




# Spectrum of Somatic Malignancy in Testicular Germ Cell Tumors—A Histopathological Review of 25 Cases with Clinical Outcome

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## Abstract

**Introduction** Germ cell tumors (GCTs) are the commonest testicular malignancy in young males. These tumors are highly chemoresponsive, however become resistant to conventional therapy when a somatic-type malignancy (SM) develops, which happens in ~3 to 6% of the cases.

**Methods** We reviewed the histologic profile of all cases of testicular/retroperitoneal GCT with SM, diagnosed over a period of 12 years in our institute. Correlation of histologic profile with clinical outcome was done wherever feasible.

**Results** A total of 25 cases of testicular/retroperitoneal GCT with SM were identified for review. The histological spectrum of SMs included carcinoma ( $n = 9$ ), sarcoma ( $n = 9$ ), embryonic-type neuroectodermal tumor (ENET) ( $n = 4$ ), and other rare histological types ( $n = 3$ ). SMs were frequently seen at the resected metastatic sites ( $n = 13$ ) and in postchemotherapy setting ( $n = 12$ ); 14 cases had concurrent GCT and SM at the time of diagnosis/initial resection and 9 cases presented as late relapses (more than 2 years after initial presentation). Four patients were treated with metastasectomy and lymph node dissection, six patients were treated with combined resection and chemotherapy, and nine patients were treated with only adjuvant chemotherapy. The patients with SM confined to testis and those treated with multimodality approach had relatively better outcome.

**Conclusion** GCTs with SM are a highly heterogeneous group of tumors with varying histologic types and management strategies. Strict adherence to histological diagnostic criteria, differentiating these tumors from close mimics such as glandular and sarcomatoid yolk sac tumors, teratomatous overgrowth, and a new second primary somatic tumor are important due to implications in management and prognosis.

## Keywords

- ▶ germ cell tumors
- ▶ somatic malignancy
- ▶ embryonic-type neuroectodermal tumors
- ▶ rhabdomyosarcoma
- ▶ teratomatous overgrowth

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## Introduction

Testicular tumors are rare, accounting for 1 to 2% of all tumors in males.<sup>1</sup> Germ cell tumors (GCTs) are the commonest testicular tumors (98%) in young males.<sup>2</sup> Despite being highly malignant tumors, most are amenable to chemotherapy (70–80% cure rate after first-line chemotherapy)<sup>3</sup> and hence, curable (95% 5-year survival rate).<sup>4–6</sup> About 3 to 6% of GCTs develop somatic-type malignancy (SM),<sup>7</sup> which is defined as the occurrence of a distinct component of somatic-type malignant neoplasm, as seen in other organs. The SM component may be epithelial or mesenchymal, and is diagnosed when it measures 5 mm or more with an infiltrative or expansile growth pattern.<sup>8,9</sup> Various histological types of SM have been described—sarcoma (commonly rhabdomyosarcoma [RMS]), adenocarcinoma, peripheral neuroectodermal tumor (PNET) (presently renamed embryonic-type neuroectodermal tumor [ENET] in World Health Organization [WHO] 2022), nephroblastoma, neuroblastoma, and other rare tumor types.<sup>10</sup>

SM occurs frequently in relapses and following chemotherapy but may be present at the time of initial presentation infrequently.<sup>10</sup> It is an important cause of resistance to conventional platinum-based chemotherapeutic regimens.<sup>11</sup> It confers poor prognosis when seen in metastatic sites.<sup>4</sup>

Though studies on therapeutic strategies and clinical outcome of this disease are available, literature on detailed histopathological features is limited to a few case series and multi-institutional studies. Herein, we provide a detailed review of pathological features of 25 cases of GCT with SM diagnosed at our institute.

## Methods

### Primary Outcome

To study the clinicopathological features of testicular GCT with SM.

### Secondary Outcome

To correlate the histological factors with clinical characteristics of the patients.

### Case Selection

The surgical pathology database was retrospectively searched for all cases of primary testicular/retroperitoneal GCTs with SM diagnosed over a period of 12 years (January 2011–June 2023), including in-house and referral cases. The histopathology slides and relevant immunohistochemical stains performed at the time of initial diagnosis were reviewed.

### Inclusion Criteria

Only cases confirming to the WHO diagnostic criteria for SM were included in the study (malignant nodules with infiltrative or expansile growth measuring at least 5 mm).

### Exclusion Criteria

Cases with teratomatous overgrowth and cases with scattered atypical stromal cells/small atypical epithelial cell clusters were excluded.

