Malignant sacrococcygeal germ cell tumors in childhood: The Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) experience

Paolo D'Angelo¹ | Maria Debora De Pasquale² | Francesco Barretta³ |
Maria Carmen Affinita⁴ | Massimo Conte⁵ | Patrizia Dall'Igna⁶ | Andrea Di
Cataldo⁷ | Alessandro Inserra⁸ | Massimo Provenzi⁹ | Lucia Quaglietta¹⁰ |
Giovanna Riccipetitioni¹¹ | Filippo Spreafico¹² | Angela Trizzino¹ |
Monica Terenziani¹² | for the AIEOP MGCT Working Group

¹ Pediatric Hematology and Oncology Unit, ARNAS "Civico, Di Cristina and Benfratelli" Hospitals, Palermo, Italy

² Pediatric Hematology and Oncology Department, Ospedale Pediatrico Bambino Gesù IRCCS, Rome, Italy

³ Unit of Clinical Epidemiology and Trial Organization, Fondazione IRCCS Istituto Nazionale dei Tumori di Milan, Milan, Italy

⁴ Hematology/Oncology Division, Department of Women's and Children's Health, University of Padua, Padua, Italy

⁵ Department of Hematology and Oncology, Istituto G. Gaslini, Genoa, Italy

⁶ Pediatric Surgery Division, Department of Women's and Children's Health, University of Padua, Padua, Italy

⁷ Pediatric Hematology and Oncology Unit, Catania University, Catania, Italy

⁸ Pediatric Surgery Unit, Ospedale Pediatrico Bambino Gesù, Rome, Italy

⁹ Pediatric Hematology and Oncology Unit, Papa Giovanni XXIII Hospital, Bergamo, Italy

¹⁰ Pediatric Oncology Unit, Santobono-Pausilipon Hospitals, Naples, Italy

¹¹ Department of Pediatric Surgery, "Buzzi" Children Hospital, Milan, Italy

¹² Pediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy

Correspondence

Paolo D'Angelo, Unità Operativa di Oncoematologia Pediatrica, A.R.N.A.S. Civico, Di Cristina e Benfratelli, Piazza Nicola Leotta, 4, 90127 Palermo, Italy.

Email: oncoematoped@arnascivico.it

Abstract

Purpose: To evaluate clinical features at diagnosis, prognostic factors, and outcomes of malignant sacrococcygeal germ cell tumors (SC-GCTs) in patients enrolled in the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) TCG 2004 protocol.

Patients and Methods: A prospective analysis was conducted on all consecutive patients diagnosed with malignant SC-GCTs between January 2004 and May 2017. Patients with stage I underwent surgery and subsequent surveillance, the others received pediatric cisplatin-etoposide-bleomycin (pPEB) regimen and eventual deferred surgery.

Results: Of 45 patients, 35 were females. Age at diagnosis ranged from 1 day to 3.6 years (median 1.6 years); 26 were stage IV. Of 38 patients who underwent surgery, pathology revealed yolk sac tumor (YST) in 27 and teratoma + YST/embryonal carcinoma in 11, while seven patients were diagnosed based on imaging and elevated levels

Abbreviations: AFP, alpha-fetoprotein; AIEOP, Associazione Italiana di Ematologia e Oncologia Pediatrica; CI, confidence interval; COG, Children's Oncology Group; CR, complete remission; EC, embryonal carcinoma; EFS, event-free survival; GCTs, germ cell tumors; IT, immature teratoma; LDH, lactate dehydrogenase; MT, mature teratoma; OS, overall survival; PD, progressive disease; pPEB, pediatric cisplatin-etoposide-bleomycin; PR, partial remission; SC-GCTs, sacrococcygeal germ cell tumors; YST, yolk sac tumor; β -hCG, beta-human chorionic gonadotropin

of alpha-fetoprotein (AFP). Of six patients approached with surgery, only one relapsed and was rescued with first-line chemotherapy. Overall, 38 out of 45 achieved complete remission, three a partial remission, and four were resistant. Ten out of 41 patients who entered remission later relapsed and nine were rescued with a second-line treatment. We observed a global failure percentage of 31% and a 5-year overall survival (OS) and event-free survival (EFS) of 95% and 69%, respectively.

