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ORIGINAL PAPER

Surveillance as a safe and effective option for treatment of stage I seminoma

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Summary ***Introduction: Stage I seminoma has a very good prognosis, yet approximately 15% have subclinical metastatic disease and will relapse after orchidectomy alone. Several management approaches have been investigated. We aimed to evaluate the clinical outcomes of real-world patients with stage I seminoma, analysing prognostic factors influencing treatment choice and oncological outcomes.***
Methods: Retrospective, single institution study, with 55 patients diagnosed with clinical stage I seminoma between 2007 and 2020. Selected patients were analysed regarding three management approaches - surveillance, adjuvant radiotherapy and adjuvant carboplatin AUC7. Overall survival and progression-free survival outcomes were analysed. Predictors of treatment choice were determined, and predictors of recurrence were analysed in patients on active surveillance.
Results: The median follow-up time was 91 months (13-165). Overall survival at 10 years was 98.2%. Stage I seminoma patients had a 1-, 3- and 10-year progression free survival of 98%, 94% and 89%, respectively. Three-year progression free survival was 92.0% for those on active surveillance (IC95%, 91.5-92.5%), 95.2% for carboplatin (IC95%, 94.8-95.6%) and 100% for those on adjuvant radiotherapy (p > 0.05). All relapses on active surveillance protocols occurred during the first 24 months. Overall, 43% of patients who underwent adjuvant treatment reported adverse effects of therapy, with higher incidence on radiotherapy group (63%).
Conclusions: Stage I seminoma have excellent prognosis, high cure rates, and low treatment-associated morbidity. Active surveillance is a safe modality when applied to selected patients. Adjuvant radiotherapy and adjuvant chemotherapy with carboplatin show similar results, with fewer adverse effects on chemotherapy arm.

KEY WORDS: Seminoma; Surveillance; Radiotherapy; Adjuvant chemotherapy; Recurrence.

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INTRODUCTION

The incidence of *Testicular Germ Cell Tumours* (TGCT) has increased during recent decades and continues to rise (1). Stage I seminoma is the most common presentation of TGCT and accounts for approximately 40% of all occurrences (2). Patients presenting with clinical stage I (CS I) have very good prognosis with an overall survival rate of 98% (3). Even metastatic patients have a good prognosis with a 5-year survival rate of 72-86% (3).
Despite modern staging procedures, approximately 15% of clinical stage I seminoma patients have subclinical metastatic disease (in the retroperitoneum) and will relapse after orchidectomy alone (4). Unselected CS I patients managed by *active surveillance* (AS) have shown an overall risk of relapse of 12-20% at five years (5).
Identification of CS I seminoma patients who are at a high risk of recurrence has largely been based on two prognostic factors: primary testicular tumour size, and the presence or absence of rete testis invasion (3, 6). Patients with and without both risk factors have a 32% and 6% risk of relapse, respectively (7). Patients with one risk factors had 12% risk of relapse (8).
Three management approaches have been investigated: surveillance, adjuvant radiotherapy and carboplatin (6, 9-14). The adjuvant treatment results were compared in large clinical trials and showed that a single injection of carboplatin at seven times the area under the curve dose (AUC) was noninferior to RT in preventing metastatic relapse and, in addition, may reduce the risk of subsequent contralateral testicular cancer (10). Furthermore, radiotherapy is associated with increased morbidity and late effects, in particular the risk of secondary cancers (15).
The priority for those patients with low stage disease is limiting the burden of therapy and treatment-related toxicity without compromising cancer control. The optimal management strategy for stage I seminoma seems to be a matter of debate and controversy. The aim of this study was to evaluate the clinical outcomes of real-world patients with CSI seminoma treated in a national referral centre. Furthermore, we aimed to analyse prognostic factor influencing treatment choice and oncological outcomes.

PATIENTS AND METHODS

The present study was approved by *Coimbra's University Hospital* (CHUC) and *Faculty of Medicine* (FMUC) ethical boards - CE-026/2022. Using the institutional prospective TGCT database, we selected patients with histologically proven pure seminoma after inguinal orchiectomy. Routine staging at diagnosis consisted in *computed tomography* (CT)

of thorax, abdomen, and pelvis, with additional clinical history and physical examination. All included patients had serum tumour markers before and after orchiectomy - *α-fetoprotein* (AFP) and *β-human chorionic gonadotropin* (BHCG).