## Parameters Studied

For cases with unequivocal diagnosis of SM, histological type of SM was assigned as per WHO 2022 terminology. Other histological features such as presence of associated GCT components were noted. The demographic details, clinical presentation, treatment, and outcome details were collected from the institutional electronic medical records database. Histological type of SM, site, and timescale of occurrence (SM occurring concurrently with GCT at initial presentation or presentation as late relapse) were compared with clinical parameters and outcome in patients with adequate available clinical information.

## Statistical Analysis

The data collected were entered in MS Excel and the mean, percentage, and statistical analysis were performed by SPSS version 20.1.

## Ethical Statement

Institutional Ethics Committee II, Institutional Review Board, Tata Memorial Center, Mumbai. All procedures performed in this study involving human participants were in accordance with the ethical standards of the Institutional Ethics Committee II, Institutional Review Board, Tata Memorial Center, Mumbai and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

## Results

About 1,650 cases of testicular GCTs were diagnosed in the study period at our institute, of which 25 cases had developed SM (1.52%). A total of 28 cases were initially diagnosed as GCTs with SM; however, on review of histopathological features, only 25 cases met the defined criteria for SM and 3 cases were excluded (teratomatous [glandular and rhabdomyomatous] overgrowth [ $n=2$ ] and seminoma with anaplastic features [ $n=1$ ]).

## Clinical Parameters

The median age at diagnosis of SM was 31.96 years with an age range of 17 to 48 years. All patients had primary testicular GCT (24/25) except one case of primary retroperitoneal GCT (1/25). SM was detected only in primary site in 11 cases (44%) (testis  $n=10$ , retroperitoneum  $n=1$ ), only in metastatic sites in 12 cases (48%), and in both testis and retroperitoneal lymph nodes (RPLNs) in 2 cases. The metastatic sites were RPLN (10/25), left supraclavicular lymph nodes (1/25), and lung (1/25). The median age of patients with SM in primary site only was 27 and that of patients with SM in metastatic sites was 32.5 years.

About 14 cases (56%) had concurrent GCT and SM at the time of initial presentation and 9 cases (36%) presented as late relapses (at least 2 years after initial presentation). About half of the patients ( $n=12$ , 48%) had received prior chemotherapy and/or radiation therapy. The mean time to development of SM in metastatic sites from the time of primary GCT diagnosis was 3.5 years (range 0–22 years).

### Pathological Parameters

At initial presentation, 21 cases had nonseminomatous GCT (NSGCT), 2 cases had mixed GCT, 1 case had a burnt-out GCT with germ cell neoplasia in situ (GCNIS); 1 case showed only SM (ENET) in the limited sections available (sections from adjacent testis was not available for review). Concomitant GCT was noted along with SM in 19 cases; teratomatous component was present in 18/19 cases; 1 case had only yolk sac tumor (YST) (1/19); 1 case had only GCNIS. In five cases, no residual GCT component was identified at the time of diagnosis of SM, of which three cases had only core biopsy material for evaluation.

