ORIGINAL ARTICLE

Clinicopathological Characteristics and Outcomes of Non-Seminomatous Germ Cell Tumours of the Testis: 17 Years' Experience

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ABSTRACT

Background: Testicular cancer, although accounting for only 1% of all male cancers, is the most common solid tumor in men aged 20-34 years, with a steadily increasing global incidence over recent decades. Due to multimodal treatment strategies such as chemotherapy, radiotherapy, and surgery, patients generally achieve excellent 5-year survival rates.

Objective: This study aimed to evaluate the clinicopathological features and long-term outcomes of testicular non-seminomatous germ cell tumors (NSGCT) at a single center in Pakistan.

Methods: A retrospective chart review was performed at the Department of Urology at the Sindh Institute of Urology and Transplantation (SIUT), Karachi, from 1998 to 2015. All patients with biopsy-confirmed NSGCT were included, with a minimum follow-up of five years. The data was collected from March 2020 till December 2020 from clinical records and analyzed to determine overall survival (OS) and disease-free survival (DFS).

Results: A total of 100 patients were evaluated, with a mean age of 28.04±8.1 years. Most patients presented with stage IIIa disease (30%), followed by stage IIIc (28%) and stage IS (23%). Regarding treatment, 12% were managed with active surveillance, 61% received chemotherapy, and 22% underwent combined chemotherapy and retroperitoneal lymph node dissection (RPLND). The 5-year overall survival (OS) and disease-free survival (DFS) rates were 82.5% (95% CI: 73.1-88.9%) and 79.0% (95% CI: 69.0-86.1%), respectively.

Conclusion: These findings suggest that patients in our setting often present with advanced disease, likely due to limited awareness and socioeconomic challenges. However, when stratified by stage, survival outcomes were comparable to those reported in other studies.

Keywords: *Clinical outcomes, non-seminomas, testicular cancer, germ cell tumors, overall survival, chemotherapy.*

INTRODUCTION

Testicular cancer (TC), comprising about 1% of all male cancers, although overall rare, is most prevalent among men aged 15 to 35 years. The global incidence has been steadily rising over the past several decades [1]. It is highest in European, North American, and Oceanian men (around 3-12 per 100,000), and lowest in Asian and African populations (<1 per 100,000). Germ cell tumors (GCTs) constitute 90%-95% of TC cases [2]. Several risk factors for TC have been identified, including personal or family history of TC and cryptorchidism [3]. They have excellent 5-year survival rates due to a multimodal treatment strategy of chemotherapy, radiotherapy, and surgery [4].

TC is divided into two main categories for treatment planning based on natural history and management: seminoma and non-seminoma. Non-seminomatous GCTs (NSGCTs) include: embryonal carcinoma (EC), yolk sac tumours (YSTs), choriocarcinoma, teratomas, and mixed GCTs. Most tumors are a mix of different types, but this does not change the treatment of most non-seminoma tumors [2].

Surgical treatment plays a greater role in the management of NSGCTs than in seminomas [5]. EC can increase serum levels of the tumor marker alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (bHCG). YST almost always leads to elevated serum AFP levels [6]. Choriocarcinoma increases blood levels of beta-HCG. Teratoma is most often seen as part of mixed GCTs. Pure testicular teratomas do not secrete AFP or HCG.

History, general physical examination, testicular examination, scrotal/testicular ultrasonography, and serum tumor marker levels like AFP, bHCG, and LDH should be performed before surgical intervention, *i.e.,* radical orchiectomy [2].