The selected patients were retrospectively analysed and assigned to three management approaches - surveillance, adjuvant radiotherapy and carboplatin.

Therapeutic modality was assigned after multidisciplinary uro-oncology discussion and informed discussion with patients. Treatment decision was influenced by pathological characteristics and risk factors, serum tumour markers and patient option.

Patients undergoing adjuvant carboplatin had a single dose of intravenous carboplatin on an outpatient basis, calculated according to Calvert equation - dose of carboplatin (mg) = area below curve 7 mg/ml/min x (GFR + 25). 16 Patients treated with radiotherapy had a total of 20-24 Gray (Gy) directed to the para-aortic and ipsilateral iliac fields.

Most of included patients were followed with clinical assessment and serum tumour markers every 3 months in the first year, every 6 months until third year, and then yearly. CT of thorax, abdomen and pelvis was performed biannually in the first two year and then yearly.

Co-Primary endpoints were the *overall survival* (OS) and *disease-free survival* (DFS).

Overall survival was defined as the time from orchiectomy to death from any cause. Progression-free survival was defined as the time from orchiectomy to imagological disease progression. Increased serum tumour markers were not considered as recurrence. Secondary endpoints were the evaluation of risk factor at the time of diagnosis and safety assessment according to *National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0*.

Statistical analysis

Descriptive analyses were performed using standard summary statistics. Overall survival, progression-free survival, and duration of response were estimated with the use of the Kaplan-Meier method. Predictors of adjuvant treatment decision were determined by Qui-square test of independency (with Yates correction). In the analysis of overall survival, patients who were alive had their data censored at the time of last contact. In the analysis of progression-free survival, patients who were alive and without disease progression had their data censored at the time of last tumour assessment. Cox multivariate analysis were performed to adjust survival for risk factors (rete testis invasion and dimensions) and adjuvant treatment. Medians are reported with corresponding 95% *confidence intervals* (CIs).

Results

From 157 patients with TCGT followed between 2007 and 2020, 55 patients had clinical stage I seminoma at diagnosis. The selected patients were retrospectively analysed and assigned to three management approaches - surveillance, adjuvant radiotherapy and carboplatin. Diagram is show in Figure 1.

We included a total of 55 patients of testicular seminoma with no evidence of metastatic disease at the time of diagnosis (CS I Seminoma). Median patient age was 35 years (range: 24 to 66). Pre-operatively, 7 patients (13%) showed elevated serum BHCG (> 5 mU/mL), and an additional 19 patients (35%) had high serum LDH levels (> 248 U/L). All patients were pre- and postorchiectomy AFP negative, and BHCG levels normalized after orchiectomy. Median tumour dimension was 40 mm (range: 7 to 120 mm). Most specimens (57%) showed tumour confined to testis, with no lymphovascular invasion (pT1). Demographic characteristics of patients and disease at the diagnosis according to treatment modality are summarized on Table 1.

Of the included patients, 25 underwent an active surveillance protocol and 30 were submitted to adjuvant therapy - 8 radiotherapy and 22 carboplatin AUC 7.

Most patients on active surveillance (60%) had no risk factors of recurrence on initial management (rete testis invasion or size > 4 cm). Only 16% had lymphovascular invasion and 4% showed positive pre-operative tumour markers. Conversely, risk factors (rete testis invasion or size > 4 cm) were present on 83% of the patients in adju-

Figure 1.
Assignment of selected patients to three management approaches - surveillance, adjuvant radiotherapy and carboplatin.

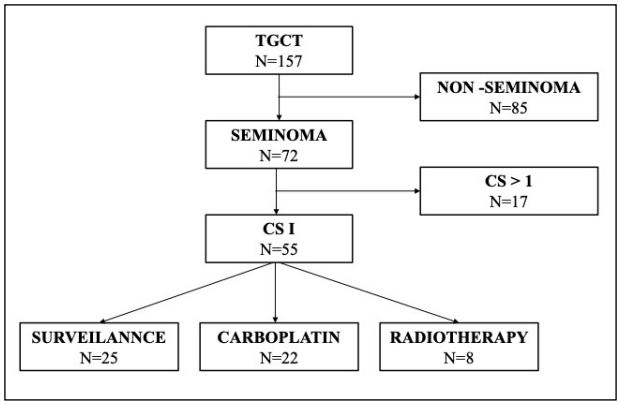


Table 1.
Demographic and disease characteristics.