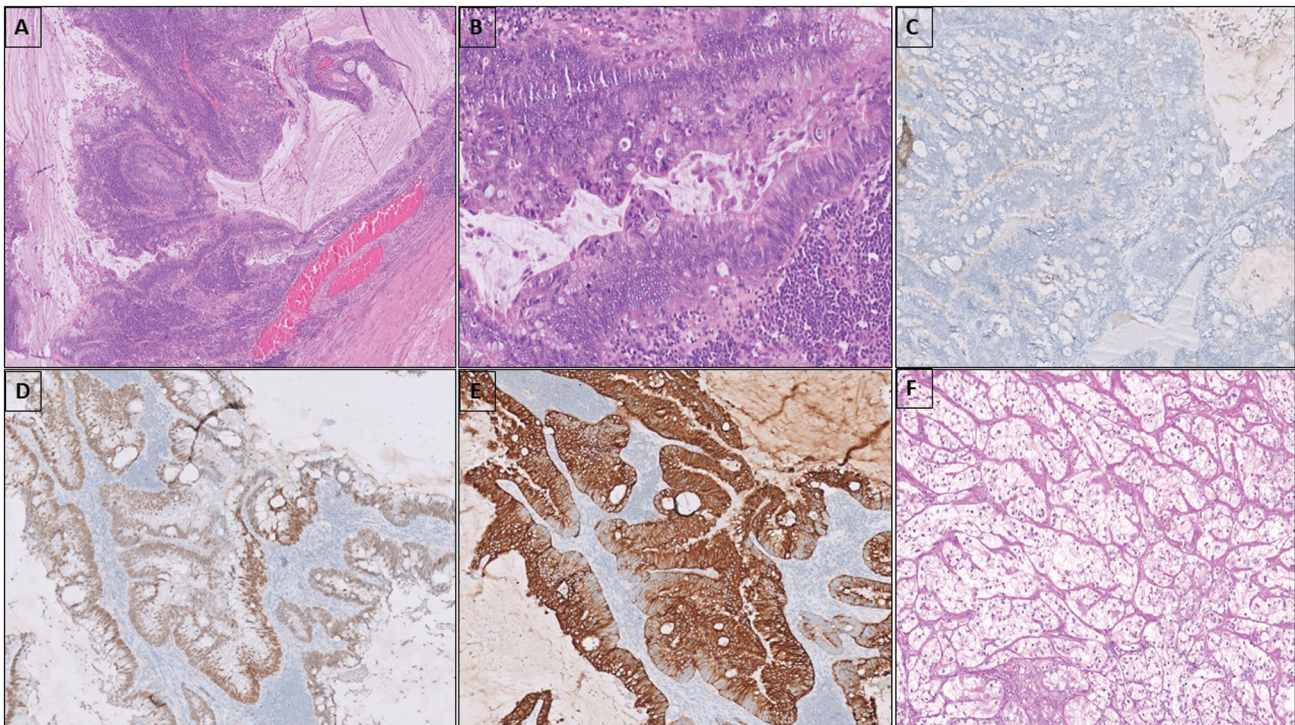
In primary site (testis/retroperitoneum), the histotypes encountered in decreasing order of frequency are sarcoma (6/11; 54.55%), ENET (2/11; 18.18%), mucinous adenocarcinoma (2/11; 18.18%), and Wilms' tumor (1/11; 9.09%). In metastatic sites, the histological types encountered in decreasing order of frequency are carcinoma (7/12; 58.33%), sarcoma (3/12; 25%), ENET (1/12; 8.33%), and desmoplastic small round cell tumor (DSRCT) (1/12; 8.33%). The two cases with presence of SM concurrently in testis and RPLN were carcinosarcoma—with adenocarcinoma and spindle cell sarcoma not otherwise specified (NOS) areas and a case of ENET with scattered SALL4-positive large cells (discussed in detail in the following section).

The histological types of SM observed were carcinoma (9/25; 36%), sarcoma (9/25; 36%), ENET (4/25; 16%), 1 case each of carcinosarcoma (1/25; 4%), Wilms' tumor (1/25; 4%), and DSRCT (1/25; 4%). Sarcoma (RMS) was the most common type of SM in testis and carcinoma (adenocarcinoma) was the most common pathology in metastatic sites. SM which

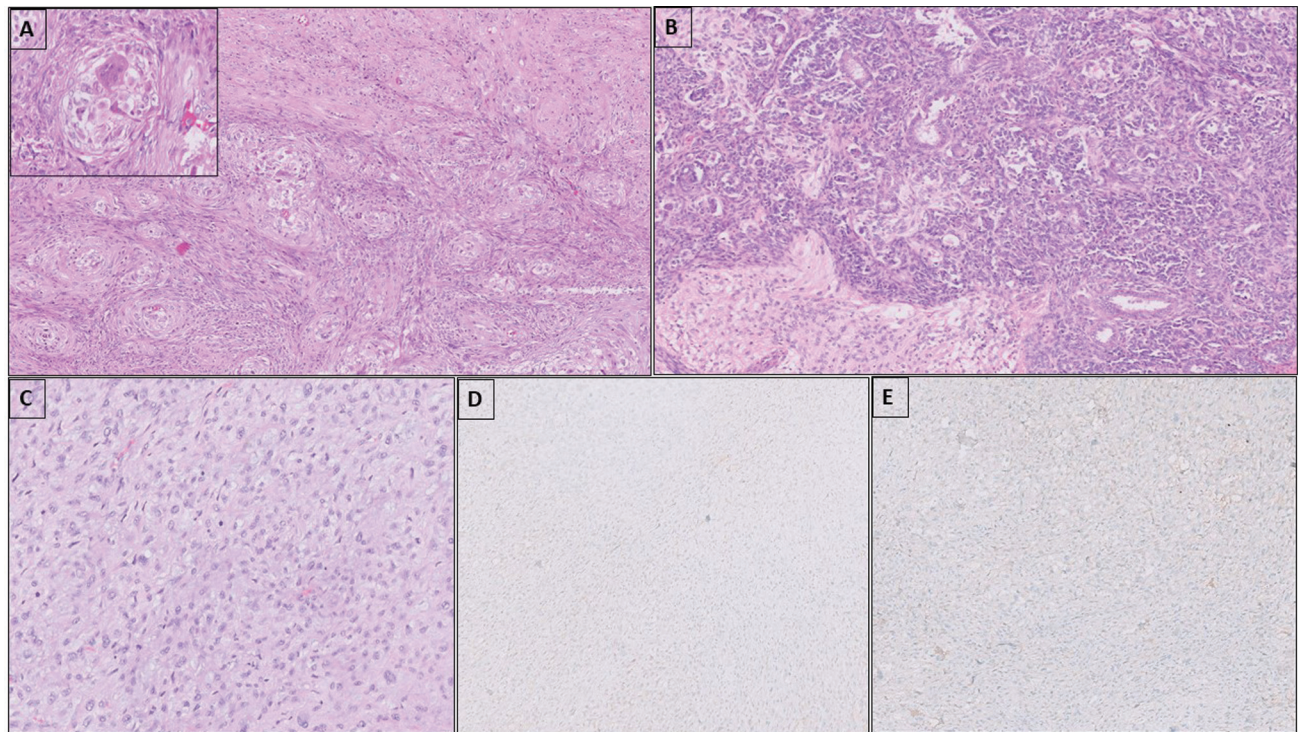
presented as late relapses were adenocarcinoma (7/9), ENET (1/4), sarcoma NOS (1/9), and RMS (1/9).