Radical orchiectomy is the established diagnostic and therapeutic step in the management of TC. The access is made through an inguinal incision, and complete removal

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Email: mnauman73@gmail.com
Received: December 17, 2025; Revised: January 11, 2026; Accepted: February 02, 2026
DOI: https://doi.org/10.37184/lnjcc.2789-0112.7.16

of the ipsilateral testicle, along with epididymis and spermatic cord, is undertaken. When there are no metastases, the rate of oncological cure after single radical orchiectomy is between 80 and 85% [6, 7]. Post-orchiectomy oncological outcomes of non-seminomas show higher relapse, especially when lymphovascular invasion (LVI) is found. Platinum-based chemotherapy and restaging are currently the available options for treating metastatic NSGCTs. If there is a recurrent or residual mass in the retroperitoneal space after chemotherapy, retroperitoneal lymph node dissection (RPLND) is performed at most centers worldwide [5]. All patients who have residual masses ≥ 1 cm after chemotherapy should undergo post-chemotherapy RPLND (PC-RPLND) [5]. RPLND has been used to treat GCTs since the 1900s.

This study aimed to evaluate the clinicopathological features and long-term outcomes of testicular non-seminomatous germ cell tumors (NSGCT) at a single center in Pakistan.

MATERIALS AND METHODS

This is a retrospective chart review of patients diagnosed with biopsy-proven NSGCTs at the Sindh Institute of Urology and Transplantation (SIUT), Karachi, Pakistan, between 1998 and 2015. The data was collected and analyzed from 30th March 2020 till December 2020, following ethical review committee approval. All patients with a biopsy-proven diagnosis of NSGCT aged 18 years or older were included in the study. The data were retrieved from patient case notes using a predetermined pro forma for up to 5 years of follow-up after diagnosis. Approval from the ethical review committee was obtained before the data collection (SIUT, ERC-2020/A-206). Patients with extra-gonadal NSGCTs were excluded. The data variables included age, presenting symptoms, side of testicular swelling, clinical stage, treatment, resection status, overall survival (OS), and disease-free survival (DFS). OS was defined as the time from randomization to death. DFS was defined as the time from randomization until evidence of disease recurrence.

NSGCTs of the testis were treated with a multimodal approach depending on disease stage and risk stratification [2]. Management started with radical inguinal orchiectomy, which is both diagnostic and therapeutic and allows accurate histological evaluation and the measurement of serum tumor markers such as AFP, β-hCG, and LDH. In stage I disease, options after orchiectomy include active surveillance in low-risk patients, adjuvant chemotherapy with one to two cycles of BEP (bleomycin, etoposide, and cisplatin), or RPLND in selected cases. Patients with stage II or III disease are treated primarily with systemic cisplatin-based chemotherapy, most commonly the BEP regimen, with treatment intensity guided by prognostic risk groups. Residual masses after chemotherapy, particularly in the retroperitoneum, are managed with surgical resection because they may contain teratoma or viable tumor. Overall, NSGCTs are highly chemosensitive, and long-term cure rates are excellent with appropriate treatment and follow-up [2].

The data were analyzed using Statistical Package for Social Sciences (SPSS) version 22.0. The continuous variables were reported as means and standard deviations (SD). Categorical variables were presented as frequencies and percentages. A chi-square test was conducted to determine the association between clinical parameters and tumour outcomes. Kaplan-Meier curves were plotted for OS and DFS. P-value <0.05 was considered statistically significant.

RESULTS

During the study period, a total of 317 patients were registered in the SIUT GCT registry, of whom 100 (31.6%) had NSGCTs; this study included these 100 patients. The median follow-up was 60 months. The mean age of all patients was 28.0 ± 8.1 years. The majority presented symptomatically (79%), while incidental findings were reported in 21%. Pain in the testicular region was reported in 44% of patients, while 24% had abdominal pain. Swelling was most frequently localized to the testicular region (75%), followed by the abdominal area (24%) and both sites (1%). Laterality on ultrasonography showed right-sided involvement in 57%, left-sided in 41%, and bilateral disease in 2%. Most patients were diagnosed at advanced stages, with stage IIIa in 30% and stage IIIc in 28%, while stage IS was observed in 23%, stage IIIb in 11%, and a minority in stage III (3%) and stage I (2%). The mean operative time of RPLND was 191.3 ± 70.1 minutes, and the mean hospital stay was 6.8 ± 3.9 days. Mean intraoperative blood loss was 50.8 ± 99.5 mL, with an average transfusion requirement of 1.8 ± 1.9 pints. Regarding adjuvant treatment, 61% of patients received chemotherapy alone, 22% received chemotherapy plus RPLND, and 12% received active surveillance, while no patients underwent RPLND alone. Among those undergoing RPLND, R0 resection was achieved in 19% and R2 resection in 2% (**Table 1**).

