Original Articles

Clinicopathological characteristics, prognostic factors and treatment outcomes of seminomatous germ cell tumours from a tertiary cancer centre in eastern India

DEEPAK DABKARA, SANDIP GANGULY, JOYDEEP GHOSH, SATYADIP MUKHERJEE, SUJOY GUPTA, INDRANIL MALLICK, SUMIT MUKHERJEE, DIVYA MIDHA, MEHELI CHATTERJEE, ARCHISMAN BASU, AMMARA HASAN, BIVAS BISWAS

ABSTRACT

Background. Seminomatous germ cell tumour (SGCT) is a rare but curable malignancy of young adults. The literature on management and outcome of SGCT is scarce from India. We report the demography and treatment outcome of SGCT at our centre.

Methods. We did a retrospective analysis of patients with SGCT treated from March 2011 to December 2018. Patients were staged appropriately with imaging, and pre- and postoperative tumour markers. High inguinal orchiectomy was performed in all with a testicular primary and received subsequent stage-adjusted adjuvant treatment. Patients were monitored for metabolic syndrome during follow-up after completion of treatment.

Results. We treated 85 patients with a median age of 37 (range 20–68) years. The primary site of the tumour was the testis in 80 (94%) and mediastinum in 5 (6%) patients. Cryptorchidism was present in 20 (25%) patients and testicular violation was present in 11 (14%) patients. Stage of the disease was I in 61, II in 13 and III in 6 patients. Adjuvant treatment in stage I disease was single-agent carboplatin (area under the curve × 7) in 38 (62%), surveillance in 20 (33%) and radiotherapy in 3 (5%) patients. Five patients in the surveillance group relapsed. The 7-year mean (SD) relapse-free survival and overall survival were 83.1% (8%) and 98.7% (1.3%), respectively. Thirty-one patients ($n = 52$, 60%) had features of metabolic syndrome.

Conclusions. SGCTs have a high cure rate. Long-term follow-up is essential for monitoring toxic effects. Early diagnosis, avoidance of testicular violation and multidisciplinary management are the key features for better long-term outcome in SGCT.

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Tata Medical Center, 14 MAR (EW), New Town, Rajarhat, Kolkata 700160, West Bengal, India
DEEPAK DABKARA, SANDIP GANGULY, JOYDEEP GHOSH, MEHELI CHATTERJEE, ARCHISMAN BASU, AMMARA HASAN, BIVAS BISWAS Department of Medical Oncology
SATYADIP MUKHERJEE, SUJOY GUPTA Department of Urosurgery
INDRANIL MALLICK Department of Radiotherapy
SUMIT MUKHERJEE Department of Radiology
DIVYA MIDHA Department of Pathology

Correspondence to BIVAS BISWAS; *bivasbiswas@gmail.com*

INTRODUCTION

Testicular germ cell tumours (TGCTs) constitute 1% of all adult malignancies.[1–3] TGCTs are the most common solid tumours between 18 and 45 years of age.[1,4] The incidence differs in countries, with lowest rates in African and Asian countries and highest in Scandinavian countries. The incidence of TGCTs is increasing since the past two decades in Europe and the USA, the reason for which is not known.[3,5,6] It is also becoming more common in low- and middle-income countries.[7] India has one of the lowest incidence of TGCTs at 0.5 per 100 000 men.[8] TGCTs comprise seminomatous and non-seminomatous tumours. Seminoma is the less aggressive of the two types of germ cell tumours (GCTs).

There is scarcity of the literature on seminomatous GCTs (SGCTs) from the Indian subcontinent with reports showing a high incidence of uncorrected cryptorchid testis, advanced stage of disease at presentation and poor response to chemotherapy.[9–13] Testicular SGCTs have excellent cure rates, and thus, the focus is on maximizing cure and minimizing the acute and long-term side-effects.[14]

We aimed to analyse the clinicopathological features, prognostic factors, treatment outcome and treatment-related side-effects in patients with SGCT evaluated and treated at our centre.

METHODS

Patients

This is a retrospective study of patients with SGCT evaluated and treated at our centre. Patients who presented to us between March 2011 and December 2018 were searched from a prospective database and hospital management services. Patients who did not take any further treatment after initial staging and evaluation

were excluded from this analysis. Ethical clearance was taken from the institute review board and patient consent waiver was obtained in view of the retrospective nature of this study.

Diagnosis and staging

All eligible patients underwent testing for routine biochemical blood parameters, baseline tumour markers (alpha-foetoprotein, beta-human chorionic gonadotropin and lactate dehydrogenase), testicular ultrasound, computed tomography (CT) of chest and whole abdomen, semen analysis and sperm banking if the family was not complete and post-orchiectomy tumour markers.