Among carcinomas, adenocarcinoma was the commonest histotype (7/9); one case had mucinous histology and remaining were adenocarcinoma, NOS (—**Fig. 1**). Two cases in this group had unusual histology—neuroendocrine carcinoma (NEC) and clear cell renal cell carcinoma (CCRCC). The tumor was present only in a small focus in RPLN and measured only 0.5 to 1 cm in both these cases. In the case of NEC, SM was detected 1 year after initial diagnosis of GCT; the tumor showed nested and pseudoglandular patterns with marked nuclear atypia and brisk mitotic activity. It was immunopositive for synaptophysin, CD56, and chromogranin while being negative for EMA, glypican 3, CD30, and cKIT. The patient was given chemotherapy (VIP regimen) and is disease free, 4 years after diagnosis. The case of CCRCC was detected 3 years after the initial diagnosis of GCT; the SM showed classical morphology of CCRCC as seen in kidney with low nuclear grade (—**Fig. 1**). The tumor cells were positive for AE1/AE3, PAX8, and CD10; negative for TFE3 and HMB45. The patient was thoroughly investigated for any occult primary in kidney and no renal mass was found on radiological evaluation. No adjuvant second-line chemotherapy was given and the patient is disease free, 5 years after diagnosis. Both these cases had residual teratomatous elements in the RPLND along with SM.

Among the sarcoma group, seven cases were RMS (7/9) and two cases were high-grade spindle cell sarcoma, NOS (2/9). All RMSs were of embryonal subtype with an appreciable number of rhabdomyoblasts; showed positivity for desmin (focal), myogenin, and/or myoD1.



**Fig. 1** Adenocarcinoma with mucinous columnar cells in glandular and papillary architecture (A). The cells show nuclear stratification and atypia with frequent mitoses (B). Tumor cells are negative for SALL4 (C), positive for SATB2 (D) and CK20 (E). The case of clear cell renal cell carcinoma composed of nests of clear cells with low nuclear grade (F).



**Fig. 2** Carcinosarcoma with nests of clear epithelioid cells and atypical spindle cells around the nests (A). Central blood vessel and multinucleated giant cell can be seen in the center of the epithelioid cell nests (inset). Teratoid Wilms' tumor with nests and sheets of blastemal cells, epithelial tubular elements, and intimately admixed mature glial tissue (B). Sarcoma, NOS with sheets of mitotically active atypical spindle cells (C); the tumor cells are negative for glypican 3 (D) and desmin (E).

The two sarcoma, NOS cases did not show any line of differentiation by immunohistochemistry (smooth muscle, skeletal muscle, and neural lineage markers were negative). The cases showed sheets and vague fascicles of spindle cells with significant nuclear atypia and frequent mitoses (**►Fig. 2**). The tumor was small in one case, measuring 0.8 cm in diameter and was confined to testis; the patient underwent RPLND and no adjuvant chemotherapy was given and patient is disease free 6 months after diagnosis. The other case presented as late relapse in RPLN had disease progression despite second-line chemotherapy.

In the ENET group ( $n = 4$ ), the tumor was confined to testis in two cases; was seen in both testis and RPLN in one case and in the other case, it was seen as a late relapse in RPLN. The tumor cells were positive for SOX11 and negative for SALL4 and YST markers; showed variable immunopositivity for synaptophysin, chromogranin, CD56, and S100. NKX2-2 and GFAP were negative in the cases tested (**►Fig. 3**). EWSR1 break-apart fluorescence in situ hybridization (FISH) was negative in one case tested for. All except one patient responded well to chemotherapy.