The OS rates were 93.6% (95% CI: 86.2-97.1%) at 1 year, 91.4% (95% CI: 83.6-95.6%) at 3 years, and 82.5% (95% CI: 73.1-88.9%) at 5 years (**Fig. 1**). The DFS rates were 93.6% (95% CI: 86.2-97.1%) at 1 year, 92.5% (95% CI: 84.9-96.3%) at 3 years and 79.0% (95% CI: 69.0-86.1%) at 5 years (**Fig. 2**). Age showed no significant association with OS or DFS at any time point. Clinical stage was not significantly associated with OS,

Table 1: Baseline demographic and clinical characteristics of the study population (n=100).

Variables	Frequency	Percentage
Clinical presentation		
Symptomatic	79	79
Incidental	21	21
Site of swelling		
Testicular	75	75
Abdominal	24	24
Both	1	1
Side of testicular swelling		
Right	41	41
Left	75	75
Bilateral	2	2
Clinical Stage		
I	2	2
IS	23	23
III	3	3
IIIa	30	30
IIIb	11	11
IIIc	28	28
Missing record	3	3
Treatment modalities		
Chemotherapy alone	61	61
Chemo + RPLND	22	22
RPLND alone	0	0
Active surveillance	12	12
Missing record	5	5
RPLND outcomes	**Mean**	**SD**
Operative time (min)[#]	191.21	70.07
Blood loss (ml)[#]	50.75	99.5
Blood transfusion (pints)[#]	1.75	1.86
Hospital stay (days)[#]	6.75	3.85

#: Mean ± SD is reported for numerical variables, RPLND, retroperitoneal lymph node dissection.

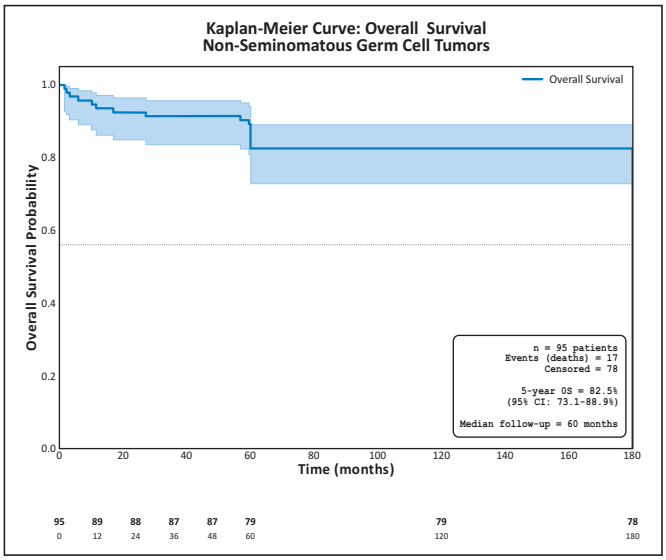

Fig. (1): Kaplan-Meier curve for overall survival (OS) in NSGCT patients.

