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Research Article

Lower-Than-Expect Relapse Rate among Contemporary Patients with Clinical Stage I Seminoma Managed on Surveillance

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Abstract

Background: There is equipoise regarding the optimal management of clinical stage (CS) I testicular seminoma. Surveillance protocols have increasingly been embraced given the low relapse rate reported (15-20%) at 5 years. We analyzed the relapse rate of CS I seminoma patients under surveillance in a contemporary series.

Patients and methods: Between 2005-2012, 48 of 74 (65%) consecutive patients diagnosed with CS I seminoma at our institution were managed by surveillance. Clinical information and follow-up data was obtained through retrospective chart review. The decision to be treated or observed was largely physician-dependent and was not based on the presence/absence of specific risk factors.

Results: Among 48 patients on surveillance, 18 (37%) had tumor size ≥ 4 cm, 16 (33%) had rete testes invasion, and 4 (8%) had lymphovascular invasion. Over a median follow-up of 39 months (IQR, 18-61), 2 patients relapsed and the 3-year relapse-free survival (RFS) was 94% (95% CI: 86-100). Both relapsed in the retroperitoneum at 10 and 29 months, and are disease-free following first-line chemotherapy. Retrospectively, the patient with late relapse had a 1.8 x 1.3 mm retrocaval mass retrospectively identified on the non-contrast CT at diagnosis and at 4 months on observation which may have represented metastatic disease that was missed. This patient did not undergo further transaxial surveillance imaging and relapsed with a large retroperitoneal mass at this location. Excluding this patient, the 3-year RFS was 98% (95% CI: 93-100).

Conclusions: Contemporary CS I seminoma patients appropriately staged and observed at our institution had a very low-risk of relapse. This evidence further supports surveillance as the preferred standard option for these patients.

INTRODUCTION

Clinical stage I seminoma is the most common presentation of germ cell tumors accounting for approximately 50% of newly diagnosed cases [1]. The optimal management of clinical stage (CS) I seminoma is controversial. Adjuvant radiotherapy, surveillance, and chemotherapy with 1-2 cycles of carboplatin are all accepted as standard treatments with long- term survival rates approaching 100% for each [2–8]. Surveillance has been adopted increasingly as the preferred treatment option given the low rates of relapse; contemporary population-based series of patients with CS I seminoma on surveillance have reported relapse rates of 15-20% at 5 years [7,8]. While the use of adjuvant radiotherapy has declined significantly across many regions, it has been replaced in some regions with surveillance, while carboplatin use has increased significantly in others [7–9]. We analyzed the outcomes of CS I seminoma patients managed at a high-volume academic center since 2005.

PATIENTS AND METHODS

Between 2005 and 2012 a total of 74 patients were retrospectively identified who underwent radical orchiectomy at our institution and were diagnosed with CS I seminoma.

All orchiectomy specimens were reviewed by genitourinary pathologists at our institution. Clinical staging was performed by post-orchiectomy computed tomography imaging of the abdomen and pelvis (CT-AP), chest CT or radiograph imaging, and serum tumor marker determinations, including beta-human choriogonadotropin (HCG), alpha-fetoprotein (AFP) and Lactic Dehydrogenase (LDH). Of these patients, 48 (65%) were managed by surveillance and 26 received immediate treatment, including adjuvant radiotherapy (N = 14), carboplatin chemotherapy (N = 11), and retroperitoneal lymph node dissection (N = 1). Treatment decisions were based on physician and/or patient preference and were not standardized. For patients on surveillance, follow-up consisted of clinical assessment, chest radiographs, and serum tumor marker determinations every 3-4 months in years 1-2, every 6 months in years 3-6, then annually thereafter. The frequency of surveillance CT-AP varied by physician and over time and patients underwent at least 1 study in year 1, 2, and 5.

Patients were identified by institutional review board-approved prospective testis cancer data base and a review of all orchiectomy specimens in our institutional pathology data base. Comparisons between treatment groups were performed using chi-square test. Survival estimates were obtained using the Kaplan-Meier method and differences between groups were compared using the log-rank test. The level of significance was set at .05. Statistical analysis was performed using commercially available software.

