Outcomes of Patients with Stage I Germ Cell Tumour; Adjuvant Chemotherapy vs Surveillance; A Single Institutional Experience

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ABSTRACT

Objective: To determine five-year survival and stratify risk factors for disease relapse in the clinical stage I germ cell tumour post orchiectomy.

Study Design: Retrospective longitudinal study.

Place and Duration of Study: Shaukat Khanum Memorial Cancer Hospital and Research Centre Lahore Pakistan, from 2008 to 2013.

Methodology: We analyzed overall survival and disease-free survival in patients with stage 1 Germ cell tumours who either received chemotherapy or were kept on active surveillance after higher orchiectomy. In addition, risk factor stratification for recurrence was determined using the clinical, radiological and histopathological parameters.

Results: Of 88 patients, 51 (58%) received chemotherapy, while 37 (42%) patients were kept on surveillance post orchiectomy for stage I germ cell tumours, including seminoma and non-seminoma histologies. Five-year overall survival and disease-free survivals were 99% and 92%, respectively, for all patients with stage 1 Germ cell tumours. Subgroup analysis showed that DFS was better in the adjuvant chemotherapy arm than the surveillance arm in both subtype histologies; however, five-year overall survival was comparable. Lymph vascular invasion and tumour size (T) was identified as risk factor for disease relapse.

Conclusion: This institutional report suggests that while identifying risk factors, active surveillance post orchiectomy can be an effective treatment option for clinical stage I germ cell tumours and is comparable with adjuvant chemotherapy. Two important factors determining survival in our study were Lymph vascular invasion and T staging.

Keywords: Chemotherapy, Germ cell tumour, Non-seminoma, Seminoma, Surveillance.

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INTRODUCTION

Testicular germ cell tumours (TGCT) are rare, account for 6% of all cancers and 1-2% of cancers in males worldwide, and usually affect young adult men. Histologically TGCT is divided into non-seminoma germ cell tumours (NSGCT) and seminomatous germ cell tumours (SGCT), comprising 56% and 44%, respectively. Most patients present at an early stage I, before the development of retroperitoneal lymphade-nopathy and distant metastasis.[1] Upfront radical orchiectomy followed by active surveillance is one of the standard options for clinical stage I disease, leading to a cure in around 70-85% of patients with TGCT.[2,3] Around 30% of clinical stage I patients harbour micrometastasis, which presents as a relapse 2-5 years after orchiectomy and can be successfully cured with chemotherapy.[4,5] Other options after orchiectomy include early intervention with retroperitoneal lymph node dissection (RPLND) or adjuvant chemotherapy. However, it can be overtreatment as it can cause unwanted side effects not limited to infertility, risk of secondary malignancy, erectile dysfunction, and organ dysfunction. In several studies, active surveillance has been advocated as the primary option for managing Stage I TGCT.[6,7]

This study aims to report the outcomes of stage 1 TGCT, comparing surveillance versus adjuvant platinum-based chemotherapy in the Pakistani population. We hypothesised that surveillance followed by salvage chemotherapy is equally effective as adjuvant chemotherapy and can be offered to the patients.

METHODOLOGY

We conducted a retrospective longitudinal study of all (n=88) post-orchidectomy patients with stage I TGCT, registered between 2008-2013 at Shaukat Khanum Memorial Cancer Hospital and Research Center, Lahore, (SKMCH&RC) Pakistan; and maintained regularly follow up. Institutional review board exemption was sought [EX-05-07-19-01]. The patients were identified from the cancer registry maintained by the hospital management information system.

Inclusion Criteria: Patients of age above 16 years with the clinical stage I disease, post orchiectomy, including

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seminoma and non-seminomatous on histology, were included in the study.

Exclusion Criteria: Patients with persistent elevation of tumour markers were excluded from the study.

Clinicopathological characteristics included age, site, tumour size, stage and histological subtype, vascular invasion, and type of adjuvant approach (radiotherapy or chemotherapy or surveillance). The post-operative staging was done by clinical examination, radiological imaging, and assessing tumour markers. Markers were monitored for normalisation. Histopathology and radiological studies were centralised at the hospital. Follow up duration was at least five years after the primary treatment for both seminoma and non-seminoma. Disease-free survival (DFS) was defined as relapse or death, whichever occurred first post orchiectomy. Overall survival (OS) was the time between diagnosis and death.