Patients who presented to us after orchiectomy at another centre also underwent similar diagnostic testing along with pathology review of the tumour blocks, whenever available. Bone scan was performed if clinically indicated or with high serum alkaline phosphatase. Patients with a mediastinal primary were diagnosed with core needle biopsy even with high tumour marker to rule out somatic differentiation or *NUT* midline carcinoma.[15]

The staging was done as per the American Joint Committee on Cancer, 7th edition.[16] For advanced-stage disease, the patient had risk stratification as per the International Germ Cell Cancer Collaborative Group (IGCCCG) classification.[17]

Treatment protocol, response evaluation and follow-up

All patients who presented with suspected testicular SGCTs underwent high inguinal orchiectomy. For stage IA and IB tumours, patients were offered surveillance or 1–2 cycle of carboplatin (area under the curve [AUC] ×7) or either para-aortic radiation for 20 Gy (least preferred). For stage IIA and non-bulky IIB, patients were offered radiotherapy and patients were treated with bleomycin, etoposide and cisplatin (BEP) or etoposide and cisplatin (EP) depending on the IGCCCG risk stratification for stage IIC and III.

Surveillance protocol after high inguinal orchiectomy consisted of clinical examination and CT scan of abdomen at 3, 6 and 12 months in the 1st year, clinical examination and CT scan of abdomen every 6 months in the 2nd and 3rd year and clinical examination every year thereafter. Response assessment was done by response evaluation criteria in solid tumours (RECIST) v 1.1,[18] wherever applicable. Post-chemotherapy resection of residual disease was done when required. Patients with mediastinal seminoma were treated with primary chemotherapy with EP or BEP followed by local therapy in the form of surgery or radiotherapy if required.

Patients were followed up for acute and long-term treatment-related side-effects as well as for recurrence. Patients who gained weight on follow-up were also evaluated for signs and symptoms of metabolic syndrome including laboratory parameters as per the American Heart Association/National Heart, Lung and Blood Institute Scientific Statement.[19] Those who had full component or partial component of metabolic syndrome were subjected to appropriate intervention:[20] weight reduction, regular exercise, lifestyle modification and use of statins whenever indicated, and were further followed up for response to intervention.

Statistical analysis

Descriptive statistics were used for demographics and clinical characteristics. Chi-square test was used to detect association between categorical variables. Student *t*-test was used to compare continuous variables between groups. Survival was estimated by the Kaplan–Meier method and compared using log-rank test. Data were censored on 31 March 2019. Recurrence-free survival (RFS) with standard error was calculated from the date of orchiectomy to the date of disease relapse in case of a testicular primary and from the date of diagnosis to the date of disease relapse in case of a mediastinal primary. Overall survival (OS) with standard error was calculated from the date of diagnosis to the date of death from any cause. Patients who were lost to follow-up or who abandoned treatment were also included for RFS and OS analysis and outcome in these patients was confirmed by telephonic contact. Treatment abandonment was included for survival analysis in the present study as it has been proposed that non-compliant and treatment abandonment patients should be included in survival analysis for studies from developing nations to provide a true picture of outcome from these countries.[21] STATA/SE 11.0 (StataCorp LP, Texas, USA) was used for statistical analysis.

RESULTS

Baseline characteristics

Ninety-five patients with a diagnosis of SGCT were registered between March 2011 and December 2018 at our centre, of which 85 patients received treatment with a median age of 37 (range 20–68) years. Nine patients (11%) were >50 years of age at presentation. Clinicopathological characteristics are given in Table I. The primary site of the tumour was testis in 80 (94%) and mediastinum in 5 (6%) patients. Cryptorchidism was present in 20 (25%) patients and only 6 patients had prior orchidopexy. Testicular violation in the form of preoperative fine-needle aspiration or biopsy before presentation to our centre was present in 11 (14%, *n*=80) patients.