Conclusions: Chemotherapy is generally effective in malignant SC-GCTs, even though almost one-third of our patients experienced events salvageable with second-line treatment. Most of the relapses occurred within 1 year from diagnosis. A close follow up with serial AFP level monitoring should be done for at least 2 years after diagnosis.

KEYWORDS

childhood, malignant neoplasms, prognostic factors, sacrococcygeal germ cell tumors

1 | INTRODUCTION

Pediatric germ cell tumors (GCTs) are rare neoplasms derived from primordial germ cells, and may arise from the gonads or extragonadal organs. They account for about 3% of all childhood malignancies, and typically have a bimodal age distribution, with a peak before 3 years of age and a second peak during adolescence.^{1,2} Extragonadal tumors are typically distributed along the midline, suggesting that these tumors arise from the abnormal migration of primordial germ cells from the allantois to the genital crest. The most common site of extragonadal GCTs in childhood is the sacrococcygeal region, followed by the anterior mediastinum, intracranial region, retroperitoneum, neck, and vagina-uterus.² The most common histology of sacrococcygeal GCTs (SC-GCTs) is teratoma, which generally are benign; the most common malignant histology is yolk sac tumor (YST) often admixed with teratoma.¹⁻³ The introduction of platinum-based chemotherapy dramatically improved the prognosis for these patients.⁴⁻⁷ We present clinical features at diagnosis, prognostic factors, and outcomes of malignant SC-GCTs enrolled in the second Italian protocol Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) TCG 2004.

2 | MATERIALS AND METHODS

The TCG 2004 is a prospective trial conducted at 17 AIEOP centers from January 2004 to May 2017. AIEOP is a cooperative network that brings together all pediatric hematology and oncology centers in Italy. Only 13 centers enrolled cases of malignant SC-GCTs and four of these registered only one patient. The eligibility criteria were: age less than 18 years, informed consent, histological diagnosis of extracranial malignant GCT, histological diagnosis of teratoma (mature and/or immature), but with pathologic values of alpha-fetoprotein (AFP) and/or beta-human chorionic gonadotropin (β -hCG), confirming the presence of malignant tissue foci and/or with metastatic localizations and/or with

carcinomatous or sarcomatous malignant tissue component histologically proven and with pathologic values of AFP and/or β -hCG.

All patients diagnosed with malignant SC-GCTs enrolled in the AIEOP TCG 2004 protocol were included in this study. The protocol was approved by the local ethical committees, and informed consent according to institutional guidelines was obtained for all patients and their guardian(s). Demographic and the clinical-pathological characteristics of patients, including sex, age, tumor size (<9 cm, >9 cm) at diagnosis, staging,⁸ the site of metastasis, the time of surgery (deferred, not deferred), histology, serum levels of AFP, β -hCG, and lactate dehydrogenase (LDH), distinguishing between normal and pathologic, and treatment data were collected.

2.1 | Evaluation at diagnosis

Initial medical evaluation included medical history, physical examination, complete blood count with differential, urinalysis, electrolytes, creatinine, bilirubin, AST, ALT, alkaline phosphatase, total protein, albumin, and measurement of serum levels of LDH, AFP, and β -hCG. Diagnostic imaging evaluation included ultrasonographic scan (US), and computed tomography (CT) or magnetic resonance imaging (MRI), according to local availability. Initial disease extension was assessed in all patients by US and CT or MRI scan of the pelvis and SC region, a bone scan (omitted in the case of newborns and in all cases where other instrumental investigations indicated there were no injuries to the skeleton), and a chest CT to detect bone and lung metastases. Brain CT scans or MRIs were performed in the presence of neurological symptoms.

