) and 18% (SE 1.8%) respectively Figure 1.

TABLE 1. Patient characteristics

		Number (%)
Age	\leq 34 years (median)	110 (54%)
	> 34 years	93 (46%)
Tumor diameter	\leq 6 cm	166 (82%)
	> 6 cm	31 (15%)
	not known	6 (3%)
Rete testis involvement	present	46 (23%)
	absent	56 (28%)
	not known	101 (50%)
Small vessel invasion	present	15 (7%)
	absent	143 (70%)
	not known	45 (22%)

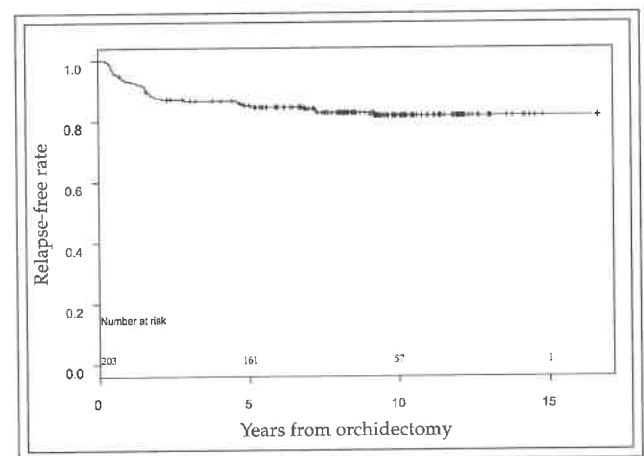


Figure 1. Relapse – free probability.

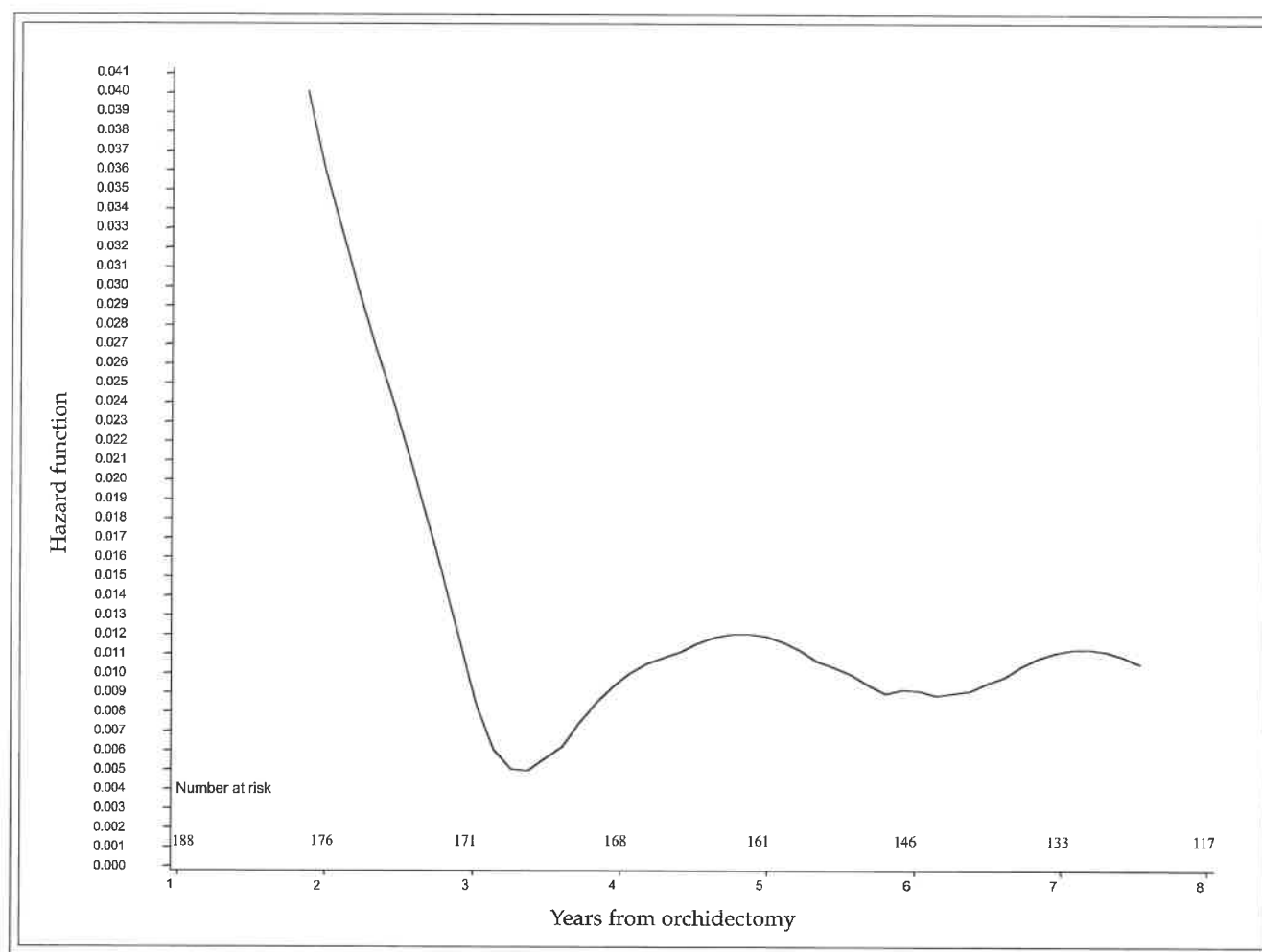


Figure 2. Hazard function.