Statistical Package for Social Sciences (SPSS) version 20.0 was used for the data analysis. First, the clinicopathological factors of the patients with Stage I TGCT were compared using Chi-square and Fisher's exact tests according to the treatment options. Next, the survival analyses and curves were determined using the Kaplan–Meier method and compared with the log-rank test. Then, univariate analysis was used to evaluate the significance of clinicopathological indicators as prognostic factors. After that, multivariate analysis with the Cox proportional hazards model was also used to find the independent prognostic factors for both DFS and OS.

Patients were followed up every three months with history, clinical examination and tumour markers for the first year, three monthly for the second year and six-monthly for the next three years. In addition, chest x-ray and abdominopelvic CT scans were performed six-monthly for the first two years and 6-12 months for the next three years.

Patients in the chemotherapy arm received 1-2 cycles of single-agent Carboplatin with the area under the curve (AUC) of 7 in seminoma, while non-seminoma patients received 1-2 cycles of BEP (Bleomycin, Etoposide, Cisplatin) chemotherapy.

RESULTS

The mean age of patients was 37 ± 13 years (range 24-50). Classical seminoma was diagnosed in 55 (62.5%), and the remaining 33 (37.5%) were non-seminoma or mixed germ cell tumours, as shown in Table-I.

Table-I: Characteristics of study participants.

Characteristics	Categories	Total Patients (%)
Age	Mean ± SD	37 ± 13 years
Localization	Right	40 (45.5)
	Left	48 (54.5)
Histopathology	Seminoma	55 (62.5)
	Non Seminoma	33 (37.5)
	Mix Germ Cell Tumor	29 (33.0)
	Embryonial	2 (2.3)
	Yolk Cell	1 (1.1)
	Teratoma	1 (1.1)
Treatment Group	Chemotherapy	51 (58.0)
	Surveillance	37 (42.0)
Stage	IA	49 (55.7)
	IB	39 (44.3)
Lymphovascular Invasion	Negative	46 (52.3)
	Positive	42 (47.7)
pT Stage	T1	56 (63.6)
	T2	28 (31.8)
	T3	4 (4.5)

Lymph vascular invasion (LVI) was positive in 26 (47.3%) seminoma and 16 (48.5%) non-seminoma group patients, as shown in Table-II. Most of the patients fell in the T1 stage, comprising 56 (63.6%) patients, followed by T2 in 28 (31.8%) and T3 in 4 (4.5%) patients. As demonstrated in Table-II, chemotherapy was given to 34 (61.8%) seminoma patients and 17 (51.5%) non-seminoma or mixed germ cell tumour patients. Moreover, surveillance was opted for a total of 37 (42%) patients with 21 (38.2%) seminoma and 16 (48.5%) non-seminoma patients. Median follow up was at least five years for all patients. Chemotherapy was platinum-based in all cases (including BEP, EP, and single-agent carboplatin) in the chemotherapy arm. Log-rank testing was shown in Table-III for parameters including age, stage, LVI, treatment strategy, patho-logical stage and localisation. Survival curves were illustrated in graphic Figures-1 & 2.

DFS and OS were analysed for the all the study participants and subgroups, including the chemotherapy and surveillance arm. DFS and OS of the entire clinical-stage I germ cell tumour is 99% and 92%, respectively (Figure-1).

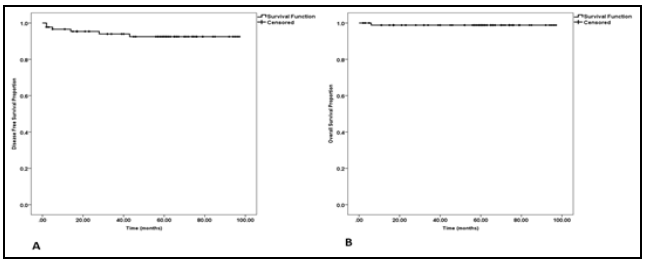

Figure-1: Five-year disease-free survival (A) and overall survival (B) for whole study population.

Among non-seminoma, 48.5% (16) patients were kept on surveillance, with five years of DFS 86 % and OS 96% observed. The relapse rate was 12.5% (2) among the surveillance group. The relapsed case was treated with salvage chemotherapy, leading to remission except for one death, as shown in Table-II.

important factor determining disease prognosis (*p*-value 0.05). Similarly, the T stage also affected 5 year-DFS; T1 had 100%, whereas T2 tumours had 92% (*p*-value: 0.001).

Tumours harbouring these characteristics were at high risk for disease relapse and metastasis, as

Table-II: Comparison of seminoma and non-seminomatous patients.

