Factors Determining Survival of Patients with Germ Cell Tumor (Single Institutional Experience)

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ABSTRACT

Objective: To determine the 5-year overall survival of all the germ cell tumour stages and to identify prognostic factors affecting advanced and metastatic disease outcomes in our institution.

Study Design: Cross-sectional analytical study.

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

Methodology: We analyzed the overall survival (OS) of the whole study population and sub-analyzed metastatic disease according to the International germ cell cancer group (IGCCCG), and their overall survival was calculated. Clinical, radiological, biochemical, and histopathological evaluation was used to identify risk factors determining disease outcome.

Results: After analysing 186 male patients with germ cell tumours, 5-year overall survival for stages I, II, and III was 99%, 72%, and 62%, respectively. IGCCCG subgroup analysis showed that five-year overall survival for seminoma was slighter worse than non-seminoma. Five-year overall survival for reasonable risk and intermediate-risk seminoma was 68% and 46%, respectively. For non-seminoma, good, intermediate, and poor-risk categories carried five-year OS as 94%, 61%, and 49%, respectively. The presence of liver/brain metastasis, size of residual disease, primary mediastinal tumour, and tumor marker failure to decline post-chemotherapy were poor prognostic factors for metastatic disease.

Conclusion: While identifying stages in germ cell tumours and classifying metastatic patients according to IGCCCG, individual factors including the location of the primary tumor, brain/ liver metastasis, a failure of tumor markers to decline less than 20% after the first chemotherapy cycle and size of residual disease are considered poor prognostic signs.

Keywords: Chemotherapy, Germ cell tumour, International germ cell cancer collaborative group (IGCCCG), Risk factors.

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INTRODUCTION

Testicular cancer is the most common malignancy affecting the young male population worldwide.[1] Almost 90% of testicular cancers are testicular germ cell tumours (TGCT), which can be histologically divided into seminomatous germ cell tumours (SGCT) and non seminomatous germ cells tumours (NSGCT). Further histological classification of NSGCT includes either mixed germ cell tumour (MGCT) or pure embryonal, yolk sac, choriocarcinoma, or teratoma. TNM/S classifies the stage whereby stage I disease is confined to the testis; stage II is limited to retroperitoneal lymph nodes with tumour markers in a good prognosis range. In contrast, stage III includes metastasis beyond retroperitoneal/extranodal in location or any patient with tumour markers in intermediate or poor prognosis range.[2, 3]

In conjugation with International germ cell cancer collaborative classification (IGCCCG), we addressed individualized risk factors determining the survival outcome in advanced and metastatic germ cell tumours focusing primarily on risk stratification and response to chemotherapy in patients treated at Shaukat Khanum Memorial Cancer Hospital, Lahore, Pakistan.

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METHODOLOGY

In this cross-sectional analytical study, 186 patients having EOC were identified between 2008 and 2013 at Shaukat Khanum Memorial Cancer & Research Center, Lahore, Pakistan. We gathered data from the cancer registry of our hospital after acquiring Institutional Review Board approval [EX-05-07-19-01].

Inclusion Criteria: All the male patients above 18 years of age having clinical stages I, II, and III, harbouring seminoma and non-seminomatous histology were included in the study.

Exclusion Criteria: None.

We studied all the patients who presented during the mentioned duration and maintained active follow up. The patients were identified from the cancer registry maintained by the hospital management infor-

mation system. Clinico-pathological characteristics included age, primary site, tumor size, stage, histological subtype, presence or absence of metastatic disease, and chemotherapy regimen were identified. The staging was done with clinical examination, CT scan and levels of tumour markers BHCG, AFP and LDH. Histopathology and radiological studies were centralized at the hospital. Patients with metastatic disease were subclassified according to IGCCCG grouping into risk categories.

Stage-I disease patients received one cycle of chemotherapy post-surgery or were kept on surveillance. Metastatic good-risk patients were treated with three cycles of Bleomycin, Etoposide, and Cisplatin (BEP) or four cycles of Etoposide and Cisplatin (EP). At the same time, intermediate and poor-risk tumours are treated with four cycles of BEP or Etoposide, Ifosfamide, and Cisplatin (VIP) or Paclitaxel, Ifosfamide, and Cisplatin (TIP). The follow-up duration was at least five years after the primary treatment for both seminoma and non-seminoma. Recurrent or relapsed cases were treated either with TIP, Vinblastine, Ifosfamide, Cisplatin (VeIP), Gemcitabine, or Oxaliplatin (Gem Ox). 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. Chest x-ray and abdomino-pelvic CT scan were performed six-monthly for the first two years and 6-12 months for the next three years. 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. According to the treatment options, the clinic-pathological factors of the patients with stage-I TGCT were compared using chi-square and Fisher exact tests. The survival analyses and curves were determined using the Kaplan- Meier method and compared with the log-rank test. Univariate analysis was used to evaluate the significance of Clinico-pathological indicators as prognostic factors. After that, multivariate analysis with the cox proportional hazards model was also used to find the independent prognostic factors for DFS and OS.