2.2 | Treatment and follow up

Upfront surgery was considered (biopsy in the case of a very large nonsecreting tumor, excision in the case of a tumor considered as

completely resectable without mutilating surgery), or after chemotherapy in order to remove all residual tumor, preferably after normalization of serum markers. Surgical recommendations included complete excision of the tumor without rupture and/or spillage of tumor cells on the tumor bed, and coccygeal excision, which is considered worldwide to be a key step of the surgical protocol to avoid recurrence. As staging system, the Children's Oncology Group (COG) classification was adopted.⁸ Centralized pathology review was suggested, but was not mandatory.

Subsequent treatments depended on the disease stage: patients with stage I disease and with tumor markers returning to normal level underwent surveillance alone. The others were treated with a pediatric cisplatin-etoposide-bleomycin (pPEB) regimen, consisting of cisplatin 25 mg/m² daily on days 1-4, etoposide 100 mg/m² daily on days 1-4, and bleomycin 15 mg/m² on day 2, once per cycle.⁹

2.3 | Response evaluation

The measurement of serum tumor markers and LDH was recommended after every course, and US or CT/MRI were performed after the second course. CT or MRI scans of the primary site, chest CT scans, and bone scans were repeated after the fourth course, at the suspension of treatment, according to the diagnosis. Response criteria were as reported elsewhere.⁹ The normalization of serum markers and the disappearance of tumor lesions on CT or MRI were classified as a complete remission (CR). Patients with negative imaging and lower tumor markers, or with imaging abnormalities at the primary tumor/regional sites and declining/normalizing tumor markers, were classified as partial remissions (PR). Patients with a greater than 25% increase in tumor size, new lesions, and rising tumor markers were classified as progressive disease (PD). Patients with PR and residual tumor underwent surgical exploration and subsequent postoperative assessments, and therapy depended on histological findings, which were classified as fibronectrotic tissue, residual teratoma, and viable malignant cells.

2.4 | Subsequent follow up

Patients were followed up with abdominal ultrasound and chest X-rays, clinical examinations, and AFP and β -hCG assay every 2 months in the first year after completing any treatment, every 3 months in the second year, then 6 monthly until the fifth year. After the fifth year, follow up was at the discretion of the local center.

2.5 | Statistical analysis

The principal end-points of the study were overall survival (OS) and event-free survival (EFS) probabilities. OS was defined as the time elapsing from diagnosis to death from any cause. Time was censored at the last follow up for patients still alive. EFS was defined as the time elapsing from diagnosis to any event (refractory disease, recurrence,

growing teratoma syndrome, or death, whichever occurred first). Time was censored at the last follow up for patients still alive and event-free. The OS and EFS curves were estimated using the Kaplan-Meier method. Univariable Cox models were performed to assess the association between the EFS and the principal "a priori" selected prognostic variables including sex, age (modeled as restricted cubic spline to obtain flexible fit),¹⁰ stage (IV vs II-III), bone metastases with or without other metastasis (yes, no), histology (YST only, YST + other), completeness of surgery (excision, biopsy, not done), tumor size (<9 cm, ≥ 9 cm), serum levels of AFP at diagnosis (pathological vs normal), and deferred surgery (yes, no). The median follow up was estimated with the reverse Kaplan-Meier method on OS data.

