Original Article

Fifteen Years of Experience in the Management of Non-Seminomatous Testicular Germ Cell Tumors at a Tertiary Care Center in Pakistan

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ABSTRACT

Objective: We evaluated the treatment outcome and associated prognostic factors for patients with nonseminomatous testicular germ cell tumours (NSGCT), who were treated in our hospital during last 15 years.

Methodology: Data was retrospectively analyzed for the 1995 through 2010 period. One hundred and twenty patients with NSGCT were identified. Descriptive Data was analyzed for the age, risk factors, site, histology, stage, chemotherapy regimen, retroperitoneal lymph node dissection (RPLND) and radiological response. The disease free survival (DFS) and overall survival (OS) were determined by Kaplan and Meier method and statistical inferences with the log-rank test. Cox proportional hazards Model was used to find different prognostic factors.

Results: Mean age of patients was 29.65 years (16-45). Pain and swelling of testis was commonest presentation (30%). Right sided were predominant (63.3%). Predominant stage was IIIC (55%) and commonest histology was mixed (embryonal cell carcinoma+yolk sac tumor+teratoma) in 45% cases. Majority of patients were poor risk according to International Germ Cell Cancer Consensus Classification (IGCCC), 41.7%. Bleomycin, etoposide and cisplatinum (BEP) chemotherapy was mostly as a first line treatment (87.5%). Postchemotherapy RPLND was performed in 31 patients (25.8%). Histology among residuals was fibrosis (48.4%), viable tumors (35.5%) and mature teratoma (16.1%). Median DFS and OS were 9 and 9.1 years respectively. Stage, IGCCC, RPLND were found important prognostic factors ($p < 0.001$).

Conclusion: Better outcome with lower disease burden and lower IGCCC and multidiscplinary approach warrants public awareness should be carried out for the testicular self-examination to reduce the time from the beginning of symptoms to time of seeking treatment.

KEY WORDS: Testicular germ cell tumors, non-seminomatous, longer followup, Treatment outcome, Pakistani men.

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INTRODUCTION

Globally, testicular cancer incidence is highest among European and American men and lowest among men of Asian and African descent. Incidence rates have been increasing around the world for at least 50 years, but mortality rates, at least in developed countries, have been declining. The reason for the decrease in mortality is related to improvements

in treatment regimens but the reason for the increase in incidence is not known.[1]

In Pakistan, due to lack of national based cancer registery, exact incidence and prevalence is not known, however one study has reported that testicular germ cell tumors constitute 0.74% of all malignant tumours and 1.24% of all male malignancies.[2] Most of the testicular germ cell tumors (TGCT) in Pakistani men are diagnosed in the third and fourth decade of life with predominant presentation as scrotal swelling and amongst these seminoma are the most common (36.5%).[3]

The established risk factors to develop TGCT are previous contralateral TGCT, familial trends, cryptorchidism and klinefelter syndrome.[4] TGCT are generally considered to have very good prognosis and even in metastatic disease the cure rates are near 80%.[5] However advanced and cisplatinum-refractory nonseminomatous germ cell tumors (NSGCT) still are the challenging entities in terms of optimizing therapy and treatment outcome. Various International guidelines are available to facilitate correct diagnosis, treatment and follow-up for NSGCT.[6]

We aimed to present our experience in managing NSGCT over last 15 years at our hospital to assess the risk factors, stage at the time of diagnosis, histological characteristics, treatment outcome and prognosis of NSGCT in Pakistani men.

METHODOLOGY

From the database of our hospital, 195 testicular germ cell tumors were retrieved between 1995 and 2010. Of whom 120 patients were identified as being non-seminomatous germ cell tumors (NSGCT). All the patients identified were treated and followed in our center. All the data was collected for initial presentation, risk factors, baseline stage, surgical procedures, histologic characteristics, first line chemotherapy regimens , number of cycles, second line chemotherapy regimen, postchemotherapy response evaluation on computed tomography (CT) imaging and tumor markers, retroperitoneal lymph node dissection (RPLND), post-chemotherapy residuals histology, salvage therapy, disease free survival, pattern of relapse, over all survival and prognostic factors for treatment outcome. Staging was done using the TNM system created by the American Joint Committee on Cancer (AJCC). Patients were also stratified according to International germ cell Consensus Classification (IGCCC) in three subgroups, i.e., good risk, intermediate risk and poor risk.