Treatment details and side-effects

Treatment details are given in Table II. Stage of disease was stage I in 61, stage II in 13 and stage III in 6 patients. Sixteen

TABLE I. Demography and baseline characteristics of testicular tumours

Variable	*n* (%)
Median (range) age (years)	37 (20–68)
Median (range) duration of symptoms (months)	4 (0.3–96)
Site of primary	
Testis	80 (94)
Mediastinum	5 (6)
Cryptorchidism	
No	60 (75)
Unilateral	13 (16)
Bilateral	7 (9)
Prior orchidopexy (*n*=20)	
No	14 (70)
Yes	6 (30)
Testicular violation	
No	69 (86)
Yes	11 (14)
Pre-surgery tumour marker	
No	29 (36)
Yes	51 (64)
Postoperative tumour marker	
No	7 (9)
Yes	73 (91)

patients were good risk, and 3 were intermediate risk among stage II and III patients (*n*=19). Inguinal orchiectomy was done in 60 (87%, *n*=69) patients and 9 (13%, *n*=69) patients had scrotal orchiectomy before presenting to us. Tumour size was available in 49 patients with median tumour size of 6.2 (range 2.5–12.5) cm. Forty (82%, *n*=49) patients had tumour size >4 cm, and lymphovascular invasion was present in 53% (30 of 57 evaluable) patients. Pre-orchiectomy tumour markers were available in 64% (33/51) of patients.

Patients with stage I seminoma after high inguinal orchiectomy received the following treatment: single-agent carboplatin (AUC ×7) in 38 (62%), surveillance in 20 (33%) and radiotherapy in 3 (5%) patients. The treatment of stages II and III testicular tumour is given in Table II. Treatment details of mediastinal tumour were BEP in 2 patients, BEP followed by surgery in 1 patient and EP in 2 patients.

Eleven (19%) patients had grade 3 or 4 treatment-related toxicities: 2 had acute kidney injury, 1 had bleomycin-induced lung toxicity (died later), 1 had grade 3 hyponatraemia with convulsion, 5 had grade 3 febrile neutropenia, 1 had grade 4 diarrhoea with febrile neutropenia and 1 had grade 3 diarrhoea with grade 3 hyponatraemia.

Metabolic syndrome

Thirty-one (60%) of 52 evaluable patients had features of metabolic syndrome during follow-up that included excessive and unexpected weight gain, deranged fasting lipid profile (high low-density lipoprotein cholesterol, low high-density lipoprotein and high triglyceride), high blood sugar and increase in blood pressure.

Outcome

Among stage I patients, 7 had a recurrence of which 5 were in the surveillance group. Tumour size was 5 cm, 7 cm, 8 cm and 8 cm, respectively, in 4 available patients. Time to recurrence was 2.4, 4.9, 5.2, 7.5 and 17 months, respectively, in the patients who relapsed after initial surveillance. One patient relapsed after 15 months of radiotherapy as initial treatment, and 1 patient relapsed after 66.3 months of treatment with single-agent carboplatin (AUC ×7).

The site of recurrence was para-aortic nodes in 4 patients on surveillance and 1 patient who received carboplatin. One patient who received radiotherapy initially had a recurrence in a retroperitoneal lymph node and bone and 1 patient on surveillance had a recurrence locally on the site of inguinal orchiectomy (had undescended testis in inguinal canal).

Treatment details at recurrence were BEP in 2, EP in 2, EP followed by retroperitoneal lymph node dissection in 1 and radiotherapy in 1 patient, and 1 patient defaulted before further treatment. None of the patients (*n*=38) in the carboplatin group and stage II or III patients had a recurrence.

After a median follow-up of 34.3 (95% confidence interval 18–41.1; range 5–106.5) months, the 7-year mean (SD) RFS and OS was 83.1% (8%) and 98.7% (1.3%), respectively (Fig. 1). Survival status is not known in 32 patients (38%) till the last data cut-off date. Of those 32 patients, 25 were with stage I SGCT who received prior adjuvant treatment as follows: 8 patients were on surveillance approach, 15 received single-agent carboplatin (AUC ×7) and 2 received radiotherapy.

Univariate and multivariate analysis

On univariate analysis (Table III), none of the clinical factors revealed significance for RFS. It may be due to very few events

TABLE II. Treatment and recurrence details

Variable	*n* (%)
Stage (*n*=80*)	
I	61 (76)
II	13 (16)
III	6 (8)
Treatment for stage I	
Surveillance	20 (33)
Single-agent carboplatin	38 (62)
Radiotherapy	3 (5)
Treatment for stages II and III	
Etoposide+cisplatin	7 (37)
Bleomycin+etoposide+cisplatin	8 (42)
Only radiotherapy	4 (21)
Orchiectomy type	
High inguinal	60 (75)
Scrotal	9 (11)
Surgery for undescended testis	11 (14)
Recurrence	
No	78 (92)
Yes	7 (8)
Metabolic syndrome (*n*=52)	
No	21 (40)
Yes	31 (60)