3 | RESULTS

A total of 45 patients with SC-GCTs were included in this study. In Table 1, we present the demographic characteristics of the study population. Females were predominant (78%). The median follow up was 7.4 years (interquartile range 5.1-11.3 years). Age at diagnosis ranged from 1 day to 3.6 years (median 1.6 years); most patients presented advanced stages with 24% in stage III and 58% in stage IV, and the lung was by far the most affected distant organ. Thirty-eight underwent surgery at diagnosis: biopsy in 26 and tumor resection (complete in two) in 12 children. For seven patients, diagnosis was based on imaging and the elevated serum level of AFP. Pathology revealed pure YST in 27, mature teratoma (MT) + multiple foci of YST in five, immature teratoma (IT) grade 2 or 3 in five (with multiple foci of YST in four and microfoci in one), and mixed tumor, YST/MT (10%)/embryonal carcinoma (EC) in one patient only, aged 1.6 years. Thirteen patients showed neurological signs or symptoms at the beginning, all with loss of sphincteric control, linked with paraparesis in three of them. Elevated serum levels of AFP and β -hCG were found in 40 and five children (all newborns), respectively: this last finding may be due to the physiological β -hCG maternal circulation, since it was always linked to the neonatal age, and the only patient with an EC component showed normal values. LDH serum levels resulted pathologic in 33, normal in nine, and were not evaluated in three (Table 2). Overall, seven patients had an age of less than 3 months at diagnosis. Six of them (five newborns and one 40-day-old girl with multiple malformations), of which two were stage I and four were stage II or III, were approached with surgery only, and these cases are summarized in Table 3. Despite the incompleteness of the resection in four of them, only one relapsed (patient 25). She underwent excision of a large primary tumor mass (15 × 12 × 10 cm) on her second day of life, with minor tumor rupture and bleeding, and grade 3 IT/YST histology was identified; she relapsed locally (with a rise in AFP serum levels) 14 months after surgery, and was rescued with first-line chemotherapy (four courses of pPEB) and subsequent complete resection. Only one newborn of the series underwent chemotherapy after a microscopically incomplete surgery in two steps. The first surgical procedure of incomplete excision of the mass en bloc with coccygectomy was conducted when she was 2 days old; histology revealed a mixed tumor composed of MT and 30% of YST; the second excision was

TABLE 1 Demographic and clinical-pathological characteristics

	N = 45
Sex, n (%)	
Female	35 (78)
Male	10 (22)
Age at diagnosis, years	
Median (IQR)	1.6 (1.0-2.0)
Neurological signs or symptoms at diagnosis, n (%)	
Loss of the sphincter control	10 (22)
Loss of the sphincter control and paraparesis	3 (7)
None	32 (71)
AFP serum level at Dx, n (%)	
High	40 (89)
Normal	5 (11)
β-hCG serum level at Dx, n (%)	
High	5 (11)
Normal	38 (84)
Not done	2 (5)
LDH serum level at Dx, n (%)	
High	33 (73)
Normal	9 (20)
Not done	3 (7)
Tumor size at Dx (max diameter), n (%)	
<9 cm	30 (67)
$\geq$ 9 cm	14 (31)
NA	1 (2)
Staging, n (%)	
I	2 (4)
II	6 (13)
III	11 (24)
IV	26 (58)
Site of metastases, n (%)^a	
Lung	23 (51)
Liver	7 (16)
Bone	6 (13)
Timing of surgery, n (%)	
Deferred	34 (76)
Not deferred	11 (24)
Completeness of surgery, n (%)	
Complete excision	2 (4)
Incomplete excision	10 (22)
Biopsy only	26 (58)
Not done	7 (16)

(Continues)

TABLE 1 (Continued)

	N = 45
Histology, n (%)^b	
YST only	27 (71)
YST + other	11 (29)

Abbreviations: AFP, alpha-fetoprotein; Dx, diagnosis; EC, embryonal carcinoma.; IQR, interquartile range; LDH, lactate dehydrogenase; NA, not available; YST, yolk sac tumor; β -hCG, beta-human chorionic gonadotropin.

^aEach percentage was calculated on the whole population of patients (many of them showed combined metastases).

^bOn 38 available patient data only.

performed to remove the pelvic residual mass when she was 2 months old, and chemotherapy with four courses of pPEB then completed her treatment. All seven patients aged <3 months at diagnosis are in CR, six in first and one in second continuous CR.