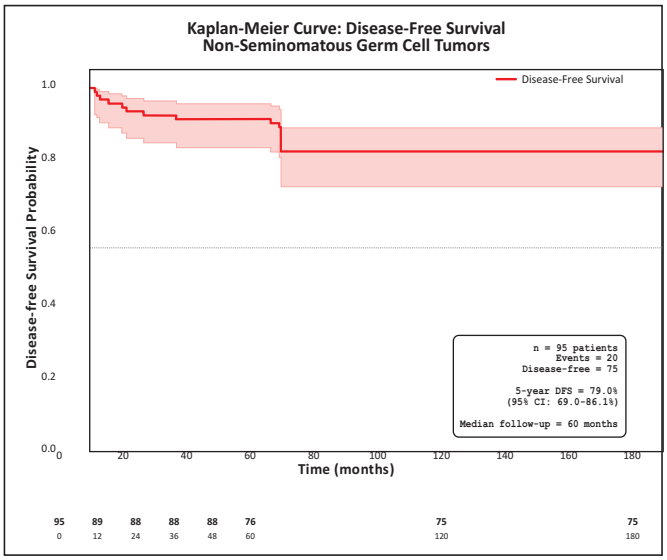

Fig. (2): Kaplan-Meier curve for disease-free survival in NSGCT patients.

DISCUSSION

This is one of the largest studies on NSGCTs by this surgeon, with medium-term outcome data. The mean age of patients in this cohort was 28 years, consistent with international reports, which report median ages ranging from 27 to 30 years [6-8]. Nearly half of the patients in this study were between 26 and 35 years, similar to other regional studies [9-11]. Compared to Indian data, where 55% of patients presented with stage III disease [12], this study demonstrated a higher proportion (72%), underscoring delayed presentation in our setting.

The presence of LVI has been validated as an independent predictor of recurrence in stage I non-seminomatous germ cell tumors (NSGCTs) [13, 14].

Clinical presentation in our cohort largely mirrored prior reports. Testicular pain was the most common symptom (44%), followed by abdominal pain (24%), while one-third were asymptomatic. These findings align with both Indian and Pakistani studies [12-14]. Testicular swelling was the predominant physical finding, with right-sided involvement slightly more frequent than left-sided (57% *vs.* 41%).

Stage distribution showed a predominance of advanced disease, with stage IIIa and IIIc accounting for 30% and 28%, respectively, comparable to regional series [9, 13,15]. Operative parameters, including mean excision time (191 minutes), were consistent with previously reported national and international data [13, 15]. Complete resection (R0) was achieved in 19% of patients, while incomplete resection (R2) was uncommon (2%).

Survival outcomes were encouraging. Five-year OS was 82.5% (95% CI: 73.1-88.9%), and DFS was 79.0%

(95% CI: 69.0-86.1%), broadly comparable to other Pakistani series [7]. The Kaplan-Meier curves were generated from data on 95 patients; 5 patients were missing due to the retrospective nature of the study. These results are also consistent with the International Germ Cell Cancer Collaborative Group (IGCCCG) data, which show OS of 80-89% and 48-67% for intermediate- and poor-risk groups, respectively [16]. Indian studies similarly reported four-year OS rates of 93.6%, 87.5%, and 52.6% for good-, intermediate-, and poor-risk categories, respectively [17, 18]. Outcomes in France and the United States also align, with five-year OS ranging from 72% to 79% [19, 20].

Chemotherapy responsiveness remained high, with 61% of patients managed with chemotherapy alone, comparable to international experience [10]. Surgical intervention following systemic therapy was required in a minority, reflecting the challenge of post-chemotherapy retroperitoneal disease. Reported OS in other global series, ranging from 70% to 80% [19, 20], is consistent with our findings.

Despite advances, several challenges persist. These include the management of residual masses after chemotherapy, balancing adjuvant treatment to avoid overtreatment, and addressing platinum-refractory disease [21]. Survivorship care remains critical. Regular testicular self-examination (TSE), supported by survivorship clinics, can facilitate early detection of contralateral tumors, which often require only orchiectomy and carry favorable outcomes [22]. Strengthening patient compliance with surveillance and public education on TSE is essential to improve outcomes [22].

