ORIGINAL ARTICLE

Influence of Prognostic Group Classification of Advanced Male Germ Cell Tumor on Treatment Outcomes

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Abstract

Background: Male germ cell tumor is a rare disease, associated with high rates of cure, including in the advanced setting. This disease mostly affects young males aged 15-34 years. The rising incidence trends of germ cell tumors in the last two decades have defined a new priority area of oncology.

Objective: To investigate the influence of prognostic group classification and histology on treatment outcomes in men treated in a single institution in Pakistan.

Methods: We developed an observational study on fifty male patients diagnosed with advanced germ cell cancer completing first-line treatment, between 2011-2014. Patients with a follow-up time of at least 5 years post-treatment were included. Patients were classified into good, intermediate, and poor prognostic groups, according to the International Germ Cell Cancer Collaborative Group classification (IGCCCG). The outcomes of all three prognostic groups were measured including response to first-line treatment according to Memorial Sloan-Kettering Cancer Center criteria and five years OS. Survival rates were calculated using Kaplan and Meier method. The level of significance was set at $P < 0.05$.

Results: Overall 50 patients were included in the study. The mean age of patients was 30.6 years + 9.49 years. The most common primary site of involvement was the right testicle *i.e.* 56.0%. Complete responses (CR) were observed in 23 (46.0%) patients. The patients classified into the good prognostic group (n=29) had significantly superior (p=0.002) five years OS (86.2%, n= 25) than intermediate and poor groups. Additionally, CR was higher for seminoma-type cancer *i.e.* 12 (63.15%) while it was limited to 11(35.48%) in non-seminoma; however, the inferior response rate in NSGCT did not translate into statistical significance in 5 years OS.

Conclusion: The IGCCCG prognostic grouping system is an effective tool for predicting treatment outcomes in terms of 5-year overall survival in our local population based in a low-middle income setting.

Keywords: *Prognostic group, Histology, Overall survival, complete response.*

INTRODUCTION

Germ cell tumors (GCTs) account for 1% of all male cancers but are the most common cancer in young males. GCT is also considered the most curable solid cancer with a cure rate of 80% even in the advanced disease stage [1, 2]. Although GCT is rare cancer, and with commonly a significant cure rate, it mostly affects young males aged between 15-34 years and its rising incidence in the past couple of decades defines an area of health priority [3]. Incidence rates of GCTs vary across different geographical regions for reasons not completely understood. The disease has a low age-standardized incidence rate (ASR) in Africa and most parts of Asia while the ASR is higher in Scandinavian countries [4].

Patients with GCTs can be prognostically classified into good-risk, intermediate, and poor-risk groups based on the International Germ Cell Cancer Collaborative Group (IGCCCG) classification of advanced male germ cell tumors [5]. Treatment protocols and outcomes depend on the prognostic group classification of the tumor. The 5-year survival according to IGCCCG prognostic group classification for good, intermediate, and poor prognostic groups are 91%, 79%, and 48%, respectively [6].

Chemotherapy regimens offered to patients with different prognostic group classifications are similar in developed and developing nations because the mainstay for the treatment of GCT is based on essential chemotherapies. The most dramatic reduction in mortality occurred in the 1970s with the introduction of cisplatin-based chemotherapy [7, 8]. However, most studies comparing the epidemiology and treatment outcomes in different risk groups come from high-income countries. Data are limited from low- and middle-income countries, especially from Asian countries. Data insufficiency was the driving force for the present study.

The objective of our study was to validate the prognostic role of the IGCCCG classification on treatment outcomes, five-year overall survival (OS), and response to first-line

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treatment in a retrospective cohort of patients based in an Asian low-middle income setting.

MATERIALS AND METHODS

We developed an observational, retrospective study conducted at the Institute of Nuclear Medicine and Oncology (INMOL) in Lahore, Pakistan. The study population included all consecutive patients diagnosed with advanced male germ cell tumors who had presented to INMOL for treatment from January 2011 to September 2014. Nonprobability consecutive sampling was done. Patients with advanced male germ cell tumors between 18 to 70 years of age and with proper follow-up records from the date of diagnosis up to the completion of 5 years post-treatment were included. Patients were classified into good, intermediate, and poor prognostic groups according to IGCCCG criteria.