All the patients remained under surveillance in our hospital and latest follow-up was recorded in 2010

Table-I: Patient characteristics.

Variables	*No. of patients (%)*
Age	29.6 years (16-45) SD 7.6
Demographic Distribution	
Sindh	103
Punjab	4
Khyber Pakhtunkhwah	2
Baluchistan	11
Possible Risk factors and Associated Genetic abnormalities	
Cryptorchidism	14 (11.7%)
Previous trauma	38 (31.7%)
Horse shoe shaped kidneys	2 (1.7%)
Familial	2 (1.7%)
Sporadic	64 (53.2%)
Initial Presentation at diagnosis	
Scrotal swelling and pain	65(54.2%)
Backache	40 (33.3%)
Weight loss > 10%	4 (3.3%)
Deep venous thrombosis	4 (3.3%)
Renal Failure	7 (5.9%)
Histology of primary tumors	
Embryonal cell carcinoma+ yolk sac tumor+Teratoma	54 (45.0%)
Embryonal cell carcinoma + yolk sac tumor	46 (38.4%)
Choriocarcinoma with or without teratoma	7 (5.8%)
Others (with or without teratoma/seminoma)	13 (10.8%)
Pre- chemotherapy tumor markers	
AFP (ng/ml) median	8.8 (range 3.4-84933.4)
HCG IU/ml	8.9 (range 4-25100)
LDH U/ml	463 (range 320-2140)
Stage at diagnosis	
IIB	4 (3.3%)
IIC	12 (10.0%)
IIIA	8 (6.7%)
IIIB	30 (25.0%)
IIIC	66 (55.0%)
IGCCC Prognostic group	
Good	4 (3.3%)
Intermediate	66 (55.0%)
Poor	50 (41.7%)
First line chemotherapy	
BEP	105 (87.5%)
EP	15 (12.5%)
Second line chemotherapy	
VIP	15 (12.5%)
GEMOX	8 (6.7%)
Site of Resection	
Retroperitoneum	27 (87.1%)
Thorax	4 (12.9%)

AFP= Alpha fetoprotien; HCG= human chorio gonadotrphin; LDH= lactate dehydrogenase;
IGCCC= International Germ Cell Cancer Consensus Classification,
BEP= bleomycin, etoposide and cisplatinum, EP= etoposide and cisplatinum,
VIP= Vinblastine, ifosfamide and cisplatinum,
GEMOX= Gemcitabine and oxaliplatin

to extrapolate survival. Statistical data were computed and analyzed using Statistical Package for the Social Sciences (SPSS) version 17.0 software. Descriptive statistics were used to characterize the most relevant clinical parameters. The disease free survival (DFS) and overall survival (OS) were determined by Kaplan and Meier method and statistical inferences with the log-rank test. Cox proportional hazards Model was used to find different prognostic factors.

RESULTS

A total of 120 patients were identified as having NSGCT. Overall mean age at diagnosis was 29.65 years. Referral to our hospital was mainly from Sind province and Baluchistan. Majority of patients had no significant risk factors. Main complaints at the time of diagnosis were scrotal swelling and pain (54%) followed by backache (33%) Table-I.

All of the patients were staged after testicular ultrasound, computed tomography (CT) scan of chest, abdomen and pelvis and tumor markers (α-fetoprotein (AFP), ß-human chorionic gonadotrophin (ß-hCG) and lactic dehydrogenase (LDH) and orchiectomy. Commonest histological variety was the mixed; embryonal cell carcinoma in combination with yolk sac tumor and teratoma (45%). After staging work up, majority of patients were found to have advanced stage disease; IIIC (55%) followed by IIIB (25%). According to International Germ Cell Cancer Consensus Classification (IGCCC), majority of patient group was intermediate risk (55%) followed by poor risk (41.7%).