RESULTS

The clinical features of 48 observed patients are summarized in Table 1. Overall, 16 (33%) had rete testis invasion, 18 (37%) had tumor size ≥ 4 cm, and 4 (8%) had lymphovascular

invasion. Of these risk factors, 23 (48%), 15 (31%), and 10 (21%) had 0, 1, or ≥ 2 risk factors, respectively. The proportion of patients with risk factors was not significantly different between treated and observed patients ($P > 0.05$). Over a median follow-up of 39 months (IQR, 18-61), the median number of CT studies was 3 (IQR: 1-11) corresponding to 1.5 CT per person-years. Relapses (both isolated retroperitoneal masses without elevated serum tumor markers) were observed in 2 patients at 9.5 and 29.4 months; 1 patient had tumor size ≥ 4 cm and rete testis invasion and the other had tumor size ≥ 4 cm and lymphovascular invasion (Table 2). Both patients are currently disease-free after salvage treatment with first-line, conventional-dose, cisplatin-based chemotherapy.

Table 1: Clinical and pathological features of the 48 patients with CS I seminoma under surveillance protocol.

Patients, n	48
Median age; year, IQR	38 (32-42)
Age ≤36 years, n (%)	22 (45)
Serum tumor markers elevated; n (%)	8 (16)
Tumor size; ≥4 cm; n (%)	18 (37)
Laterality; n (%)	
R/L	22(45)/ 25(52)
Bilateral	1 (2)
LVI, n (%)	4 (8)
Rete testis invasión; n (%)	16 (33)
Median follow-up; months (IQR)	39 (18-61)
Median CT scans; IQR	3 (1-11)

The patient with late relapse had a right-sided tumor and underwent surveillance transaxial imaging with a non-contrast CT at diagnosis and at 4 months only. Despite routine follow-up with chest radiographs, serum tumor marker determinations, and clinical assessment, he presented at 29.4 months with back pain and subsequent CT imaging revealed a 15 x 7 cm retroperitoneal mass. Retrospectively, we identified a stable 1.8 x 1.3 cm retrocaval mass on the non-contrast studies performed at diagnosis and 4 months follow-up which may have represented metastatic disease and was missed.

Considering all 48 patients, the 3-year RFS was 94% (95% CI: 86-100). Excluding the patient with late relapse who may have had CS IIA disease at diagnosis, the 3-year RFS 98% (95% CI: 93-100). Of the treated patients, no relapses were observed and all are alive at last follow-up.

DISCUSSION

Over the last decade, the management of CS I seminoma has undergone a significant paradigm shift away from adjuvant radiotherapy in favor of surveillance and adjuvant chemotherapy with single-agent carboplatin [7–9]. The preference for carboplatin versus surveillance varies significantly by geographic region as there are no validated prognostic factors for a risk-adapted approach. While some clinical guidelines and organizations favor surveillance as the optimal strategy, other guidelines favor a risk-adapted approach [2-5,10,11]. An increase in the incidence of germ cell tumors has been observed worldwide for poorly defined reasons, largely related to an increase in the incidence of CS I seminoma. It is not known if the behavior of contemporary seminomas is similar to those diagnosed in the past. In a single-institution experience with CS I seminoma, we observed a lower-than-expected relapse rate (2-6%) compared to historical series (15-20%), albeit in a small number of patients over short-term follow-up. The low observed relapse rate may be due to improved patient selection, stage migration, and/or changes in the biology of contemporary seminoma. This low relapse rate would suggest these patients, with rare exceptions, should be managed by surveillance. Confirmation of our findings in larger series with longer follow-up is needed.

The outcomes of patients with CS I seminoma from the largest published series are summarized in Table 2. In general, relapse rates over follow-up ranging from 2-3 years or longer is reported in 13-19% and the vast majority of relapses occur within the retroperitoneal lymph nodes. Most mature series date to the early 1980's and the staging of these patients may not be as accurate as today given the technological advances in transaxial abdominal and pelvic imaging. However, two large, contemporary, population-based series have reported relapse rates within this range. Tandstad et al. reported a 5-year relapse rate of 14% among 512 Swedish and Norwegian patients on surveillance diagnosed between 2000 and 2006. A similar study of 313 CS I seminoma surveillance patients from British Columbia and Oregon treated between 1999- 2008 revealed a 19% relapse

Table 2: Patterns of relapse for patients with CS I seminoma under surveillance protocol.