Overall, 39 out of 45 (87%) patients underwent chemotherapy and four suffered from disease progression. A good response to chemotherapy was achieved in 35 patients (CR or PR), 31 of which underwent deferred surgery. Globally, thirty-seven patients entered CR (two of them with surgery only), four obtained PR (and achieved CR through deferred surgery), and four were nonresponders. Of these four nonresponders, the first one aged 2 years, YST, stage III for lymph nodes and peritoneal involvement, showed local progression, an increase in AFP levels, and multiple central nervous system metastases; a second-line treatment according to the ICE regimen¹¹ proved ineffective and she died of PD 6 months after the diagnosis. The second one, aged 2.7 years at diagnosis, YST, stage IV for bilateral lung metastases, which showed local and marker-related progression after three courses of pPEB, received a second-line therapy and obtained a second continuous CR; unfortunately she died due to a fatal ventricular arrhythmia, following a heart transplant, performed because of heart failure, more than 10 years after the discontinuation of antitubercular treatment. The third nonresponder patient, YST, stage IV for liver metastases, showed local progression and an increase in serum marker levels. She underwent deferred surgery (resection of the primary en bloc with coccigectomy) and shifted to second-line chemotherapy according to the ICE schedule, which enabled a second continuous CR. The fourth patient, YST, stage IV for liver, bone, and lung metastases, showed a mixed response of the primary and metastatic disease and an increase of AFP serum levels after four courses, and was rescued with two courses of ICE, surgery, and subsequent high-dose chemotherapy (HDCT) and autologous peripheral blood stem cells transplant (PBSCT).

Of 40 patients with abnormal AFP at diagnosis, 35 showed a complete normalization, two a partial reduction, and three an increase of serum level.

Overall, of 41 patients entering a remission status (six infants with surgery only), 10 (24%) relapsed: nine with localized recurrence (one combined with bone metastases) and one with exclusively metastatic spread, and all of them showed increasing serum levels of AFP (Table 4). One was the already mentioned newborn that, following the local relapse and marker increase (14 months after surgery), received four

TABLE 2 Marker levels measured in the whole series

Patient number	Age at Diagnosis (years)	AFP serum level presurgery (ng/mL)	Surgery	AFP serum level postsurgery (ng/mL)	Beta-hCG serum level at diagnosis (IU/mL)	LDH serum level at diagnosis (IU/L)
1	2.0	80 514	Biopsy	NA	Normal	1241
2	0.9	39 997	Biopsy	NA	Normal	1164
3	1.4	106 877	Biopsy	NA	Normal	1363
4	0.8	71 000	No	NA	Normal	1205
5	1.8	42 270	Biopsy	NA	Normal	1732
6	2.5	28 723	Biopsy	NA	Normal	Normal
7	2.0	>50 000	No	NA	Normal	1062
8	1.4	133 770	Incomplete excision	325	Normal	730
9	1.8	141 847	Biopsy	NA	Normal	704
10	2.0	20 000	Biopsy	NA	Normal	Normal
11	1.9	74 540	Biopsy	NA	Normal	1194
12	1.1	65 180	Biopsy	NA	Normal	Normal
13	1.5	262 140	No	NA	Normal	Normal
14	1.2	114 619	Biopsy	NA	Normal	Normal
15	2.2	61 670	No	NA	Normal	Normal
16	1.7	138 951	No	NA	Normal	699
17	1.7	>150 000	Biopsy	NA	Nd	Nd
18	0.9	20 239	Biopsy	NA	Normal	1435
19	1.6	35 160	Biopsy	NA	Normal	940
20	0.0	75 700 ^a	Incomplete excision	7447	23	872
21	1.3	75 000	Biopsy	NA	Normal	930
22	1.7	351	Incomplete excision	337	Normal	491
23	1.6	86 764	Biopsy	NA	Normal	591
24	1.7	49 600	Biopsy	NA	Normal	1166
25	0.0	91 167 ^a	Incomplete excision	2131	106	1014
26	0.0	154 598	Incomplete excision	1584	45	630
27	1.1	187 890	Biopsy	NA	Normal	689
28	1.5	3754	Incomplete excision	283	Normal	1003
29	0.1	563 ^a	Complete excision	115	Normal	900
30	3.3	24 000	Biopsy	NA	Normal	900
31	0.0	6936 ^a	Complete excision	937	Normal	1436
32	1.0	204 131	Biopsy	NA	Normal	1066
33	0.7	37 323	Incomplete excision	2200	Nd	Nd
34	3.6	17 208	Biopsy	NA	Normal	Normal
35	1.5	167 400	Biopsy	NA	Normal	Normal
36	1.8	53 950	Biopsy	NA	Normal	705
37	2.3	60 500	No	NA	Normal	691
38	0.0	201 800	Incomplete excision	71 380	81	Nd
39	1.6	60 500	No	NA	Normal	914
40	0.0	31 244 ^a	Incomplete excision	1351	38	430
41	3.3	25 086	Biopsy	NA	Normal	496
42	1.3	235 180	Biopsy	NA	Normal	952