The chemotherapy regimen as first line therapy was bleomycin, etoposide and cisplatinum (BEP) in most of patients (87.5%) with median 4 cycles (3-6) followed by duplet chemotherapy etoposide and cisplatinum (EP) Table-I. The acute grade 3 hematological toxicities were; Neutropenia 25 patients (20.8%), febrile neutropenia 20 patients (16.7%) and thrombocytopenia in 18 patients (15%). Grade 3 non-hematological toxicities were nephrotoxicity in 5 patients (4.2%), neurotoxicity in 15 patients (12.5%), pulmonary dysfunction in 5 patients (4.2%), cardiotoxicity in two patients (1.6%) and treatment related deaths were 10 (8.3%). The radiologic response to chemotherapy was shown in Table-II. The tumor volume reduction rate was 98.91 (95% confidence interval 89.74-100). The tumor reduction rate was calculated by using formula {pre-chemotherapy tumor volume (cc) – post-chemotherapy tumor volume (cc) X 100 ÷ pre-chemotherapy tumor volume (cc)}.[7]

On post-chemotherapy response evaluation, residual disease was found in 31 (25.8%) patients, majority of them had retroperitoneal conglomerate. All patients underwent retroperitoneal lymph node dissection (RPLND) of bilateral nature. Eight patients received additional chemotherapy and radiation before RPLND. Histological findings among residuals were the fibrosis (48.4%), viable tumors (35.5%) and mature teratoma (16.1%). According to these findings, predictive model was made for possible histology in postchemotherapy residuals in NSGCT at time of RPLND Table-III. Additional correlation of postchemotherapy residuals and histologic characteristics was also made which showed that postchemotherapy residual of size > 5 cm have more likelihood of viable tumor component.

At median follow up of 15 years (3-17), median progression free survival (PFS) rate was 9 years and overall survival (OS) rate was 9.1 years. The baseline tumor stage, IGCCC risk groups and postchemotherapy residuals' histology (viable vs. necrosis) were found important prognostic factor for the PFS and OS with p value 0.001. Total 23 patients were found to have cisplatinum refractory recurrent/metastatic disease. In such situation the chemotherapy VIP (Vinblastine, ifosfamide and cisplatinum) and GEMOX (gemcitabine and oxaliplatin) were commonly used. A sub-group of patients with recurrent disease (30) aslo received salvage radiotherapy to infradiaphragmatic disease. Additionally, using Cox Proportional Hazards Model, the baseline tumor stage, basline AFP tumor marker, IGCCC risk groups and postchemotherapy residuals size were found important clinical prognostic factors for predicting the recurrence in patients NSGCT Table-IV.

Table-II: Postchemotherapy Radiological Response.

Parameters	*Prechemotherapy tumor volume (cm^3)*	*Postchemotherapy tumor volume (cm^3)*	*Volume reduction rate (%)*	*P value*
Mean	151.01	3.35	98.91	0.0001
95% Confidence interval of difference	100.32-201.77	2.17-4.54	89.74-100	0.0001
Standarad deviation	280.6	6.55	2.14	0.0001

Table-III: Prediction model of histology in postchemotherapy residuals in non-seminomatous germ cell tumors.

Predictors	*Necrosis/fibrosis 15 Patients*	*Viable tumor/immature teratoma11 Patients*	*Mature teratoma 5 Patients*
Prechemotherapy			
1. Histology			
Embryonal cell carcinoma+ yolk sac tumor + Teratoma	6	5	3
Embryonal cell carcinoma + yolk sac tumor	6	6	--
Choriocarcinoma with or without teratoma	1	--	1
Others (with or without teratoma/seminoma)	2	--	1
2. Stage			
IIB	1	--	--
IIC	1	--	2
IIIA	1	--	1
IIIB	5	2	1
IIIC	7	9	1
3. IGCCC group			
Good	1	--	--
Intermediate	10	3	4
Poor	4	8	1
4. Baseline tumor markers			
AFP (ng/ml)			
< 250 ng/ml	11	2	1
> 250 ng/ml	4	9	4
HCG IU/ml			
< 500 IU/ml	8	6	2
> 500 IU/ml	7	5	3
LDH U/ml			
5. Retroperitoneal nodal mass			
< 5cm	9	3	1
> 5 cm	6	8	4
During chemotherapy			
1. Regression (%)	70 % (25-100%)	65% (30-195%)	63% (30-87%)
Postchemotherapy			
1. Tumor markers			
AFP (ng/ml)			
Elevated	2	3	1
Normal	13	8	4
HCG IU/ml			
Elevated	5	1	--
Normal	10	10	5
LDH U/ml			
Elevated	--	1	2
Normal	15	10	3
2. Retroperitoneal nodal mass			
0- 0.5 cm	1	--	--
0.6- 1 cm	2	--	2
1.1- 2 cm	2	2	--
2.1- 5 cm	6	3	3
> 5 cm	4	6	--

Table-IV: Cox Proportional Hazards Model (univariate and multivariate analyses) showing different clinical parameters predicting for disease recurrence in patients with metastatic non-seminomatous germ cell tumor underwent adjuvant resection.