Age, yr	CS	Interval to relapse, mo	Site of relapse	High-risk factors (No.)	Treatment at relapse	Follow-up, mo	Status
55	IB	29.4	Retroperitoneal	LVI (1)	BEP x 3	45	CR
45	IB	9.5	Retroperitoneal	7,5 cm, Rete testis invasion (2)	BEP x 3	99	CR

CS: Clinical Stage; RPN: Retroperitoneal; LVI: Lymphovascular Invasion; BEP: Bleomycin Etoposide Cisplatin; CR: Complete Response

rate over a median follow-up of 34 months. Our study differs from these contemporary series in that all patients came from a single, high-volume, academic hospitals and had staging imaging studies evaluated by testis cancer experts and orchiectomy specimens were all reviewed by genitourinary pathologists. Furthermore, the number of surveillance CT imaging studies performed in our series was considerable less than that of Tandstad et al. (20 examinations per patient over 10 years) but similar to that of Kollmannsberger et al. (2-6 examinations per patient over 3 years). Differences in the proportion of patients with risks factors for occult metastasis between studies does not explain the differences in relapse rates as the percentage of patients with tumor size > 4 cm, rete testis invasion, and lymphovascular invasion is similar across all 3 studies. The Royal Marsden Hospital recently updated their experience in CS I seminoma and reported relapses in 17 of 103 patients (16.5%) prior to 1988 and only 5 relapses among 147 at-risk patients (3.4%) since 1988, confirming the lower-than-expected relapse rate that we observed. However, the authors suggest their low relapse rate may be due to the selective use of adjuvant therapy (though no supporting data is provided).

The incidence of germ cell tumors appears to be increasing worldwide, largely due to an increase in the incidence of seminoma [12–16]. A stage migration of GCT and younger age at diagnosis has also been observed in several countries owing, in part, to increased awareness and earlier diagnosis. In the United Kingdom the change in stage distribution over time is largely restricted to an increase in localized seminoma and a decrease in metastatic NSGCT; rates of localized NSGCT and metastatic seminoma are largely unchanged [13]. Currently, localized seminoma is the most common presentation of GCT, representing approximately 50% of all men with GCT [16]. Thus, contemporary testicular germ cell tumors have more favorable prognostic features on average compared with those diagnosed in the 1970's and 1980's. It is conceivable that the lower-than-expected relapse rate observed among our surveillance patients is a reflection of a more favorable prognosis within each clinical stage in the context of overall stage migration. Indeed, the observed stage migration suggests underlying biological differences between similar GCT's over different time eras which may explain the low relapse rate we have observed. Confirmation of our observations in other series with more patients and longer follow-up is needed to support this concept.

Our findings, if confirmed, have important implications for the management of CS I seminoma. Indeed, the low rate of relapse (< 10%) suggests surveillance is the preferred approach for all patients, particularly given the ability to salvage relapses with conventional therapy in virtually all cases. The drawbacks of surveillance include the need for long-term surveillance including frequent CT imaging (with attendant risk of radiation-induced malignancies) and the limited utility of serum tumor markers. The advantages of single-agent carboplatin include a low-risk of relapse, acceptable short-term toxicity, and reduced risk of metachronous contralateral primary tumors. However, the drawbacks of carboplatin are the need for periodic CT imaging, potential risks of chemorefractory relapses, and late toxicity.

Our study has important limitations given the small size, single-center experience, and relatively short follow-up. Recurrence after 3 to 5 years from orchiectomy have been reported in several surveillance series highlighting the need for follow-up > 5 years, although late relapses have not been observed across all series [17–24]. Confirmation of our findings in larger studies is needed. Nevertheless, our observations are potentially important to physicians who manage testis cancer to sensitize them to a potentially lower risk of relapse among contemporary CS I seminoma patients on surveillance.

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