*Only testicular primary

TABLE III. Univariate analysis for relapse-free survival

Variable	*n*	Hazard ratio	95% CI	p value
Age (years)				
≤37	49	1		
>37	36	3.2	0.62–17.03	0.16
Duration of symptoms (months)				
≤4	44	1		
>4	40	0.52	0.1–2.71	0.44
Site of primary				
Testis	80	1		
Mediastinum	5	1.55e–15	–	1.0
Cryptorchidism				
No	60	1		
Yes	20	1.1	0.21–5.71	0.91
Testicular violation				
No	69	1		
Yes	11	1.80e–16	–	1.0
Orchiectomy type				
High inguinal	60	1		
Others	20	1.36	0.26–7.13	0.72
Stage of disease				
I	61	1		
II	13	5.46e–17	–	1.0
III	6	5.67e–17	–	1.0
Treatment type (*n*=61)*				
Surveillance	20	1		
Radiotherapy	3	0.94	0.3–2.1	0.95
Carboplatin only	38	5.93e–18	–	1.0
Tumour size in cm (*n*=41)*				
≤4	7	1		
>4	34	7.99e+14	–	

* Stage I seminoma

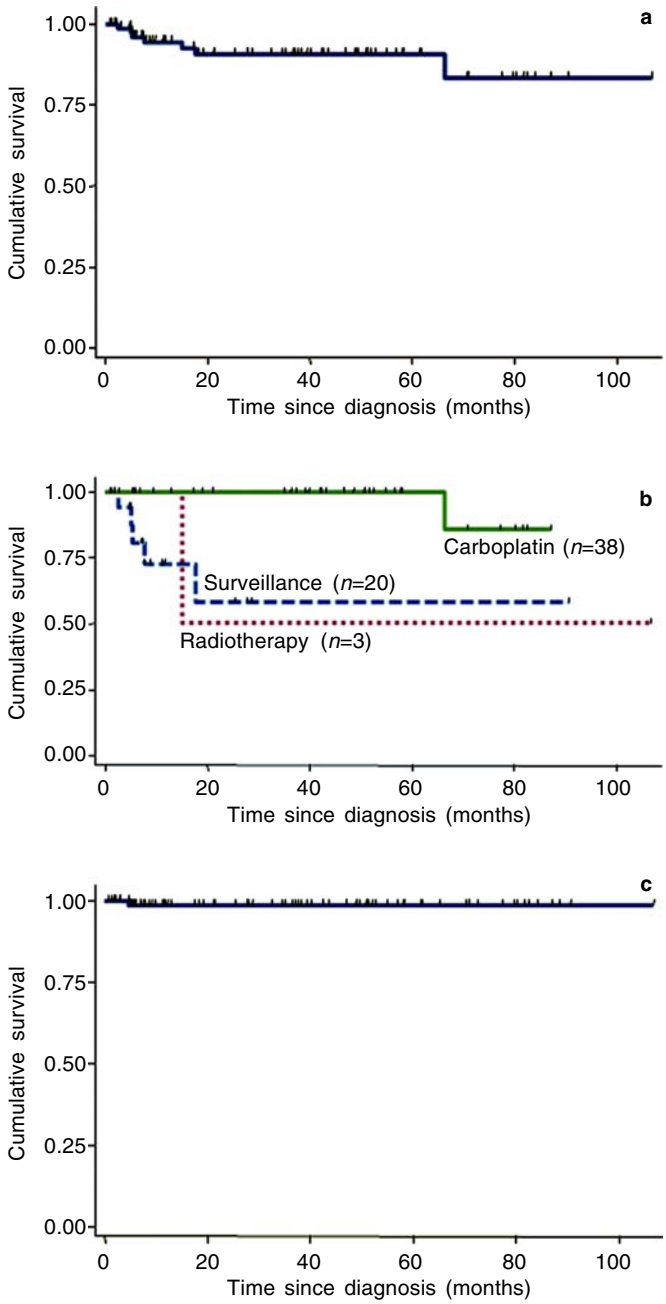

FIG 1. Kaplan–Meier survival estimate for relapse-free survival (in months) of whole cohort (a). Kaplan–Meier survival estimate for relapse-free survival (in months) according to adjuvant treatment received in stage I seminoma (n=61) (b). Kaplan–Meier survival estimate for overall survival (in months) of whole cohort (c)

(recurrence) in the whole cohort, and hence, multivariate analysis was not performed. As there was only one documented death in the whole cohort, no univariate analysis was performed for OS.