The actuarial risk of relapse at 10 years, in men free of relapse at 5 years was 4% (SE 0.5%). A hazard plot shows the risk of relapse at any point in time from orchidectomy Figure 2. The greatest risk of relapse is within the first 3 years but does not become zero at any point Figure 2. All patients were salvaged with radiotherapy (25), chemotherapy (8) or surgery (2), four patients in the radiotherapy group subsequently relapsed outside the irradiated volume and had successful salvage with chemotherapy. Only one patient died of disease, he had primary chemotherapy at relapse, failed this and all subsequent chemotherapy. The 5-year and 10-year overall survival rates were both 97% (SE 1.2%). The 5-year and 10-year cause-specific survival rates were 99.5% (SE 0.5%).

Method of detection and pattern of late relapse

As previously reported,⁸ sites of relapse in this group of patients occurred in the para-aortic region, pelvic

and inguinal nodes, lung and mediastinum. Eighty-nine percent of the relapses occurred in the para-aortic region alone. Relapses were detected on abdominopelvic CT scanning, although one patient had concurrent rise in serum tumor markers and two patients had concurrent palpable inguinal lymph nodes.

CT scan detected all five late relapses (beyond 5 years). One patient had a 2 cm pre-caval nodal mass, three had a 3 cm nodal mass in the left para-aortic region and the other, who also had lung metastases, had a 5.5 cm right para-aortic mass at the level of the aortic bifurcation. This patient's prior scan had been more than 2 years previously as he had defaulted on follow-up.

Salvage treatment

All five patients that relapsed after 5 years were successfully salvaged. Three were treated with

radiotherapy to the para-aortic region and pelvic lymph nodes. One patient underwent retroperitoneal lymphadenectomy; he had previous radiotherapy for a contralateral seminoma. The remaining patient with lung metastases was salvaged with chemotherapy. All these patients remain alive and relapse free with a follow up of 0.7, 1.8, 3.4, 4.8 and 6.8 years after their salvage treatment.

Discussion

The risk of relapse in Stage I seminoma within the first 5 years after orchidectomy is documented to be around 15% to 20%.⁶⁻¹¹ Surveillance and treatment only at the time of relapse will avoid treatment-related side effects, particularly, preservation of fertility for the majority of patients that will not relapse. There is little published data on the risk of relapse in patients on surveillance after 5 years from orchidectomy. We observed a 4% risk of relapse in patients beyond 5 years from surgery. This risk may be regarded as small but it is clinically significant and supports the need for continued follow up of surveillance patients beyond 5 years. As all five late relapses occurred within the para-aortic nodes, this provides an argument for CT scanning of the abdomen as a minimum beyond 5 years. The need to continue tumor marker measurements and chest x rays is less conclusive from the present data, however, we cannot make any firm recommendation with regard to this. For the men with late relapse, no particular prognostic factor was more evident that would have predicted relapse. It is interesting that four of five were 30 years old or less at diagnosis, but there were too few of these patients to draw any conclusions. Currently, our policy is to manage these patients in the cancer centre. However in future, it may be possible to perhaps, after initial follow-up centrally, continue surveillance in the community with rapid access to the centre should recurrence be discovered.

Bearing in mind that there is a continued long-term risk of relapse beyond 5 years, alternative strategies for the management of these patients should still be considered. Although salvage treatment is successful in the vast majority of patients, psychological and other morbidity associated with relapse should not be underestimated. Pilot studies of single agent carboplatin chemotherapy in this setting have so far shown a low risk of relapse.^{12,13} The United Kingdom Medical Research Council is investigating this strategy in the phase III setting. The results of this large trial, which has randomized patients to carboplatin versus radiotherapy, are awaited with interest. If a low rate

of relapse with minimal toxicity is confirmed, then this may offer patients another viable alternative to radiotherapy or surveillance.

Conclusion

There is a small, but clinically significant, risk of relapse more than 5 years after radical orchidectomy alone for stage I seminoma. These data will be of interest to clinicians and patients faced with the choice of adjuvant treatment or surveillance, and will inform the design of surveillance protocols. In particular, the continued risk of seminoma relapse supports the need for long term surveillance. □

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