RESULTS

A of total 186 patients were included in the study. The mean age was 36 ± 12 years (Table-I). Seminoma constituted 90 patients (48.4%) while non-seminoma included 96 (51.6%) cases. Among the non-seminoma population, mixed germ cell histology was a pure embryonal, pure yolk sac and teratoma patients.

Table-I: Descriptive Statistics.

Parameters	Categories	n (%)
Age	Mean ± SD	36 ± 12
Site	Left	100 (53.8)
	Right	86 (46.2)
Histopathology	Seminoma	90 (48.4)
	Non-seminoma	96 (51.6)
	Embryonal	2 (1.1)
	Mix germ	92 (49.5)
	Teratoma	1 (0.5)
	Yolk sac	1 (0.5)
ECOG	0	28 (15.1)
	1	125 (67.2)
	2	27 (14.5)
	3	3 (1.6)
	4	3 (1.6)
Stage	I	88 (47.3)
	II	11 (5.9)
	IIIA	16 (8.6)
	IIIB	27 (14.5)
	IIIC	44 (23.7)
Brain Mets	No	178 (95.7
	Yes	8 (4.3)
Liver Mets	No	159 (85.5)
	Yes	27 (14.5)
Non-Regional Nodal Spread	No	162 (87.1)
	Yes	24 (12.9)
RP-LN-Size	< 5cm	125 (67.2)
	≥ 5cm	61 (32.8)
Primary Mediastinal	No	160 (86.0)
	Yes	26 (14.0)

Eastern cooperative oncology group performance status (ECOG-PS) was concluded as ECOG-PS 0 for 28 (15.1%) cases, ECOG-PS 1 for 125 (67.2%) cases, ECOG-PS 2 for 27 (14.5%) patients, ECOG-PS 3 for 3 (1.6%) cases and ECOG-PS 4 for 3 (1.6%) patients. Patient turnover according to the stage was stage-I 88 (47.3%), stage-II 11 (5.9%), stage-IIIA 16 (8.6%), stage-IIIB 27 (14.5%), and stage IIIC 44 (23.7%) patients. Brain metastasis was present in 8 (4.3%) patients. Liver metastasis were identified in 27 (14.5%) patients. Non-regional metastasis was present in 24 (12.9%) patients while absent in 162 (87.1%) patients. Primary mediastinal tumor was present in 26 (14.0%) patients. Metastatic (stage-II and III), seminoma, and non-seminoma were classified according to IGCCCG. Good and intermediate-risk seminoma were calculated as 16 (45.7%) and 19 (54.3%) patients, while non-seminoma was found to be good, intermediate, and poor-risk as 19 (30.2%), 18 (28.6%), and 26 (41.3%) patients respectively. Five-year overall survival (OS) for the whole study population was shown in Figure-1a, specifying 99%, 72%, and 62% for stages I, II, and III, respectively.

Table-II highlighted the risk factor IGCCCG, based on good, intermediate, and poor-risk categories and individual risk factors that significantly impact overall survival for metastatic disease comprising stage-II and stage III.

Table-II: Overall survival in advance and metastatic disease.

Factors	Categories	5-year overall survival	*p*-value
Seminoma	Good	68%	0.14
	Intermediate	46%	
	Poor	-	
Non-Seminoma	Good	94%	0.01
	Intermediate	61%	
	Poor	49%	
Seminoma (Residual Disease)	≤3cm	82%	0.001
	>3cm	15%	
Non-Seminoma (Residual Disease)	≤1cm	86%	0.001
	>1cm	39%	
Primary Mediastinal	No	71%	0.001
	Yes	37%	
Brain Mets	No	67%	0.01
	Yes	14%	
Liver Mets	No	69%	0.05
	Yes	45%	
Fall in Markers After the First Chemotherapy	No	28%	0.001
	Yes	76%	

These factors include IGCCCG based good, intermediate, and poor-risk disease affecting 5-year overall survival. Moreover, the primary tumor location, particularly mediastinal and brain/liver metastasis, falls in markers after the first cycle of chemotherapy and size-specific residual disease. Good and intermediate-risk seminoma five-year overall survival comprises 68% and 46% (Figure-1b). For non-seminoma, good, intermediate, and poor-risk disease, five-year OS was 94%, 61%, and 49%, respectively (Figure-1b).