DISCUSSION

This is real-world data of SGCT patients treated at a tertiary care cancer centre in India. Testicular cancers are rare in India with an incidence of 0.5–1 per 100 000 population.[8] Many patients are not referred or are referred late to tertiary care hospitals from community physicians or surgeons. Most patients who are referred to our centre are either referred after orchiectomy (with/without testicular biopsy), do not have preoperative tumour markers or do not have properly fixed tissue for review, inadequate histopathology reports, which sometimes make treatment decisions difficult. The results of our study reflect those findings.

Data on pure SGCTs from India are scarce (Table IV). Cryptorchidism is a well-known risk factor for GCT of testis, and orchidopexy reduces the chances of the development of TGCT. Studies from India (Table IV) showed a high incidence of uncorrected cryptorchid testis and development of GCT in undescended testis.

The majority (62%) of stage I patients at our centre received chemotherapy and 33% opted for surveillance. This is in contrast to guidelines suggesting surveillance to be the preferred approach for stage I TGCT. This is mainly because of logistics including high cost involved in repeated imaging, long distance from home to healthcare facility and frequent follow-up. Five patients in stage I who were on surveillance had a relapse and all were successfully salvaged. This was in concordance with other large studies on stage I seminoma on surveillance.[22]

Late metabolic syndrome is a well-known complication seen in long-term survivors of GCTs. de Haas *et al.*[23] suggested early development of metabolic syndrome in a large proportion of patients treated with chemotherapy for TGCT. We found patients of TGCT to have significant weight gain, deranged blood sugar profile and deranged lipid profiles after treatment. Sixty per cent of our patients (31/52) had one or multiple components of metabolic syndrome[19] and they were advised weight reduction, regular exercise, lifestyle modification and use of statin whenever indicated.[20] None of the Indian publications[9–13] reported any information about metabolic syndrome.

Our study is a real-world experience of pure SGCT patients. It highlights important points that might help in improving the outcomes in developing countries such as India. Delay in consultation with a physician, reflected by symptom duration of up to 96 months, can compromise the outcome in a highly curable disease. A proportion of patients (18%) had tumour in the uncorrected undescended testis and 14% patients had

TABLE IV. Publications on seminomatous germ cell tumours of the testis from India

Study	n	Median/Mean age (years)	Stage			Cryptorchidism		
			I	II	III	n (%)	Unilateral	Bilateral
Bhutani *et al.*[9] (1993–99)	15	30	6	4	5	8 (11)	4	4
Anjanappa *et al.*[12] (2005–14)	63	35	36	25	2	10 (16)	–	–
Raina *et al.*[11] (1989–95)	63	26	31	19	13	12 (19)	10	2
Joshi *et al.*[10] (2013–14)	36	39	–	–	–	5 (14)	–	–
Saju *et al.*[13] (2001–15)	128	35	45	83*		23 (18)	–	–
Our study (2011–18)	80	37	61	13	6	20 (25)	13	7

* Combined stages II and III

testicular violation which upstages the disease from T1 to T4, and it can also upstage the disease due to disturbed lymphatic channels from stage I to stages II or III. Patients referred with inadequate information on histopathology can get over- or under-treatment. Although the current guidelines prefer surveillance for pT1 to pT3 seminoma, in developing countries, single-agent carboplatin is preferred sometimes for pT2 and pT3 disease, due to compliance and financial reasons as reflected by 25 of 61 (41%) stage I seminoma patients in our study defaulting while on follow-up.

To improve the outcome and compliance to treatment, all TGCTs should be ideally treated at tertiary care centres and it requires awareness among community physicians and surgeons about testicular SGCT being a highly curable disease with adequate and timely treatment.

The strength of our study was that all patients were treated after discussion in a multidisciplinary tumour board. All patient-related information was recorded prospectively in an electronic medical database with no data loss. All patients were followed up closely and salvaged appropriately on early detection of recurrence. Patients were monitored for treatment-related long-term complications such as metabolic syndrome and intervened timely. On the contrary, the limitations of our study included a short duration of follow-up to detect late relapse in SGCTs. Many patients were lost while on follow-up, which limits estimation of RFS and OS.

Conclusions

Testicular SGCT is a rare malignancy with high cure rates. Patients should be treated in a tertiary care centre with multi-disciplinary management. In view of high cure rates, the patient should be followed up for long time for early detection of treatment-related complications such as metabolic syndrome and second malignancies. Surveillance remains a challenge in stage I tumour due to logistics and poor compliance to strict follow-up. Our study is a real-world picture of management, patient compliance and outcome of treatment in a resource-limited setting.

Conflicts of interest. None declared

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