Exclusion criteria were: histopathology other than germ cell tumor, and patients with incomplete first-line treatment due to any cause. Patients who had already received any chemotherapy/radiation or patients with multiple primary tumors.

Case records of patients with advanced male germ cell tumors were reviewed including histopathology, pre, and post-treatment imaging scans, blood reports, and the record of follow-up visits, the date of the last contact, and the date of death. Data collection included age, histology, disease presentation, primary site, and presence and location of metastatic sites. Additionally, we collected data on the serum levels of alpha-fetoprotein (AFP), beta-human chorionic gonadotropin (HCG), and lactate dehydrogenase (LDH) after orchiectomy, before the start of the first-line treatment and after completion of the first-line treatment. Patients were divided into two groups according to the histology of cancer, *i.e.* Non-seminoma and seminoma, and then further categorized into good, intermediate, and poor prognosis groups as per IGCCC criteria.

Treatment Protocol

After the radical inguinal orchiectomy, patients in the good prognostic group seminoma stage IIC and III either received three cycles of BEP (Bleomycin, Etoposide, Cisplatin) or four cycles of Etoposide, Cisplatin (EP); when in the Intermediate prognostic group seminoma stage IIC and III, they received four cycles of BEP and patients with non-seminomatous germ cell tumor (NSGCT) stage IS with good prognostic group received either three cycles of BEP or four cycles of EP; patients with intermediate or poor prognostic group received four cycles of BEP, stage II and III patients with good prognostic group received three cycles of BEP and with intermediate or poor prognostic group received four cycles of BEP. The treatment protocols were based on institutional practice and mirrored international guidelines. The decision of opting out of Bleomycin-based regimens was taken based on patients' spirometry-Pulmonary Function Test (PFT) results, based on the potential lung toxicity of this drug, according to the international guideline recommendation. All patients with complete response (CR) were kept on follow-up only; those patients with the incomplete response (IR) were offered other available treatments.

Statistical Analysis

Qualitative variables were measured in frequencies and percentages *e.g.* site, stage and treatment outcomes. Quantitative variables were described as mean and standard deviation *e.g.* age and survival outcomes.

Response to initial first-line treatment was evaluated following the standard Memorial Sloan Kettering Cancer Center (MSKCC) response criteria. The response was categorized as either a complete response (CR) or an incomplete response (IR). CR to chemotherapy alone was defined as the complete disappearance of all clinical, radiographic, and biochemical findings of testicular cancer after first-line treatment. All responses less than CR were considered IR.

The outcome measures included the response to first-line treatment and survival time. Survival rates were calculated using the method of Kaplan and Meier. The overall survival (OS) was measured from the date of initial diagnosis of the disease to the last follow-up or death from any cause and compared using a log-rank test. The level of significance was set at $P < 0.05$ and data analysis was performed on SPSS version 20.

RESULTS

Disease Characteristics

A total of 71 patients with histopathological diagnosis of testicular germ cell tumor presented to INMOL between January 2011 to September 2014: 50 out of them were selected for the study according to inclusion criteria, having complete medical records for data collection. We excluded 21 patients because we could not access information on the full treatment plan and delivery and for inadequate follow-up. The mean age of patients was 30.6 years + 9.49 (range, 18-65 years). The major primary site of involvement was the right testicle in 28 (56.0%) followed by the left testicle in 16 (32.0%) and retroperitoneal in 6 (12.0%) patients (**Table 1**).

Table 1: Demographics of the patient population.