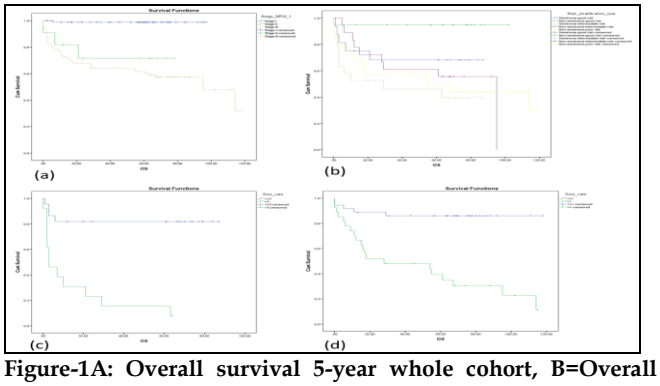

Figure-1A: Overall survival 5-year whole cohort, B=Overall survival of metastatic disease according to IGCCCG risk, C= Five-year overall survival of the residual disease in seminoma, D=Five-year overall survival of the residual disease in non-seminoma.

The presence of residual disease post-therapy substantially affected five-year overall survival and the risk of recurrence in the future. Our study demonstrated the impact of residual disease on OS, as shown in Figures-1C & 1D. For seminoma, residual disease <3cm had a 5-year OS of 82% versus residual disease having >3cm of residual disease, as shown in Table-III.

Table-III: Overall survival of the study population.

Factor	Categories	5-year overall survival	*p*-value
Stage			0.001
	I	99%	
	II	72%	
	III	62%	

For the non-seminoma group, 5-year OS for residual disease less than 1 cm was 86% versus 39% for residual size having more than 1 cm size as shown in Figures-1c and 1d. The primary location of the tumour carries a significant impact on behaviour and disease clinical response. The primary mediastinal tumor generally carries poor outcomes. As shown in Figure-2A, primary mediastinal tumours had a 5-year OS of 37% vs 71% for non-mediastinal tumours.

The impact of brain metastasis, liver metastasis, and fall in markers after the first cycle of chemotherapy on five-year survival is shown in Figures-2A-2D. Brain metastasis strongly impacts disease behaviour, survival, functional status, and quality of life. Functional decline and neurological complications are well known for brain metastasis. The five-year OS of patients with brain metastasis was significantly lower (14%) than non-brain metastatic disease. In our study, for patients with liver metastasis, 5-year OS was 45% vs 69% with non-liver metastatic disease, respectively. Finally, a fall in markers more than twenty percent after the first cycle of chemotherapy was associated with better 5-year survival and was 76% (Figure-2D).

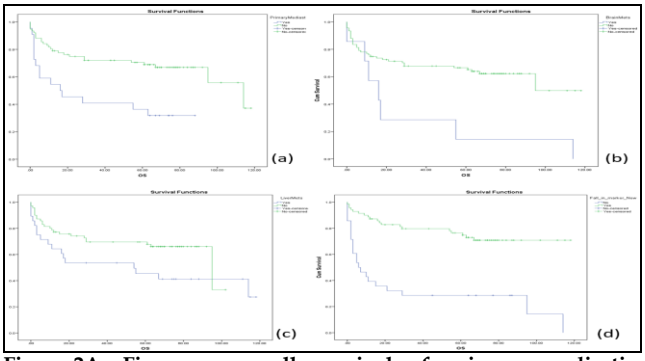

Figure-2A: Five-year overall survival of primary mediastinal versus non-mediastinal, B=Five-year overall survival of metastatic brain disease, C=Five-year overall survival of the metastatic liver disease, D=Five-year overall survival in relation to significant.

DISCUSSION

Our results demonstrated similar survival trends in stage, primary site, presence or absence of liver/ brain disease and residual disease after chemotherapy. In addition, a fall in tumour markers by more than 20% after the first chemotherapy cycle was associated with better survival.

Germ cell tumours are a few solid organ tumours potentially curable even in advanced or metastatic settings reaching up to 80% cure rate.[3,4] Different models have been proposed, considering risk stratification for advanced and metastatic germ cell tumours. Until recently, international germ cell cancer collaborative classification (IGCCCG) has addressed these questions by largely classifying the tumour stages with prognostications considering the potential risk factors. Based on tumour histology, size, location, distant metastasis (pulmonary vs. non-pulmonary) serum tumour markers, IGCCCG has classified seminomas into Good and intermediate-risk, while non-seminomas are classified into good, intermediate, and poor-risk categories. Good-risk tumours are treated with three cycles of Bleomycin, Etoposide, And Cisplatin (BEP) or four cycles of Etoposide and Cisplatin (EP). In contrast, intermediate to poor-risk tumours are treated with four cycles of BEP or Etoposide, Ifosfamide and Cisplatin (VIP) or Paclitaxel, Ifosfamide, Cisplatin (TIP).[5] Five-year overall survival in good, intermediate, and poor-risk categories is 91%, 79%, and 48%, respectively, from reported pooled data.[6]

