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ORIGINAL PAPER

Stage I seminoma: Outcome of different treatment modalities and changes in patterns of care. A single institution experience

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Summary *Background: The mainstay for management of stage I seminoma is high inguinal orchiectomy with post-orchiectomy therapeutic options including active surveillance, chemotherapy or radiation therapy.*
Objectives: To analyze different post-orchiectomy treatment modalities outcomes of stage I seminoma patients presented to NCI, Cairo University in the period from 2005-2019.
Patients and methods: A retrospective review of all patients' records with clinical stage I seminoma who presented to our institute in the period from 2005-2019 was done. Adjuvant treatment details were extracted, and we compared overall survival (OS) and disease free survival (DFS) for different modalities and changes in patterns of care over this period.
Results: Thirty-five patients were identified with thirty three patients eligible for analysis. Median age was 35 years (range, 19-52). Fourteen patients were kept under active surveillance, eleven patients received adjuvant carboplatin and eight patients received adjuvant radiation to para-aortic chain. Five-year OS was 100% for all patients regardless post-operative approach. Five-year DFS was 100% for patients who received adjuvant chemotherapy or radiotherapy versus 93% for patients who were kept under active surveillance (p = 0.03).
Conclusions: Clinical stage I seminoma is a favorable disease entity with favorable disease related outcomes regardless post-operative approach. Active surveillance is reasonable and safe given equal survival to active treatment.

KEY WORDS: *Seminoma; Stage I; Surveillance; Radiotherapy; Chemotherapy.*

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INTRODUCTION

Testicular cancers are rare tumors with an incidence of less than 1% of all male tumors (1). The standard management of testicular tumors starts with high inguinal orchiectomy followed by a stage and pathology dictated management (2). Clinical stage I seminoma has a very favorable outcome after surgery (3). Management options for stage I disease have evolved over the past decades from adjuvant radiation to para-aortic chain to chemotherapy with single agent carboplatin and finally moving to active surveillance with equal survival among all strategies (4). Herein, we review our experience and changes in patterns of care over time.

PATIENTS AND METHODS

This is a retrospective study including patients with pathologically proven Stage I seminoma, who presented to the *National Cancer Institute, Cairo University*, during the period from 2005 to 2019.

Data was retrieved from the patients' medical records. The collected data included age, pathological subtype, post-operative stage, date and type of surgery, pre & post-operative tumor markers, details of adjuvant treatment, patterns of failure and patients' status at last follow up.

All patients had inguinal orchiectomy followed by staging *computed tomography* (CT) of abdomen & pelvis to exclude nodal or distant disease and serum tumor marker assessments (alpha-fetoprotein and beta-hCG).

Patients who were kept under active surveillance, were followed every 3 months in the first 2 years. In each visit history and physical examination was performed, serum tumor markers levels (LDH, beta-hCG, alpha-fetoprotein) were obtained, and imaging was done every 6 months. In the third year of follow up, the interval of the visits was every 6 months and imaging and markers were ordered annually. In the following years of follow up, the interval was annually with no imaging unless clinically indicated. All patient were adherent to the follow up schedule.

In patients who received adjuvant chemotherapy, one cycle of Carboplatin (AUC 7, based on the formula 7x [glomerular filtration rate (GFR, ml/min) +25 mg] was given to all patients except one patient who was given two cycles. Patients were kept under follow up every 6 months in the first and second year then follow up was annually, with serum tumor markers (LDH, beta-hCG, alpha-fetoprotein) obtained at each visit and imaging if clinically indicated.

In patients who received adjuvant radiation radiotherapy; the field of radiation was *para-aortic lymph nodes* field (PALN). The field extended from T11/T12 superiorly till L5/S1 inferiorly using *anterior-posterior-posterio-anterior* (AP/PA) field arrangement or multiple (4) fields. *Clinical target volume* (CTV) comprised the para-caval, pre-caval and inter aorto-caval nodes. The prescribed dose was (25.5Gy/1.5Gy/17 fraction) or (19.8Gy/1.8Gy/11 fraction). Following the end of the course, follow up was every 6 months in the first and second year then kept annually.

Statistical methodology

Data management and analysis was performed using *Statistical Package for Social Sciences* (SPSS) *vs.* 25. Numerical data were checked for normality and were statistically described as means (standard deviations) or medians (ranges) as appropriate. Categorical data were described as numbers and percentages. Survival analysis was done using Kaplan-Meier method with comparison between two or more survival curves using log rank test with Bonferroni adjustment when necessary. All statistically significant factors on Kaplan-Meier analysis entered the multivariate Cox regression analysis using forward *likelihood-ratio* (LR) method for variable selection. Hazard ratios were computed for significant factors in the last step of Cox-regression with 95% confidence interval estimates. All tests were 2 tailed and P-value < 0.05 was considered statistically significant.