Characteristic	Frequency	Percent
Presenting complaints		
Abdominal mass	2	4
Testicular mass	12	24
Testicular swelling	30	60
Abdominal pain	4	8
Testicular pain	2	4
Primary Site		
Right testicle	28	56.0
Left testicle	16	32.0
Retroperitoneal	6	12.0

Characteristic	Frequency	Percent
Histology		
Embryonal carcinoma	3	6.0
Immature teratoma	4	8.0
Mixed germ cell	20	40.0
Seminoma	19	38.0
Yolk sac	4	8.0
Stage		
IS	3	6.0
IIB	5	10.0
IIC	9	18.0
IIIA	12	24.0
IIIB	13	26.0
IIIC	08	16.0
Prognostic Group		
Good	29	58.0
Intermediate	13	26.0
Poor	8	16.0

A total of 29 (58%) patients were classified in the good prognostic group 13 (26%) in the intermediate and 8 (16%) patients were classified in the poor prognostic group (**Table 1**).

Treatment Outcomes

Response to Treatment

Out of the total of 50 patients, CR was observed in 23 (46.0%) patients, while 27 (54.0%) had incomplete treatment responses (**Table 2**). Twenty-one (n=21/29) patients achieved CR in the good prognostic group (72.4%). In the intermediate group, and the poor risk group, only 1 patient in each group had CR, 7.7% (n=1/13) and 12.5% in the poor prognostic group (n= 1/8), respectively.

Patients were also studied according to the histology: Seminoma and non-seminoma (NSGCT). A total number of 19 (38.0%) patients had seminoma and 31 (62.0%) had NSGCT.

Table 2: Overall treatment response according to prognostic group classification and Histopathology.

Prognostic group	Incomplete response n (%)	Complete Response n(%)
Overall(50)	27(54.0)	23(46.0)
Good (29)	8(27.6)	21(72.4)
Intermediate (13)	12(92.3)	1(7.7)
Poor (8)	7(87.5)	1(12.5)
Response w.r.t Histopathology		
Seminoma (n=19)	7 (36.8)	12 (63.15)
NSGCT(n=31)	20 (64.5)	11 (35.48)

Table 3: Five-year Overall survival of advanced male germ cell tumors.

Prognostic Group Classification	Total Number of patients (n)	Number of Deaths n (%)	5 year OS n (%)	Log Rank (Mantel-Cox) P value
Good	29	4(13.8)	25(86.2)	0.002
Intermediate	13	4(30.8)	9(69.2)	
Poor	8	5(62.5)	3(37.5)	
Overall	50	13(26.0)	37(74.0)	-
Histopathology				
Seminoma	19	4(21.1)	15(78.9)	0.540
Non-seminoma	31	9(29.0)	22(71.0)	
Overall	50	13(26.0)	37(74.0)	-

A complete response to first-line treatment was higher in seminoma patients *i.e.* 12 (63.15%) while it was limited to 11(35.48%) in NSGCT (**Table 2**). Interestingly, such a difference was not reflected in five-year overall survival (P= 0.540), (**Table 3**).

Survival Analysis

Patients classified into a good prognostic group (n=29) had a 5-year OS of 86.2% (n= 25) while intermediate and poor prognostic groups had a 5-year OS of 69.25% (n=9) and 37.5% (n= 3) respectively (**Table 3, Fig. 1**).

A statistically significant difference (P = 0.002) existed in the five-year overall survival of the patients in good, intermediate, and poor prognostic groups (**Table 3, Fig. 1**).