### Cases with Unusual Histological Features

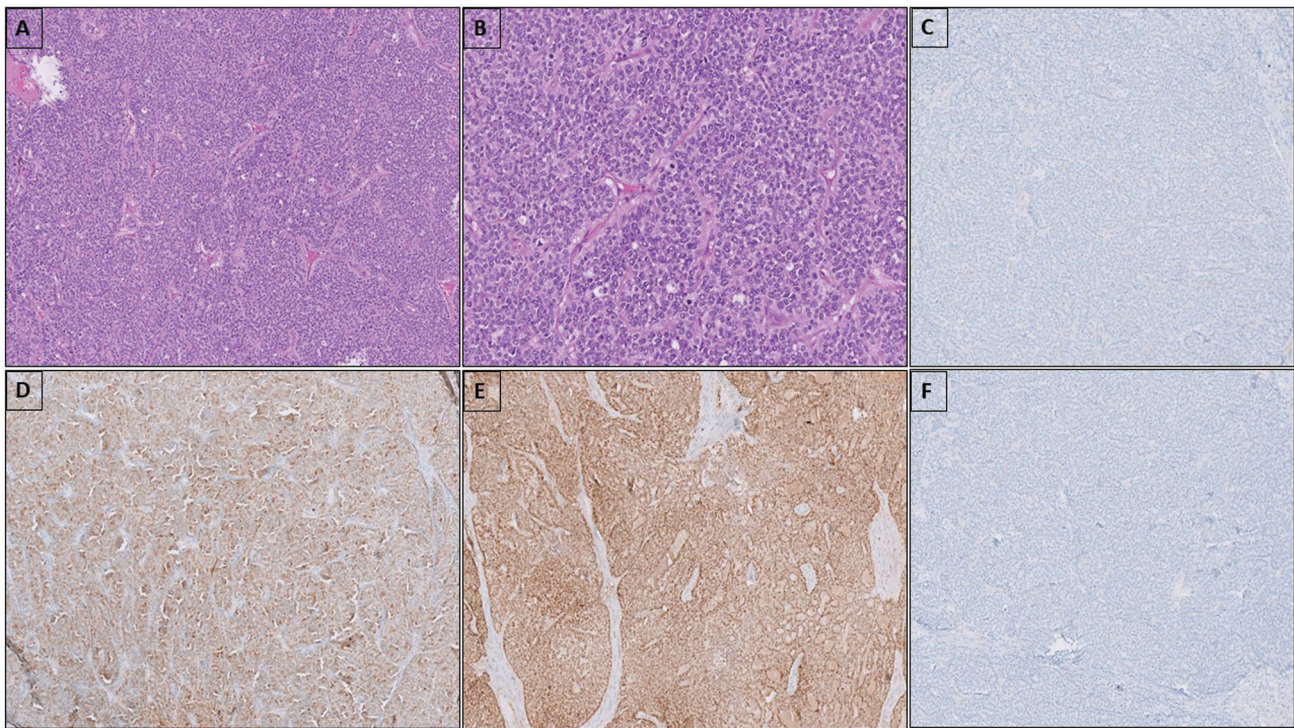
The case of carcinosarcoma showed intimately admixed epithelial and sarcomatous components, seen in primary site and RPLN. In testis, sarcomatous component was dominant, composed of sheets and vague fascicles of atypical spindle cells with frequent mitosis along with small nests of epithelial cells with clear cytoplasm. At places epithelial cells were seen condensed around thin-walled blood vessels

(**►Fig. 2**). In RPLN, epithelial component was prominent and showed features of adenocarcinoma, NOS with infiltrating, irregular angulated atypical glands. Immunostains for SALL4, OCT3/4, desmin, CD34, and inhibin were negative in both epithelial and spindle cell components. The residual GCT component present was a small focus of YST in the RPLN.

In the case of triphasic Wilms' tumor we encountered, there was intimately admixed glial elements, seen along with NSGCT elements, the SM being present at primary site at the time of initial presentation. The tumor showed a predominant blastemal component along with intermingled islands of teratoid/glial elements (mature and immature) in a neuropil-rich matrix (**►Fig. 2**).

The case of DSRCT was detected in RPLNs, 2 years following the occurrence of GCT. The tumor showed malignant round cell morphology with fibrous stroma and a polyphenotypic immunoprofile. The tumor cells were immunopositive for AE1/AE3, desmin, WT1, synaptophysin, MIC-2, and FLI1. Reverse transcriptase polymerase chain reaction for EWSR1-WT1 and EWSR1-FLI1 gene fusions, both were negative.