Variables	Categories	Seminomatous 55 (62.2%)	Non-Seminomatous 33 (37.8)	*p*-value
Age	Mean ± Standard Deviation	42 ± 14	32 ± 10	0.001
Histopathology	Seminoma	55 (100.0)	-	0.001
	Mix Germ Cell Tumor	-	29 (87.9)	
	Embryonal	-	2 (6.1)	
	Yolk Cell	-	1 (3.0)	
	Teratoma	-	1 (3.0)	
Stage	IA	35 (63.6)	14 (42.4)	0.07
	IB	20 (36.3)	19 (57.5)	
Lymph-vascular Invasion	Negative	29 (52.7)	17 (51.5)	0.91
	Positive	26 (47.3)	16 (48.5)	
Disease Status	Remission	51 (93.0)	31 (93.9)	1.00
	Relapse on Chemotherapy	1 (2.9)	-	
	Relapse on Surveillance	3(14)	2(12.5)	
Treatment Strategy	Chemotherapy	34 (61.8)	17 (51.5)	0.40
	Surveillance	21 (38.2)	16 (48.5)	
Patient Status	Death	-	1 (3.0)	0.37
	Alive	55 (100.0)	32 (97.0)	
pT Stage	T1	36 (65.5)	20 (60.6)	0.18
	T2	15 (27.3)	13 (39.4)	
	T3	4 (7.3)	-	
Localization	Right	21 (38.2)	27 (81.8)	0.001
	Left	34 (61.8)	6 (18.2)	

While among the seminoma group, 38.2% (21) were kept on surveillance post orchiectomy, leading to a five-year DFS of 86% and OS of 100%. The disease relapse rate was 14% (3). All relapsed cases were successfully treated with platinum-based chemotherapy and achieved remission (Figure-2).

Among the non-seminoma group, 51.5% (17) were treated with one cycle of platinum-based adjuvant chemotherapy following orchidectomy based on high-risk features including LVI and Tumour size. No relapse case or death was observed, concluding with DFS and OS of 100%. While among the seminoma group, 61.8% (35) patients were given adjuvant chemotherapy. The relapse rate was 2.9% (1), and calculated DFS and OS were 95% and 100%, respec-tively. This group reported no death as the relapsed case was successfully treated with salvage therapy.

Lymphovascular invasion, tumour size and T stage are essential factors in our study defining disease-free and overall survival. As shown in Table-III, 5-year DFS in LVI positive group was 87% and in the negative group was 97%, which shows that LVI is an

evidenced by a significant *p*-value. Keeping in view of these findings, surveillance versus adjuvant chemotherapy decisions can be ascertained in a multidisciplinary fashion.

DISCUSSION

More than 75% of germ cell tumours present as clinical stage I disease.[8] Active surveillance post orchiectomy, RPLND or adjuvant chemotherapy with platinum-based chemotherapy remains the standard of care for clinical stage I disease.[9,10] All three options carry excellent survival outcomes,[11] however, which option to follow, remains a controversial.[12] Post orchiectomy active surveillance remains the safe and effective option, as demonstrated in previous literature.[13] Due to the lack of active surveillance outcome data at the local facility, we carried out this study to prioritise the treatment option.

In this study, 48.5 % (16) patients with NSGCT were kept on surveillance post orchiectomy; the recurrence rate was 6.1%, with only two patients relapsed in the first year of follow up. Unfortunately, one patient

who refused chemotherapy despite being LVI positive could not survive, while the other patient treated successfully with platinum-based chemo-therapy. Five-year OS was 96% for the active survei-llance arm compared to adjuvant chemotherapy. Our study favours active surveillance as a safe and effective treatment option in clinical stage I NSGCT in limited-resource countries.

Table-III: Five-year disease-free survival and log-rank test with reference to patient and tumor characteristics.

Factors	Categories	5-Year Disease Free Survival	Log Rank Test
Age	≤30	91	0.94
	>30	93	
Stage	IA	100	0.001
	IB	84	
Lympho-vascular Invasion	Negative	97	0.05
	Positive	87	
Treatment Strategy	NS + C	100	0.21
	NS + S	86	
	S + C	95	
	S + S	86	
pT stage	T1	100	0.001
	T2	92	
	T3	NA	
Localization	Right	95	0.25
	Left	89	