(Continues)

TABLE 2 (Continued)

Patient number	Age at Diagnosis (years)	AFP serum level presurgery (ng/mL)	Surgery	AFP serum level postsurgery (ng/mL)	Beta-hCG serum level at diagnosis (IU/mL)	LDH serum level at diagnosis (IU/L)
43	2.6	55 619	Biopsy	NA	Normal	Normal
44	1.9	15 737	Incomplete excision	4437	Normal	575
45	2.4	9775	Biopsy	NA	Normal	731

Abbreviations: AFP, alpha-fetoprotein; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; NA, not applicable; Nd, not done.

^aNormal value according to age.

TABLE 3 Characteristics of patients treated with surgery only

Pt no.	Age at Dx	Initial surgery	Stage	AFP (ng/mL)	Histology at Dx	Relapse	Subsequent therapy
20	1 day	Incompl for micro residue	II	75 700	G3 IT with multiple foci of YST	No	
25	2 days	Incompl for tumor rupture	II	91 167	G3 IT with multiple foci of YST	Local (+14 mo)	Surg and pPEB × 4
26	3 days	Incompl for marginal surg	II	154 598	G2 IT with multiple foci of YST	No	
29	40 days	Complete surg	I	563	G2 IT with multiple foci of YST	No	
31	12 days	Complete surg	I	6936	MT with multiple foci of YST	No	
38	3 days	Incompl for macro residue	III	201 800	G3 IT with microfoci of YST	No	

Abbreviations: AFP, alpha-fetoprotein; Dx, diagnosis; G, grading; Incompl, incomplete; IT, immature teratoma; macro, macroscopic; micro, microscopic; mo, months; MT, mature teratoma; pPEB, pediatric cisplatin-epidoxime-bleomycin; Pt, patient; surg, surgery; YST, yolk sac tumor.

courses of pPEB and subsequent complete surgery; nine were rescued with a second-line treatment according to the ICE regimen, plus surgery in six of them, and HDCT with subsequent autologous PBSCT in six. Three children also underwent local radiotherapy (see Table 3).¹¹

Only one of the relapsed patients (aged 1.7 years at diagnosis, YST, stage IV for bilateral lung metastases, AFP > 150 000 ng/mL at diagnosis) died due to progression of the disease after several more lines of treatment. Of the remaining nine patients, eight are in second contin-

TABLE 4 Characteristics of the relapsed patients

Pt no.	Age at Dx	Initial surgery	Stage	Histology at Dx	Time to relapse	AFP at relapse (ng/mL)	Treatment at relapse	Upfront or def surg	Histology at def surg	Status at last FU
2	1.0 y	Biopsy	IV	YST	17 mos	61	Surg + ICE × 4	Yes (upfront)	YST	2° CR
8	1.4 y	Incomplete	II	YST	7 mos	289	ICE × 4 + HDCT	No	–	2° CR
9	1.8 y	Biopsy	IV	YST	7 mos	176	ICE × 2 + HDCT + RT	No	–	2° CR
12	1.1 y	Biopsy	IV	YST	9 mos	2954	ICE × 2 + HDCT	No	–	2° CR
15	2.2 y	Clinical diagnosis	IV	AFP 61 670	9 mos	37	Surg + ICE × 4	Yes (upfront)	YST	2° CR
17	1.7 y	Biopsy	IV	YST	6 mos	1240	ICE × 2 + RT + HDCT	No	–	DOD
19	1.6 y	Biopsy	III	MT + YST ^a	8 mos	280	ICE × 3 + Surg + HDCT	Yes (deferred)	MT	2° CR
25	2 days	Incomplete for tumor rupture	II	G3 IT + YST	14 mos	190	Surg + pPEB × 4	Yes (upfront)	YST	2° CR
33	0.7 y	Incomplete	IV	YST	7 mos	4800	ICE × 4 + HDCT + Surg	Yes (deferred)	Myoepithelioma	2° CR
37	2.3 y	Clinical diagnosis	IV	AFP 60 500	6 mos	196	ICE × 2 + Surg + RT	Yes (deferred)	FNT	4° CR