All the patients treated with different modalities were compared in terms of *overall survival* (OS), *disease-free survival* (DFS), *loco-regional control* (LRC) and *metastatic-free survival* (MFS).

OS was calculated from the date of diagnosis to the date of death or last follow-up, *Disease free survival* (DFS) was calculated from the date of surgery to the date of loco-regional recurrence or metastasis whichever comes first. *Metastasis free survival* (MFS) was calculated from the date of surgery to the date of metastasis.

Para-aortic nodal relapse was not considered as metastatic event but a loco-regional failure. Time to loco-regional control (LRC) was calculated from the date of surgery to the date of loco-regional recurrence.

Table 1.
Demographic, clinical data and pathological subtypes in patients of Stage I seminoma.

N = 35	N (%)
Age (median 35, range 19-52)	
< 35	20 (57)
> 35	15 (43)
History of undescended testis	
Yes	6 (17)
No	29 (83)
History of contralateral seminoma	
Yes	1 (3)
No	34 (97)
Pathological subtypes	
Classic	32 (91)
Spermatocytic	3 (9)
Anaplastic	0 (0)

Table 2.
Characteristics of the patients in each modality.

	Active surveillance (14)	Chemotherapy (11)	Radiotherapy (8)
Age			
< 35	11	4	5
> 35	3	7	3
History of undescended testis	2	3	1
History of contralateral seminoma	1	0	0
Pathological subtype			
Classic	14	9	7
Spermatocytic	0	2	1

Results

In the period from 2005 to 2019, thirty five patients with clinical stage I seminoma presented to *National Cancer Institute, Cairo University*. Thirty three patients were included in our analysis and two patients were excluded from survival analysis due to lost follow up.

Median age in our cohort was 35 years (range, 19-52). Thirty two patients (91%) had classic subtype and three patients (9%) had spermatocytic subtype. Patients' clinical and demographic characteristics are summarized in Table 1.

Fourteen patients (42%) were kept under active surveillance, eight patients (24%) received adjuvant radiation therapy to para-aortic nodal chain and eleven patients (34%) received adjuvant carboplatin, with 10 patients receiving only 1 cycle and one patients receiving 2 cycles. Patients' clinical and demographic data in each arm are summarized in Table 2.

Five-year overall survival rate was 100% in the whole cohort and median overall survival was not reached. No overall survival difference was seen between patients who were subjected to active treatment and patients who were kept under active surveillance.

In terms of disease-free survival, five year DFS rate was 100% for patients who received active treatment (whether chemotherapy or radiotherapy) versus 93% for patients who were kept under active surveillance (p = 0.03). Among those who were kept under active surveillance, one patient developed para-aortic nodal recurrence after 4 years. He was managed by salvage chemotherapy (3 cycles BEP) and he achieved complete response and was disease free till data cutoff.

In terms of *loco-regional control* (LRC), five-year LRC was 100% for patients who received active treatment (chemotherapy or radiotherapy) versus 93% in patients who were kept under active surveillance (p = 0.03).

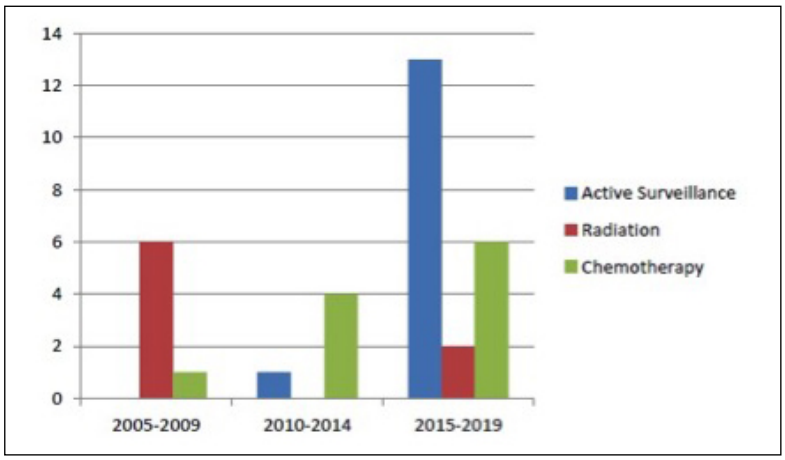
We tested proposed factors that would affect disease local control (namely, rete testis invasion and tumor size), however, none of them had a significant difference in relation to LRC in univariate analysis. Fifteen patients had rete-testis invasion versus 18 patients without invasion, with 5 year LRC of 80 versus 100 percent, respectively (p = 0.439). Sixteen patients had tumor size > 4 cm versus seventeen patients with tumor size < 4 cm, with five year LRC 100 percent and 75 percent, respectively (p=0.317).

In terms of metastasis-free survival (MFS), five-year MFS rate was 100% in all patients, regardless the modality used.

There has been a change in the pattern of care in our study population over the studied years.