Variables	*Hazrad ratio*	*(95% CI)*	*p value*
Initial Stage Stage II Vs. stage III	1.38	1.38-2.87	0.001
Initial histopathology Single histology Vs Mixed	0.99	0.17-1.07	0.1
Baseline AFP >250 Vs. > 250	3.47	1.75-5.36	0.001
Baseline HCG <1000 Vs. >1000	0.55	0.51-1.20	0.99
IGCCC risk groups Good Vs. Intermediate/poor	1.55	1.25-3.33	0.001
Prechemotherapy retroperitoneal nodal mass < 10 cm Vs. > 10 cm	1.23	1.11-2.75	0.001
Chemotherapy First line Vs. secondline	0.81	0.55-1.20	0.7
Postchemotherapy Residual nodal mass < 2 cm Vs. >2 cm	1.17	1.10-2.70	0.001
Postchemotherapy AFP levels Normal Vs. elevated	0.98	0.66-1.10	0.1
Postchemotherapy HCG levels Normal Vs. elevated	0.98	0.66-1.10	0.1
Histology findings of residualsNecrosis Vs. Viable tissue/immature teratoma	0.88	0.78-1.30	0.7

DISCUSSION

TGCT are rare in our country as in the other parts of world i.e. less than 1%. The frequency of TGCT we reported previously at our hospital was same and usually manifested during the 3rd decade of life.[8] Interestingly, more NSGCT cases were documented in our hospital data as compared to the seminomas of testis. The possible explanation for this scenario could be the poor referral of seminomas patients to tertiary care centers by primary surgeons who think the seminomas as curtaive cancer without any further interventions after orchiectomy. Cryptoorchidism was seen in 12% of our patient group, which was consistent with international data.[9] Unfortunately, majority of NGCT patients were advanced stage and were intermediate or poor according to IGCCC risk group; however the DFS and OS rates were not dismal, i.e. 9 and 9.1 years respectively, as mentioned by other studies.[10,11] Further sub-analysis of study showed that baseline stage, IGCCC risk groups are important prognostic factors to determine the PFS and OS rates. Our encouraging results of better tumor reduction rate and prolonged DFS in NSGCT with cisplatinum based combination chemotherapy (BEP) were also consistent with international data.[12,13] Both the acute hematological and late neurotoxicity were significantly greater in patients who received BEP. Twenty patients treated with BEP died of sepsis, bleomycin and febrile neutropenia. Higher morbidity and mortality in our series explains the non-compliance of patients for regular follow up, poor self reporting of side effects and delayed management. Interestingly, 79.2% of survivors had succeeded in their attempts of achieving posttreatment paternity, only 20.8% patients were found to be infertile. Recent studies have shown that reduced number BEP cycles are helpful in preserving the future paternity.[14] Further, sperm banks shall be encouraged by competeting authorities.

Post-chemotherapy adjunct resection of residual masses after first or second-line chemotherapy remains an essential part of the treatment of NSGCT; however results are awaited for ongoing trials for the role of positron emission tomography (PET) for postchemotherapy residuals, so that RPLND be avoided in certain patients.[15, 16] We found better PFS and OS rates for those patients who underwent RPLND after chemotherapy.

Additionally, some of our patients received salvage radiotherapy to bulky disease without any further second line chemotherapy and were found disease free at time of analysis. There has been little research about the potential role of radiotherapy as salvage treatment for recurrent NSGCT following first line chemotherapy.[17] We recommend further evaluation is needed to confirm the potential role of radiotherapy as salvage treatment.

In conclusion, to our knowledge this is the first report on long term treatment outcome of NSGCT in Pakistani men. Although better PFS and OS rates were achieved retrospectively, but advanced stage and poor IGCCC risk groups in our patient population warrants a national level health campaign to teach the general public for self examination of scrotum and testis for early diagnosis and better treatment outcome.

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