Abbreviations: AFP, alpha-fetoprotein (ng/mL); CR, complete remission; def, deferred; DOD, dead of disease; Dx, diagnosis; FNT, fibronectin tissue; G3, grading 3; HDCT, high-dose chemotherapy; ICE, ifosfamide-carboplatin-epidoxime; IT, immature teratoma; mos, months; MT, mature teratoma; pPEB, pediatric cisplatin-epidoxime-bleomycin; Pt, patient; RT, radiotherapy; Surg, surgery; y, years; YST, yolk sac tumor.

^aAFP at diagnosis 35 160 ng/mL.

TABLE 5 Characteristics of the patients with associated neurological involvement at diagnosis

Pt no.	Age at Dx	Neurological signs and symptoms at Dx	Stage	Sites of MTS	Initial surgical approach	Neurological outcome at follow up
3	1.4 y	Sphincterial disorders	IV	Lung + bone	Biopsy	Complete recovery
9	1.8 y	Anal sphincterial dysfunction	IV	Bone	Biopsy	Complete recovery
10	2.0 y	Paraparesis and urination disorders	III		Biopsy + laminectomy	Persistence of disturbances
11	1.9 y	Sphincterial disorders	IV	Lung + bone (L5)	Biopsy	Persistence of disturbances
12	1.0 y	Paraparesis and sphincterial disorders	IV	Lung + bone + liver	Biopsy	Persistence of disturbances
13	1.5 y	Paraparesis and sphincterial disorders	III		None	Persistence of disturbances
21	1.3 y	Urinary incontinence	IV	Lung + bone	Biopsy	Persistence of disturbances
25	1 day	Urinary incontinence	II		Coccygectomy + complete resec + tumor bleeding	Persistence of disturbances
32	1.0 y	Neurological bladder	IV	Lung + bone + liver	Biopsy	Need of intermittent catheterization
40	2 days	Equin foot and neurological bladder	II		Two steps resec with microsc residue	Persistence of disturbance
42	1.3 y	Severe sphincterial disorders	IV	Lung + bone	Biopsy	Complete recovery
43	2.6 y	Sphincterial disorders	IV	Lung	Biopsy	Complete recovery
45	2.4 y	Sphincterial disorders	IV	Lung	Biopsy	Complete recovery

Abbreviations: Dx, diagnosis; microsc, microscopic; MTS, metastases; Pt, patient; resec, resection; y, years.

uous CR and one is in fourth continuous CR after two further relapses and related systemic and local treatments. Concerning the patient 33 showed a new increase of serum AFP 2 months after stop therapy and a relapse in the soft tissues of the left buttock was diagnosed. She underwent chemotherapy with four courses of ICE and subsequent HDCT and PBSCT, with normalization of AFP. A subsequent surgical look on the left buttock revealed a residual neoplastic proliferation characterized by negativity of markers for endodermic sinus tumor (AFP, SALL4, glypican) and more generally for tumors of the germinal line (OCT3/4 and CD30), while positivity of cytokeratins, EMA, smooth muscle actin, and focally protein S100 was suggestive of a nonmalignant neoplastic differentiation, called "myoepithelioma." No treatment has been done for this completely resected benign tumor.

Five out of 13 patients with neurological signs and symptoms at diagnosis (loss of sphincteric control with paraparesis in three cases) recovered completely (Table 5).

Five-year OS and EFS were 95% (95% confidence interval [CI]: 89–100%) and 69% (95% CI: 56–84%), respectively (Figure 1). None of the prognostic factors that we took into consideration showed a statistically significant impact on prognosis in univariable analysis (Table 6).