An intriguing histological finding we observed in a case of ENET was presence of singly scattered large cells with prominent nuclei amidst malignant round blue cells. The smaller cells were positive for synaptophysin, SALL4, and NKX2.2, and negative for desmin, myogenin, calretinin, and D2-40; the scattered large cells were positive for SALL4, D2-40, and OCT3/4. The tumor had mature teratomatous elements and GCNIS was noted in the adjacent testicular parenchyma. There was no seminoma/YST components.



**Fig. 3** Embryonic-type neuroectodermal tumor composed of sheets and nests of monomorphic round cells with scant cytoplasm and fine granular chromatin (A, B). Tumor cells are negative for NKX2-2 (C), diffusely positive for S100 (D) and SOX11 (E). Staining for OCT 3/4 is negative (F).

This unusual occurrence of admixed large cells in ENET has not been observed previously, to the best of our knowledge. Considering their immunophenotype we could best regard these cells to be entrapped GCNIS cells.

### Outcome Details

Clinical follow-up details were available for 19 patients, 18 patients were alive and 1 was deceased, with mean follow-up duration being 4.88 years (range 0.5–17 years).

Treatment details following the diagnosis of SM were available for 20 patients; 9 patients received only chemotherapy; 5 patients underwent surgical and medical (chemotherapy) management; 4 patients underwent surgical management only; 1 patient was treated with combined chemotherapy and radiotherapy; 1 patient received chemotherapy, radiotherapy, and surgery.

One patient died of surgical complications (post-RPLND) and all other patients were alive for the available follow-up period. Nine patients were disease free and asymptomatic; four patients did not respond well to second-line chemotherapy and had been put on palliative intent management, one patient had stable residual disease after treatment and was being followed up, and four patients had not completed treatment at the time of last follow-up.

Among the patients who had disease progression after second-line therapy (4/19), two were sarcoma (2/4), one DSRCT (1/4), and one ENET (1/4). Other than the testicular ENET, three cases had SM at metastatic sites.

Among the patients treated with surgical resection alone ( $n=4$ ) or combined surgical resection and chemotherapy/radiotherapy ( $n=7$ ), most showed good response to treatment

(8/11) and were disease free; two patients (DSRCT and RMS; both detected in metastatic sites) developed progressive disease despite multimodality management and one patient (RMS detected in RPLN) died due to surgery-related complications. Among the patients treated only with chemotherapy ( $n=9$ ), two patients developed progressive disease (sarcoma NOS and ENET with large cells) and one patient had residual disease (adenocarcinoma) after the completion of chemotherapy; three patients are yet to complete the chemotherapy course; two patients were disease free after the completion of treatment; outcome details are not available for a patient.

### Discussion

Occurrence of SMs in GCT was described as early as 1946 and included in WHO 2004 under the term “teratoma with somatic-type malignancy”; later renamed “GCTs with somatic type malignancy.”<sup>12</sup> SM is believed to arise from pluripotent germ cells or malignant transformation of teratomatous/yolk-sac elements. Some studies have reported occurrence of SM after chemotherapy, which may be due to its DNA damaging effect.<sup>10,13</sup> Pathogenetically, SMs retain the characteristic molecular abnormality, isochromosome 12p seen in postpubertal-type GCTs which can be detected as 12p amplification by FISH.<sup>7</sup>

SMs are most frequently encountered in metastatic sites as primary treatment failure or late disease relapses.<sup>14,15</sup> This finding was reiterated in our study as in nearly 56% of cases SM was seen in metastatic sites and more than half of the patients had received prior chemotherapy. The overall prevalence of SM was less in our cohort than the 3 to 6%

prevalence observed in most other studies. More cases were identified in the past 5 years in our cohort (17/25), probably due to better understanding of this entity and clearer diagnostic criteria. The histological spectrum of SM described in GCT is diverse (sarcomas, carcinomas of various phenotypes, PNET, glial tumors, and nephroblastomas), sarcomas being the commonest in most series (63%).<sup>5</sup> In our series, we observed an equal occurrence of carcinoma and sarcoma with the next frequent being ENET; some rare tumor types such as nephroblastoma, CCRCC, carcinosarcoma, DSRCT, and neuroendocrine carcinoma were also encountered.

We observed carcinomas more frequently in metastatic sites as late relapses, the commonest type being adenocarcinoma, similar to the observation in various studies.<sup>16</sup> The CCRCC and neuroendocrine carcinoma cases we encountered have been not or only sparsely described in literature, respectively. There has been a single report of papillary renal cell carcinoma arising as SM in RPLNs and no other additional renal tumor types have been described previously.<sup>12,17</sup> Both these tumors were present only in a small focus in our cases, measuring <1 cm and did not progress.