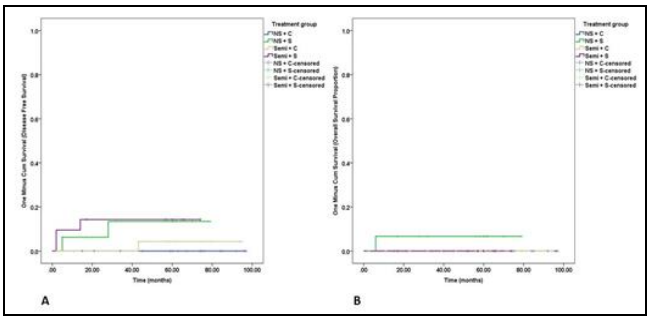

Figure-2: Five-year disease-free survival (A) and overall survival (B) with different treatment options. (NS + C: non-seminoma on chemotherapy; NS + S: non-seminoma on surveillance; Semi + C: seminoma on chemotherapy; Semi + S: seminoma on surveillance).

Our results show the same trend as previously demonstrated in different studies. For example, Daugaard *et al,* studied 1226 patients with CSI NSGCT and reported a DFS of 99.3% on surveillance.[4] A similar study by Kollmannsberger *et al,* reported 100% disease-specific survival upon treating relapsed patients on surveillance.[6]

Clinical stage I seminoma carries outstanding outcomes despite the treatment options for post orchiectomy. RPLND, adjuvant chemotherapy and active surveillance have similar results if an adaptive risk approach is used.[14] In our study, 38.2% (21) patients were kept on surveillance, while 61.8% (35) patients were treated with adjuvant chemotherapy. The relapse rate was 7% (4) in the surveillance arm. These four patients relapsed within a year of treatment and were successfully rescued with chemotherapy. No death was reported in either arm, giving OS 100 % in both arms. Adjuvant chemotherapy significantly reduced the DFS but had no significant effect on OS. Petreli *et al,* concluded after studying around twelve thousand patients with CS1 STGCT that adjuvant chemotherapy significantly reduced relapse rates but did not correspond to the five-year OS.[15]

We also looked into the factors determining survival in germ cell tumours. LVI, tumour size and T staging turned out to be important factors determining the survival. The adaptive risk approach is the key to selecting treatment options in clinical stage I germ cell tumour after orchiectomy.[16,17] Despite modern modalities of radiological diagnosis, 30% of clinical stage I germ cell tumours harbour micrometastasis at initial diagnosis. Therefore, active surveillance should have opted carefully for the selected patients. The high-risk factor for disease recurrence includes LVI and tumour size, as depicted in our log-rank tests and supported by present literature.[18] The high-risk tumour has a recurrence probability of 30% compared to 12% for low-risk disease. Most patients with LVI negative and T1 are candidates for observation. Less consensus is sought for the patient with pathological stage T2-T4. A minority of patients with pathological T2 tumours may choose surveillance, but they should understand the risk of recurrence.

Platinum-based adjuvant chemotherapy is an effective and reasonable treatment option for patients with clinical stage I germ cell tumours for long term disease control.[19] However, haematological toxicity, febrile neutropenia and kidney injury are short term side effects of chemotherapy. Long term sequelae include infertility, hypogonadism, ototoxicity, pulmonary fibrosis, cardiovascular complications and secondary malignancy, particularly acute leukaemia.[20] Therefore, patient selection for adjuvant chemotherapy is a critical and shared decision between the patient and treating physician while elaborating all aspects of therapy. A low threshold for adjuvant chemotherapy should have opted for patients who are considered unreliable to follow strict surveillance protocol.

LIMITATIONS OF STUDY

There were certain limitations to the study. First, the number of patients has limited as well as this study is a

cross-sectional descriptive analysis. Second, two groups were not appropriately matched. Nevertheless, we intend to continue this study with a large data set and a longer follow up of 10 years to prove or disprove a significant difference in the outcome of the two options for stage 1 Germ cell tumours.

CONCLUSION

Both treatment options, including surveillance or adjuvant chemotherapy post orchiectomy, are equally good in this institutional experience. Patients can be safely observed without high-risk features (LVI and more than T1 stage) instead of opting for adjuvant chemotherapy or RPLND. With an adaptive risk approach, surveillance is a cost-effective measure given resource limitations in our country, provided patients are compliant in terms of strict follow-up. Adjuvant chemotherapy may have better outcomes in early-stage germ cell tumours if a large group of patients are studied. We intend to continue this study with a large number of patients to understand the treatment strategy better.

Conflict of Interest: None.

Authors' Contribution

SAK: Research idea, manuscript writing, MA: Assisted in study design, analysis plan, MRH: Literature search, AW:, IR: Data collection, SY: Manuscript writing, NS: Proof reading, RMS: Concept, study design, MAB: Study design, data analysis.

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