Characteristic	Surveillance (n = 25)	Carboplatin (n = 22)	Radiotherapy (n = 8)	P value
Age - yrs.				
Median	33	35	36	T-Test
Range	26-66	24-54	25-41	p > 0.05
Pre-operative Serum Tumor Markers				
Positive	7 (28%)	11 (50%)	3 (37%)	X^2
Negative	18 (72%)	11 (50%)	5 (63%)	p > 0.05
Stage				
IA	3 (12%)	14 (64%)	3 (37%)	X^2
IB	22 (88%)	8 (36%)	5 (63%)	p < 0.05
Rete Testis Invasion				
Yes	5 (20%)	12 (55%)	5 (37%)	X^2
No	20 (80%)	10 (45%)	3 (63%)	p > 0.05
Tumour dimension (cm)				
Median	3	5	4	T-Test
Range	1.2-12	1-12	2.2-8	p > 0.05

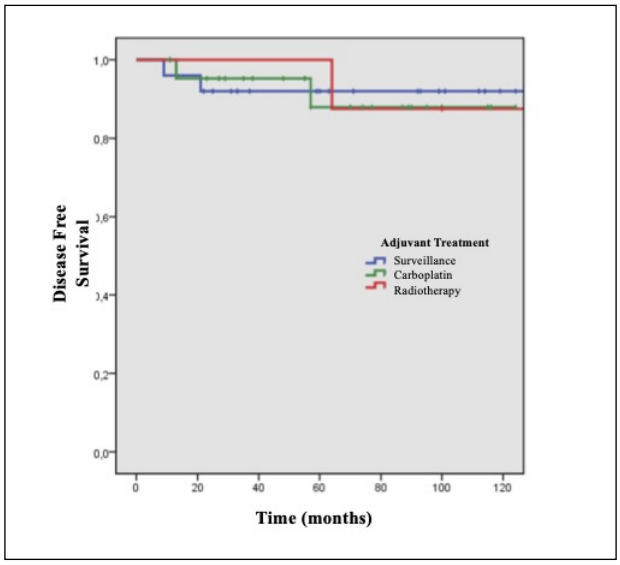
BHCG: β-human chorionic gonadotropin; LDH: lactate dehydrogenase.

Table 2.
Risk factor and treatment groups.

	Active surveillance (n = 25)	Adjuvant therapy (n = 30)
Rete Testis invasion and/or size > 4 cm	15 (40%)	25 (83%)
> pT1	4 (16%)	20 (66%)
Serum Tumor Markers	1 (4%)	6 (20%)

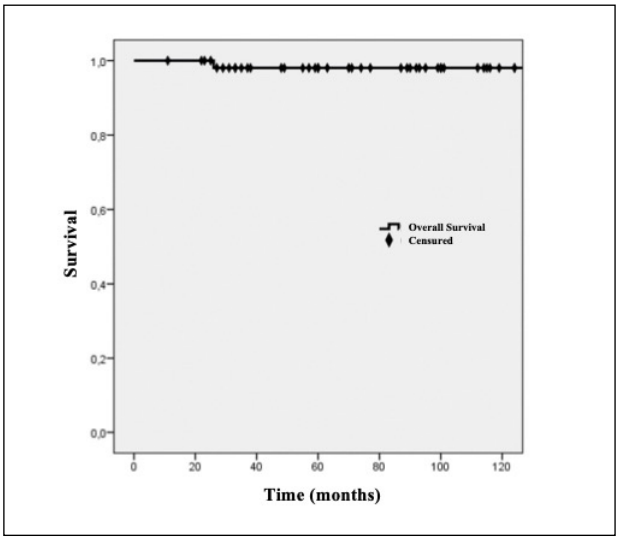
vant treatment groups. Therefore, we conducted a comparative analysis on baseline characteristics, which verified that only pT stage was statistically different between treatment groups.
Considering subgroups of adjuvant treatment, 86% patients on Carboplatin group and 75% on radiotherapy had one or two risk factors. Comparative analysis is summarized on Table 2. Tumour maximal dimensions ($p < 0.05$) and limphovascular invasion ($p < 0.05$) were predictors of adjuvant treatment decision in this setting. Median time from orchiectomy to adjuvant treatment was 37 days (range 24-92).