The outcome of patients with testicular germ cell tumours is variable according to the stage, tumour histology, response to chemotherapy in the form of fall in tumour marker, location of nodal metastasis, and organ involvement.[7] For advanced and metastatic disease, IGCCCG risk stratification has led to understanding the outcome.[7] We have endeavoured to identify not only to classify metastatic germ cell cases according to IGCCCG but also to identify individual factors for risk assessment.

The stage is an independent risk factor for germ cell tumours affecting the survival rate. Germ cell tumour is divided according to histology and extent of the disease by TNM staging system.[8] The approximate stage-wise distribution for stages I, II, and III WAS 68%, 20%, and 12%, respectively. Our study has demonstrated the five-year survival of stages I, II, and III: 99%, 72%, and 62%, respectively. Our results were compatible with international pooled data for stage-wise outcomes.

Primary mediastinal germ cell tumours are a type of extragonadal germ cell tumour with the worst outcomes in all germ cell tumour subtypes. These tumours are further divided into seminoma or non-seminoma mediastinal germ cell tumour, with the latter carrying inferior outcomes with treatment.[10] In our paper five-year, OS for the primary mediastinal tumour was only 37% compared to the non-mediastinal germ cell tumour, 71%.

Non-pulmonary metastasis, particularly liver and brain metastasis, is a strong risk factor in survival outcomes in advanced germ cell tumours. Hence, de novo brain metastasis or occurrence during therapy concerns early detection and therapy.[11] Only 1% of patients with germ cell tumor and 10% with advanced metastatic disease presented with brain metastasis carrying poor long-term outcomes.[12] High-dose treatment is mandatory for treating such patients for disease control and improving the quality of life. The second most common metastasis site in germ cell tumours is the liver accounting for 15-27% in advanced-stage germ cell tumours carrying inferior outcomes among most staging systems. Post chemotherapy, resection of the residual lesion provides data for a better outcome.[13] The advanced disease with liver metastasis in our study population carried a 5-year OS of only 45%. Our study data was consistent with international data defining survival outcomes In IGCCCG poor-risk patients with liver metastasis.[7]

Response to chemotherapy is assessed radiologically, assessing tumour size reduction and biochemically by fall in the tumour makers, particularly for non-seminoma variants. Tumour markers decline is also helpful in other malignancies, including prostate cancer, in which the rate of decline for prostate-specific antigen is a measuring tool. Among germ cell tumours, the rate of decline in tumour markers reflects the response to therapy and chemo-sensitivity of disease.[14,15] We have observed a survival rate of 28% only in patients who failed to demonstrate a fall in markers after the first chemotherapy cycle.

After primary therapy for advanced germ cell tumours, the residual disease is predictive and prognostically significant. Post-Cisplatin-based chemo-therapy for metastatic disease, 15-20% of patients have residual disease constituting 40-50% mature teratoma and 15-20% viable disease.[16,17] National comprehensive cancer centre (NCCN) and European society of medical oncology conference consensus recommend retroperitoneal lymph node dissection or radiotherapy for

seminomatous residual disease more than 3 cm and non-seminomatous residual disease more than 1 cm 4. Histology of residual disease is an important factor in the disease outcome as histology varies between teratoma and viable disease. Residual teratoma carried 70-80% chances of long-term disease-free survival than viable disease.[18] In our study outcome, patients with a residual disease carried poor outcomes. Patients with seminoma with more than 3 cm residual disease carry a 5-year OS of only 15%. While non-seminoma patients with the residual disease, more than 1 cm carried a 5-year OS of 39% vs 86% in patients with less than 1 cm of residual disease. Oncologists, radiation experts, and urologists should consider this residual disease an important future perspective for overall disease control.

CONCLUSION

While identifying stages in germ cell tumours and classifying metastatic patients according to IGCCCG, individual factors including the location of the primary tumor, brain/liver metastasis, a failure of tumor markers to decline less than 20% after the first chemotherapy cycle and size of residual disease are considered poor prognostic signs.

Authors' Contribution

SAK: Research idea and writing, MA: Co-author, assisted in study design, analysis plan, SAMH:, UA: Data collection, MRH: Literature search, JI: Manuscript writing, UKA: Proof reading, NS:, RMS: Concept and study design.

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