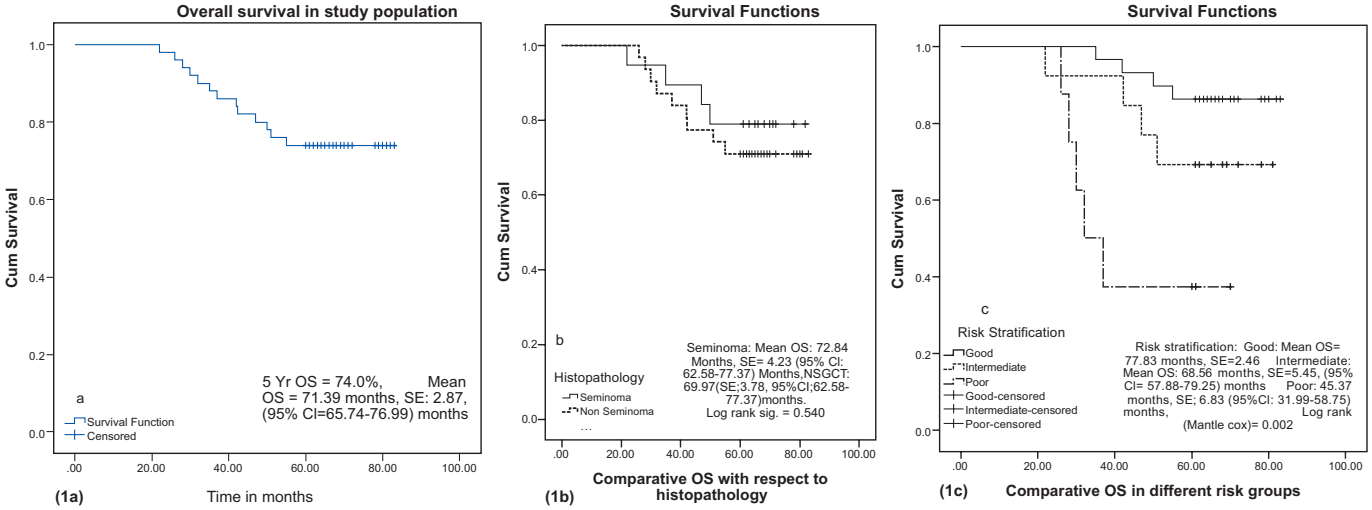

Fig. (1): (a) Overall survival of advanced male germ cell tumors, **(b)** Overall survival of germ cell tumor for Histopathology, **(c)** Overall survival of germ cell tumor concerning risk stratification.

When we compared the 5-year overall survival rates of Seminoma and NSGCT, there was no significant difference between the two groups P= 0.540 (**Table 3, Fig. 1**).

The mean OS was 71.36 (SE; 2.87, 95%CI = 65.74-76.99) months (**Fig. 1a**). Mean OS concerning histopathology and prognostic group classification were also determined to find the difference of mean in OS was calculated (**Fig. 1b-c**).

Mean OS was not affected by histopathology *i.e.* mean OS in seminoma *vs.* NSGCT was 72.84 *vs.* 69.97 months. Applying Log Rank (Mantel-Cox), the difference in mean OS was (P = 0.540) not statistically significant (**Fig. 1b**).

Comparative survival concerning prognostic groups was significantly different (P = 0.002). We observed a mean OS of 77.83 months in good prognostic group patients while intermediate and poor prognostic patients had a mean OS of 68.56 and 45.37 months, respectively (**Fig. 1c and d**).

DISCUSSION

In our study, we have focused on the individual and combined effect of prognostic group classification and tumor histopathology on treatment response and five-year OS in a cohort of male patients based in Pakistan, an Asian low-middle-income country. The study aimed at reporting response and survival outcome data in a setting with limited reports in the literature, and to confirm the prognostic role of the international, standardized, guidelines-based evidence tools developed in high-income settings.

GCTs are commonly present in different histological types. These histological types have varying response rates to radiation and chemotherapy. This is because some histological subtypes are radiosensitive while others are chemosensitive [9]. The IGCCCG prognostic group classification is most commonly used to predict the treatment and survival outcomes in testicular germ cell tumors and also affects the response to treatment.

The commonest stage at the time of diagnosis was stage III (66%). and when classified according to IGCCCG prognostic group classification, the Good prognostic group was the most commonest (58%) in our study population. All disease characteristics were compared with other reported studies and there were no significant differences when compared to other studies, suggesting that in Pakistan, the disease presentation may not vary to other disease settings with more resilient health settings [10, 11]. Such similarity may reflect the absence of good screening programs in all countries.