Figure 2.
Overall survival. Ten-year overall survival (OS) was 98.2%, with an average overall survival of 162 months (95% CI, 157 to 167 months) - median not reached.



Survival analysis
Median follow-up time was 91 months (range 13 - 165 months), with 98% of patients being followed for more than 2 years. No patient was lost to follow-up. Ten-year *overall survival* (OS) was 98.2%, with an average overall survival of 162 months (95% CI, 157 to 167 months) - median not reached (Figure 2). One patient died due to febrile neutropenia following second line chemotherapy.
At the time of present analysis, relapses were observed in 5 patients. Stage I seminoma patients had a 1-, 3- and 10-year PFS of 98%, 94% and 89%, respectively. Three-year PFS was 92.0% for those on active surveillance (95% CI, 91.5 to 92.5%), 95.2% for carboplatin (95% CI, 94.8 to 95.6%) and 100% for those on adjuvant radiotherapy,

Figure 3.
PFS analysis. Three-year PFS was 92.0% for those on active surveillance (95% CI, 91.5 to 92.5%), 95.2% for carboplatin (95% CI, 94.8 to 95.6%) and 100% for those on adjuvant radiotherapy, with no statistically difference between groups of treatment (p > 0.05).



with no statistically difference between groups of treatment ($p > 0.05$). PFS analysis is illustrated on Figure 3. Median time to relapse for patients with tumour recurrence was 21 months (range: 9-64). All relapses on active surveillance protocols occurred during the first 24 months (9 and 21 months). Adjuvant treatment groups showed later relapses - Carboplatin at 13 and 57 months and radiotherapy at 64 months. All relapses were retroperitoneal and detected on follow up CT scan. No patient had symptoms on relapse. These patients were treated with second line therapy with 4 cycles of BEP (*Bleomycin, Etoposide, and Cisplatin*). Of those, 4 patients were free of disease at last follow up. One patient on surveillance group died of the disease, as mentioned before, after relapse and second line treatment. One patient on radiotherapy group showed seminoma on contralateral testis and was submitted to orchiectomy.

Safety
Safety analysis was performed with retrospective analysis of clinical records in the adjuvant treatment groups. Treatment-related adverse events of any grade were reported in 43% of the patients. Patients on Carboplatin group reported 27% grade 1-2 events, with no grade 3-5 events. Most common adverse effect of chemotherapy was nausea and vomitus. Radiotherapy group had 63% reported adverse events, with 13% grade ≥ 3. One patient had secondary neoplasia after radiation treatment.

Predictors of recurrence
We analysed the potential predictors of recurrence in patients with no adjuvant treatment. Elevated preoperative β-hCG (> 5 mU/mL), pT > 1, rete testis invasion, and tumour size > 4 cm were not predictors of recurrence in patients on active surveillance (Pearson X^2; $p > 0.05$).
Two patients with no risk factors for relapse (rete testis

Table 3.
Predictors of recurrence.

CS I (n = 55)			
Rete Testis invasion and/or size > 4 cm (n = 34)		**No Risk Factors (n = 21)**	
Recurrence	Disease free	Recurrence	Disease free
3 (5.5%)	32 (58.2%)	2 (3.6%)	18 (32.7%)

invasion or > 4 cm) recurred on follow up, both in AS group. Three patients who recurred after adjuvant treatment, had both risk factors. Table 3 shows the recurrence rates despite treatment modality. To eliminate the effect of adjuvant treatment, we conducted a Cox Regression with the following predictors: adjuvant treatment, rete testis invasion and dichotomous dimensions. There were no differences in PFS in the model ($X^2 = 0.95$; $p > 0.05$). Adjusted *hazard ratio* (HR) for adjuvant treatment was 0.6 (95% CI, 0.1 to 4.0, p = 0.5). Adjusted HR of 1.3 for rete testis invasion (95% CI, 0.1 to 15.2, p = 0.8) and HR of 2.2 for dimensions (95% CI, 0.2 to 17.3, p = 0.4).