Emerging biomarkers, particularly microRNA-371-3p, demonstrate superior sensitivity and specificity compared with conventional markers (AFP, HCG, LDH) [23-25]. These hold promise for earlier detection, monitoring treatment response, and guiding decisions regarding adjuvant therapy or recurrence surveillance, potentially reducing reliance on imaging. Advances in molecular oncology, including the study of genetic determinants of cisplatin resistance and tumor-specific antigens such as claudin-6, may enable novel therapeutic strategies for recurrent or resistant disease [25].

This study has several notable strengths. First, it includes a relatively long follow-up period, with a minimum of 5 years for all patients, allowing robust assessment of long-term oncological outcomes, such as OS and DFS, in patients with NSGCT. Second, all cases were biopsy-confirmed and managed at a single high-volume tertiary care center, ensuring diagnostic consistency and uniformity in staging, treatment decisions, and follow-up protocols. Third, the study provides valuable data from a low- and middle-income country setting, where published evidence on TC—particularly NSGCTs—is limited. This adds important regional insight and enhances the relevance of the findings for similar healthcare environments. Fourth, the inclusion of patients treated over an extended period reflects real-world clinical practice and captures outcomes across different disease stages and treatment approaches. Fifth, all treatment was provided free of cost, ensuring that no patient was left out due to financial constraints.

Finally, by stratifying outcomes by disease stage and treatment modality, the study allows meaningful comparisons with international data. It demonstrates that, despite late presentation, stage-adjusted survival outcomes are comparable to those reported in the literature. This strengthens the external validity of the conclusions and highlights the effectiveness of multimodal management in this setting.

There are some limitations to this study. These include a retrospective study design, a single-center origin, and a relatively small sample size. We also did not retrieve or analyze the residential data regarding the timing of diagnosis or outcomes. In addition, although the study spans a long time period (1998-2015), changes in diagnostic modalities, staging systems, chemotherapy regimens, and supportive care over time could have influenced outcomes, introducing heterogeneity in management. Finally, the study focused primarily on OS and DFS; other important outcomes, such as fertility preservation, long-term treatment-related morbidity, and patient-reported outcomes, were not assessed. Prospective, multicenter studies with standardized treatment protocols and comprehensive follow-up are needed to define outcomes better and address these limitations.

CONCLUSION

This study demonstrates that outcomes for NSGCT patients in our setting are broadly comparable to international benchmarks, despite a higher proportion of patients presenting at an advanced stage. Five-year overall and DFS rates were consistent with regional and global series, underscoring the effectiveness of current multimodal treatment approaches. Persistent challenges include delayed diagnosis, optimal management of residual disease, and platinum-refractory cases. Strengthening survivorship care, particularly through structured surveillance programs and patient education on TSE, remains essential. Future progress will depend on earlier detection, integration of novel biomarkers such as microRNA-371-3p, and collaborative research aimed at refining risk stratification and minimizing treatment-related toxicities.

ETHICS APPROVAL

Ethical approval was obtained from the ethical review committee before the data collection (vide SIUT, ERC-2020/A-206). All procedures performed in studies involving human participants followed the ethical standards of the institution and the Helsinki Declaration.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA

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

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

AUTHORS' CONTRIBUTION

Muhammad Nauman conceptualized the study.

Muahmmad Nauman, Mudassir Hussain and Haris Jamil performed literature search and designed the study.

Muhammad Nauman, Haris Jamil and Muhammed Mubarak collected the data.

Muhammad Nauman, Hairs Jamil and Asad Shahzad analysed the data.

Muhammad Nauman, Hairs Jamil, Rehan Mohsin, Gauhar Sultan drafted the manuscript.

Muhammed Mubarak and Syed Adibul Hassan Rizvi critically reviewed and revised the manuscript.

GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this manuscript, the authors made limited use of a generative artificial intelligence tool (Skywork AI) exclusively for language refinement, stylistic suggestions, and minor proofreading in selected sections of the text. The tool was not used for study design, data analysis, result interpretation, or the generation of scientific content. All AI-assisted outputs were critically reviewed, edited, and validated by the authors, who take full responsibility for the accuracy, originality, and integrity of the final published work.

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