Half of the patients present with seminoma, based on literature data, with a trend of the epidemiological rise [12, 13]. In our study population, 31 out of 50 (62.0%) patients had NSGCT histopathology while only 19 (38.0%) had Seminoma. Nonetheless, five-year OS in good prognostic group patients having Seminoma histopathology was 87.5%, and that in NSGCT good prognostic group patients was 84.6% (**Table 3**) without any statistically significant difference, which shows that the IGCCCG Prognostic group carries the most important prognostic information, including in our setting, and consistently with literature data. Treatment response was, however, superior in Seminoma as compared to NSGCT *i.e.* 63.15% *vs.* 35.48% (**Table 2**), reflecting a higher chemo-sensitivity.

This study showed that there was a significant difference between the three groups and CR was higher in good prognostic group patients but lower in intermediate and poor prognostic group patients. When results were compared with other reported studies, it was found that the results of the good prognostic group were nearly similar but the intermediate and poor prognostic group results of our study were inferior as compared to other studies [14, 15].

A recent study from Brazil by Vasconcellos *et al.* has compared the five-year OS for GCTs concerning histology and prognostic group classification. Their study comprised 300 patients with a median age of 28.0 years. The mean age in our population is 30.6 years. Vasconcellos *et al.* found that five-year OS in their entire cohort was 85% and a significant difference in OS was observed for histology (P = 0.00015). They have found the absolute difference of OS in Seminoma and NSGCT *i.e.* 96.8% in Seminoma and 75.7% in NSGCT [16]. Two third of their patients had NSGCT histology which is similar to our study (62.0% NSGCT patients). Such a prognostic difference was not reported in our study and may be related to the smaller sample size of our cohort.

Furthermore, although NSGCT has comparable five years OS in both our study and in that of Vasconcellos *et al.* (75.7% *vs.* 71.0%), the five years OS for seminoma according to Vasconcellos *et al.* is 96.8% *vs.* 78.9% in our case [16]. This difference can be explained by information that we could not capture from our data analysis, on treatment compliance, rates of treatment completion, and chemotherapy dose intensity. Other international studies also report higher survival statistics for seminoma patients [17-19]. A Danish population-based study reported a five-year OS in seminoma good prognostic group patients of 93%. They have attributed good outcomes to the Danish surveillance program [20].

The results of our study affirm the significant effect of prognostic group classification on the treatment outcome of the patients with male germ cell tumors in terms of five-year overall survival and mean overall survival. The effect was also evident in response to first-line treatment in our patient population. Both seminoma and non-seminoma patients had a similar effect on prognostic groups. The histopathology, however, did

not significantly influence the treatment response and survival outcome in our study.

One limitation of our study is the small sample size and the retrospective nature of the investigation. We believe there is a need to design a higher-powered study to confirm whether the difference we see in five years of OS in our study population is a result of demographics or disease-related factors. The major strength is that we collected data in a setting where the literature reports are very limited.

CONCLUSION

The prognostic significance of the IGCCCG classification is reproducible in Asian patients based in a low-middle income country, giving information on the expected overall survival and treatment response. Patients classified into the good prognostic group according to IGCCCG criteria showed improved results in terms of CR to initial first-line treatment and 5-year overall survival, regardless of histology. Further research is warranted, to clarify if histology has an independent prognostic value, based on larger cohorts of patients.

ETHICAL APPROVAL

The study was approved by the Institutional Ethical Committee of INMOL. The IRB approval form is attached. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki declaration.

CONSENT FOR PUBLICATION

Written informed consent was taken from the participants.

AVAILABILITY OF DATA

Data is available from the corresponding author on a reasonable request.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report concerning this manuscript.

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AUTHOR CONTRIBUTION

Dr. Zeeshan Rasool designed the study and collected data from medical records. Dr. Shah Zeb Khan and Dr. Ahmed Farooq analyzed the data. All the authors drafted the manuscript. All authors have critically reviewed and approved the final draft and are responsible for the content.

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