Discussion

Approximately 76% of patients with testicular seminoma in a Portuguese referral centre present with stage I disease at diagnosis, results that are comparable to recent epidemiologic studies and a previous Portuguese referral centre study (1, 17). These patients have excellent prognosis, with high cure rates (3). Therefore, the treatment of stage I seminoma mostly addresses the principles of fast diagnosis and staging, short time between diagnosis and orchiectomy, and precise and fast decision of adjuvant treatment, aiming to avoid deaths without increasing the morbidity of treatment. Adjuvant treatment recommendation mostly relies on a risk adapted strategy and last decision must be made by the individual patient. In stage I seminoma, primary testicular tumour size and invasion of the rete testis have been identified as predictors for relapse (7, 9). Although, two recent systematic reviews have questioned the prognostic value of these risk factors, and so far, there is no ideal prognostic factor for relapse in patients with stage I seminoma (3, 18). Both systematic reviews highlighted the low quality of the studies included and that the level of evidence is too low to recommend the use of these pathological risk factors to drive adjuvant treatment decisions (3, 18). Nevertheless, absence of rete testis invasion together with a tumour diameter < 4 cm is associated with a very low risk of recurrence (6%) (19). Therefore, these are the most suitable patients for AS.

In our centre experience, both tumour maximal dimensions (continuous) and lymphovascular invasion influenced the choice of adjuvant treatment. Using dimensions as a continuous variable may help counseling patients about their expected tumor recurrence risk (12). Risk factors of relapse were analysed on AS patients to eliminate the bias of adjuvant treatment.

Pre-operative β-hCG; rete testis invasion; dimensions; > pT1 were not significant predictors of relapse. In the evaluation of recurrence without considering treatment modality, only 4% patients relapsed with no risk factors. Patients with risk factors recurred in 6%. Although the global model was not significant, patients with rete testis invasion (HR of 1.3) and higher dimensions (HR of 2.2) were associated with worse PFS.

Overall survival in the CSI Seminoma in our centre was 98.2%. OS was comparable to most studies, and confirms excellent prognosis and high cure rates, even in the longer follow up of our design. Nine percent of patients had recurrence of disease. At 3-year PFS no treatment modality showed to be superior, although more patients were free of disease in adjuvant treatment group at this time cut-off. Patients on AS showed earlier relapses (first 24 months) which justifies an intense follow up with CT scan in the first two years.

Growing experience with active surveillance has demonstrated that nearly 80% of CSI Seminoma can expect to be cured without adjuvant treatment, and almost all recurrences can be successfully rescued (14). Possible disadvantages of clinical surveillance are incremental costs, need of patient compliance to the follow-up protocol, psychological distress, and the chance of early relapses (20). Low number of relapses in our study support active surveillance as a safe option with comparable results to adjuvant treatment. Both patients who relapse in AS are alive and free of disease. AS allows to mitigate the morbidity of adjuvant therapies, complying with the principles of treatment of testicular neoplasms when good selection criteria are applied.

Patients on adjuvant treatment groups presented more aggressive characteristics at orchidectomy (size, vascular invasion and pT), as well as a higher percentage of positive markers preoperatively. As discussed earlier, PFS was similar, even with more aggressive disease at diagnosis. Radiotherapy, once the treatment of choice, is being abandoned as adjuvant treatment. Despite long term PFS of 96% and OS of 98%, significantly morbidity is associated with this modality, especially a two to three-fold increased risk of second malignancies (21). Our experience also shows a low number of patients who underwent radiotherapy, confirming the tendency to abandon this modality in stage I seminoma, which confirms the change in pattern of care indicated by previous studies (22).

Carboplatin generally has excellent tolerability and is not associated with grade 3 or 4 adverse effects. On the other hand, RT presented more frequent adverse effects and the risk of secondary neoplasia. Given the low age at diagnosis of patients with testicular neoplasia, one of the main objectives in treatment must be decreased morbidity.

Study limitations where its low number of participants, retrospective design, and the lack of inclusion criteria in the different modalities.

Conclusions

Patients with stage I seminoma have excellent prognosis, high cure rates, and low treatment-associated morbidity. Active surveillance is a safe modality, with results comparable to other modalities, when applied to selected patients. Intense follow up on the first 2 years after orchiectomy is mandatory. Adjuvant radiotherapy and adjuvant chemotherapy with carboplatin show similar results, with fewer adverse effects in patients who underwent chemotherapy.

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