In the period from 2005 till 2009 the majority of the patients were treated with adjuvant radiation therapy. In the period from 2010 till 2014 chemotherapy was the modality of choice, while in the recent years from 2015 till 2019 active surveillance was the treatment of choice (Figure 1).

Figure 1.
Change in the patterns of care along time from 2005 till 2019.



Discussion

This retrospective study included 33 patients with stage I seminoma who presented to NCI - Cairo University in the period from 2005 to 2019. Several epidemiological and clinical factors were studied as well as treatment strategies potentially influencing *disease-free survival* (DFS) in addition to *overall survival* (OS) and *loco regional recurrence* (LRR).

In our study the median OS was not reached, with 5 year overall survival 100% in stage I seminoma. This is consistent with many other data. For example, a five-year survival of 99.0% was reported in SEER statistics published in the year 20165. In another large cohort study of NCDB involving 33,094 patients, a ten year survival rate of 95% was reported for patients who received active treatment and 93.4% for patients who were kept under active surveillance (4). In another series coming from a tertiary Portuguese center addressing testicular cancer, the five year survival rate for seminoma patients' was 100 percent (6).

The 5 year disease-free survival in patients received adjuvant radiotherapy to para-aortic chain or single agent carboplatin was 100 percent, which is consistent with the study conducted by *Oliver et al.* comparing adjuvant 1 cycle carboplatin versus radiotherapy showing relapse-free survival rates at 5 years of 94.7 and 96 percent, respectively (7).

The 5 year DFS and the 5-year loco-regional control in our study was 93% in arm of surveillance with complete cure of the relapse and 100% in both radiation and chemotherapy groups. In a study conducted by *Dieckmann et al.*, the use of one course of adjuvant carboplatin, surveillance and radiotherapy were compared to each other. The results showed a disease-specific survival of 100% irrespective of the post-operative approach. Crude relapse rates were 8.2, 2.4, 5.0, and 1.5% for surveillance, radiotherapy, 1 cycle carboplatin, and 2 cycles carboplatin, respectively, after a median follow up of 30 months. In this study, all recurrences were salvageable leading to a disease-specific survival rate of 100 percent, with no statistical difference in the incidences of relapses among the four treatment arms (log-rank, $p = 0.0573$) (8).

In this study, the proposed risk factors of local recurrence in stage I seminoma (namely, rete-testis invasion and tumor size > 4 cm) didn't show any adverse impact on local control for patients. In comparison to literature, this might be a little bit different. A risk-adapted adjuvant management was adopted by the *Swedish and Norwegian Testicular Cancer Group* based on their prospective trial involving almost 900 patients. The study population developed 69 relapses; with 29 relapses among patients who were managed by surveillance and 40 relapses in patients managed with adjuvant 1 cycle carboplatin. The invasion of the rete testis [*hazard ratio* (HR) 1.9, $p = 0.011$] and tumor diameter > 4 cm (HR 2.7, $p < 0.001$) were identified as risk factors for disease relapse. In patients without any of these factors, the relapse rate was 4.0% for patients in surveillance arm versus 2.2% in patients receiving adjuvant carboplatin. In patients with one or two risk factors, the relapse rate was 15.5% in patients managed by surveillance versus 9.3% in patients receiving adjuvant carboplatin (9).

In another systematic review including nineteen studies addressing prognostic factors for disease relapse in clinical stage I seminoma patients' managed by surveillance (10), rete testis invasion was identified as a significant factor for relapse in only 4 out of 13 studies, while tumor size was a significant factor for relapse in 10 out of 14 studies. The authors' conclusion was that size of tumor is the most important prognostic factor for disease relapse, but the authors failed to define a clear cutoff value for tumor size and that rete-testis invasion was a minor risk factor for disease recurrence.

However, the most recent version of NCCN guidelines still recommends for active surveillance as the preferred option of management for patients with clinical stage I seminoma, regardless tumor size or rete-testis invasion, given the equal survival of surveillance versus active treatment, potential long term treatment toxicities especially with the expected long term survival of the patients and high salvage rates of any recurrences, provided that patients will commit to the surveillance protocol (11).

This study also shows a change in our pattern of care with time from adjuvant radiation to para-aortic chain towards single agent carboplatin and active surveillance, given the change in the international guidelines.

Study limitations include the retrospective nature of the study with the inherent selection bias in this type of studies (reserving active treatment for fit and younger patients or those who cannot adhere to the follow up schedule), the heterogeneous groups of patients with imbalance between treatment arms and lack of QoL assessment with each treatment modality.

In summary, our study highlights and confirms the data stating that stage I seminoma can be treated by different adjuvant modalities (radiotherapy, carboplatin or active surveillance) with similar outcomes in terms of DFS, LRC and OS. Active surveillance remains an appealing treatment option given similar survival compared to active treatment and complete cure after salvage with chemotherapy in relapsing patients.

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Conflict of interest: The authors declare no potential conflict of interest.