The commonest type of sarcoma in our series was embryonal RMS, as reported in studies previously. During the initial screening, we found two cases of rhabdomyomatous overgrowth misdiagnosed as RMS. Rhabdomyomatous overgrowth has been described following chemotherapy and is composed of sheets of maturing skeletal muscle cells without any malignant round cell areas, necrosis, or apoptosis. Hence, detecting immature rhabdomyoblasts or embryonal areas is needed to ascertain a diagnosis of RMS as a SM. In our study, among the RMS group, all except one case showed good response to chemotherapy, with disease-free interval of 1 to 57 months.

The sarcoma, NOS cases did not show any line of differentiation by immunohistochemistry. The closest differential to be considered in such cases is sarcomatoid YST. The sarcomatoid areas in YST can be low or high grade,<sup>18</sup> usually show foci with epithelioid pattern and are immunopositive for SALL4 and glypican 3. Sarcomatoid YST is resistant to platinum-based chemotherapy and has an aggressive clinical course, much like GCT with SM.<sup>14</sup>

The so-called testicular PNETs are distinct from the PNET/Ewings sarcoma of bone and soft tissue. The testicular PNETs are negative for FLI1 and CD99; do not show EWSR1 gene rearrangements, a hallmark of PNET. These tumors are generally confined to testis, frequently contain areas resembling medulloepithelioma, medulloblastoma, and a range of neuroglial tumors.<sup>14,19</sup> Therefore, these tumors are considered to represent “central” rather than peripheral-type neuroectodermal tumors and have been renamed ENET in the WHO fifth edition.<sup>8,20</sup> ENETs when confined to testis are increasingly being recognized to have better outcome. In comparison, metastatic ENET may have a poorer outcome, as seen in one of our cases which progressed despite second-line chemotherapy.

One of our cases was diagnosed as DSRCT based on histological and immunohistochemical features, although molecular findings were not supportive. Occurrence of this tumor as a SM has not been described previously.

Most of the SMs are consistently associated with teratoma, hence the need to carefully distinguish these tumors from immature teratomatous elements, benign teratomatous overgrowth, and teratomas showing nuclear atypia. Teratomatous overgrowth and atypia in stromal cells are well known to occur after chemotherapy. Any form of teratomatous overgrowth can mimic disease progression, presenting with increasing size of the mass clinically; however, it does not behave in a malignant fashion. In our review, two cases initially misdiagnosed as SM were reclassified as teratomatous overgrowth after histological review.

As somatic malignant transformation is common in metastatic sites and can present as late relapses,<sup>16</sup> metastasis from a new primary nongerml cell neoplasm becomes a diagnostic consideration. In such instances, young age of the patient, prior history of GCT, presence of 12p gain, and absence of primary tumor after systematic evaluation points to a diagnosis of SM.<sup>5</sup>

The various histotypes of SM and relevant clinical parameters described in the literature with significant case numbers are summarized in ►Table 1. In most studies, poor clinical outcome of GCT with SM was observed only when SM involved metastatic sites.<sup>14</sup> In our series too, most of the patients with SM confined to testis had better outcome with only one patient found to have residual disease posttreatment. Also, some studies have questioned the strict size-based diagnostic criteria for SM, as a case with small focus of ENET (not meeting the 5 mm criteria) presented later with widespread disease.<sup>7</sup> In our series, three cases which had SM occupying less than 1 cm area in slide showed a good outcome, despite the aggressive histological type (neuroendocrine carcinoma, CCRCC, and high-grade sarcoma).

Owing to the rarity of these tumors, the current management strategy is very heterogeneous and the decision is on a case-to-case basis. Most large series suggest combining surgical resection with some form of adjuvant chemotherapy decided based on histotype of SM for a sustained response. With the current ease of availability of molecular testing strategies, SMs are being found to harbor mutations in genes such as TP53, RAS which are not usually seen in GCT. Hence, the role of tumor specific (SM type specific) targeted therapy approaches may be evaluated for a possible clinical benefit in this rare disease entity.<sup>7</sup>

## Conclusion

SMs arising in testicular GCT are a rare, heterogeneous group of tumors histologically, with varying clinical outcomes. SMs arising in metastatic sites and those presenting as late

**Table 1** Comparison of histological and clinical features among the various studies on SM in the literature

	Our study	Magers et al (2014) <sup>5</sup>	Lobo et al (2022) <sup>7</sup>	Hwang et al (2022) <sup>4</sup>	Scheckel et al (2019) <sup>21</sup>	Sharma et al (2019) <sup>10</sup>
Study overview	Morphology, immunophenotype and outcome	Morphology and immunophenotype	Histological spectrum and molecular features	Histological type and clinical outcome	Management and clinical outcome	Management and clinical outcome
Study period	12 y	23 y, single institution	16 y, two institutions	15 y, single institution	35 y, single institution	18 y, single institution
Number of cases	25	124 cases of testicular GCT (excluded PNET and Wilms) 84 histologically confirmed as SM after IHCs	30 (testicular and primary retroperitoneal GCT)	63 (excluded sarcomatoid YST)	24 (testicular, mediastinal and pineal)	30
No. of cases with SM in testis	13	4	14	22	2	-
No. of cases with SM in metastatic sites	14	-	22	41	22	-
Presence of associated GCT	All except two (one showed only GCNIS and other showed only ENET)	Initial diagnosis of GCT known in 50% patients	Initial diagnosis of GCT established in all cases	All except one case of ENET	-	-
Concomitant initial presentation of SM with GCT	14	7 cases	14 (5 were ENET)	-	12	9
H/O chemotherapy and/or radiation therapy before SM	9	83%	15	35		21
Carcinoma	9 (adenocarcinoma, clear cell RCC, neuroendocrine carcinoma)	44 (adenocarcinoma, carcinoma NOS and sarcomatoid carcinoma)	11 (including papillary RCC, neuroendocrine carcinoma)	21 (adenocarcinoma, carcinoma NOS, neuroendocrine carcinoma)	12 (adenocarcinomas)	3
Sarcoma	9 (RMS, sarcoma NOS)	39 cases (RMS, myxofibrosarcoma, sarcoma NOS, UPS, LMS, OGS, gliosarcoma)	6	21 (RMS, angiosarcoma, sarcoma NOS)	12 (RMS and sarcoma, NOS)	16
ENET	4 (one with scattered SALL4-positive large cells)	-	8	15	-	10

(Continued)

Table 1 (Continued)

	Our study	Magers et al (2014) <sup>5</sup>	Lobo et al (2022) <sup>7</sup>	Hwang et al (2022) <sup>4</sup>	Scheckel et al (2019) <sup>21</sup>	Sharma et al (2019) <sup>10</sup>
Other rare tumor types	Two cases of carcinosarcoma, one case of DSRCT	High-grade glioma	Neuroblastoma, low-grade glial tumor	Nephroblastoma, mixed RMS, and small cell carcinoma	-	Nephroblastoma
IHC	Relevant markers pertaining to histotype	Reclassification of 37 cases as glandular/sarcomatoid YST	-	NA	-	-
Commonest histological type in metastatic sites	Carcinoma	-	Adenocarcinoma	Carcinoma	-	-
Molecular studies	-	NA	12p FISH, EWSR1 rearrangement in ENET	NA	-	-
Clinical outcome	Carcinoma frequent in late relapses, ENET and sarcoma frequent at initial presentation; SM at metastasis—poor outcome; small SM size (<1 cm) had good outcome; those treated with both surgery and chemotherapy had better outcome	Sarcomatoid SM more aggressive than glandular SM	Late relapse, high-grade sarcomatous SM, ENET, extragonadal primary predictive of poor outcome	Poor survival in metastatic SM group and carcinoma histological type	Carcinomas had better overall survival compared with sarcoma group	Late relapse had poor outcome

Abbreviations: DSRCT, desmoplastic small round cell tumor; ENET, embryonic-type neuroectodermal tumor; FISH, fluorescence in situ hybridization; GCNIS, germ cell neoplasia in situ; CCT, germ cell tumor; H/O, history of; IHC, immunohistochemistry; LMS, leiomyosarcoma; NA, not available; NOS, not otherwise specified; OGS, osteosarcoma; PNET, peripheral neuroectodermal tumor; RCC, renal cell carcinoma; RMS, rhabdomyosarcoma; SM, somatic-type malignancy; UPS, undifferentiated pleomorphic sarcoma; YST, yolk sac tumor.



relapses show relatively poor outcome. Small tumors (<1 cm) had favorable clinical outcome even without adjuvant chemotherapy. Differentiating GCT with SM from sarcomatoid or glandular YSTs, new independent somatic tumors, teratomatous overgrowth, and reactive stromal atypia postchemotherapy in teratoma has important clinical implications. Though standard therapeutic modalities are not described, multimodal management may have a better outcome.

#### Ethics

Ethical clearance was obtained from the institutional ethics committee (IEC-II Tata Memorial Center—IEC project number 4294/06.12.2023) and the study was performed in accordance with the ethical standards of our IEC and 1964 Declaration of Helsinki and its later amendments. Waiver of consent was obtained from the IEC.

#### Institutional Ethics Committee Approval Status of the Study

Approved.

#### Funding

None.

#### Conflict of Interest

None declared.

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