4 | DISCUSSION

Sacroccygeal teratomas are the most common GCT of infancy and early childhood, accounting for 40% of all non-CNS GCTs. While most

of these tumors have only mature or IT elements, 11–35% could contain malignant elements, with this proportion increasing with age. The most commonly found malignant element is YST. Rarely, these tumors may include another malignant component, usually EC or even more rarely a nongerm cell/somatic malignant component such as primitive neuroectodermal tumor. The earlier published series on GCTs displayed very poor results in children with malignant SC-GCTs,^{7,13,14} yet more recently this site is no longer regarded as a poor prognostic factor of survival after the introduction of platinum-based chemotherapy regimens.^{14,15} These results were achieved by the administration of chemotherapy in almost all patients, when the size and site of the primary tumor and the high rate of regional lymph node involvement or concomitant distant metastases generally preclude a complete upfront surgical resection. The impact of clinically advanced disease at diagnosis is well known in this site: the incidence of metastasis at diagnosis in our series (58%) is higher than that reported in the German MAKEI protocol (where it is 45%),¹⁶ but fairly similar to the 59% level reported in the North American COG series.^{17,18}

The introduction of multidrug chemotherapy has dramatically improved the outcome of pediatric patients with malignant GCTs.^{3,6,7} The 5-year survival for these patients now approaches 90%, and the identification of patients at a high risk of treatment failure is a crucial challenge.

Several reports have aimed at defining prognostic factors in malignant GCTs.^{4,5,13,14} High levels of serum AFP (>10 000 ng/mL), extragonadal site, the stage of disease, the size of the primary tumor, and the

FIGURE 1 Overall survival (panel A) and event-free survival (panel B) curves for the whole series

completeness of surgery are generally considered important prognostic factors.^{19,20}

In our series, it is noteworthy that only one patient out of six approached only with surgical treatment (due to the young age) relapsed, despite the incompleteness of the resection and stage disease >I in most of them, in contrast with the observation of Egler et al²⁰ of relapse in all the patients other than stage I treated with surgery only. This small subgroup of patients, which has not received any kind of adjuvant treatment precisely because of their rarity and the interest they arouse, should be the subject of an international cooperative study.

The present series of patients registered in the AIEOP TCG 2004 protocol confirms that malignant SC-GCTs have a fairly good overall prognosis with a risk-adapted therapeutic strategy showing a 5-year OS of 95%. We observed an unsatisfactory EFS probability of 69%, even if this was an improvement over the previous Italian cooperative protocol. Particularly, we observed a high proportion of refractory (almost 10%) and relapsing patients (24%), which thus defined a global percentage of treatment failure above 30%. This could be due to unfavorable characteristics of our setting of patients at diagnosis, especially the higher percentage of metastatic disease (58%) with involvement

TABLE 6 Results of the univariable Cox models for event-free survival

	HR	95% CI	P
Sex			.366
Male vs female	0.50	0.11-2.24	
Age at diagnosis (years)			.697
2 vs 1 ^a	0.92	0.51-1.97	
Stage			.359
IV vs II-III	1.72	0.54-5.49	
Bone metastasis			.274
Yes vs no	1.91	0.60-6.12	
Histology^b			.280
YST vs YST + other	2.31	0.51-10.55	
Surgery			.945
Excision vs not done	1.32	0.24-7.19	
Biopsy vs not done	1.13	0.24-5.31	
Tumor size (cm)^c			.959
≥9 vs <9	1.03	0.31-3.43	
AFP serum level at diagnosis			.606
Pathologic vs normal	1.71	0.22-13.00	
Deferred surgery			.199
Yes vs no	0.47	0.15-1.49	

Abbreviations: AFP, alpha-fetoprotein; CI, confidence interval; HR, hazard ratio; P, Wald test P-value; UK, unknown; YST, yolk sac tumor.

^aModeled as restricted cubic spline; values reported third versus first quartile.

^bOn 38 patients with histological diagnosis.

^cOne patient excluded due to missing data.

also of bone and liver (respectively, in six and seven patients), and the number of patients with locally advanced disease (stage III was diagnosed in 11 out of 45 patients). Perhaps the reduction of the therapeutic burden, with lower doses of bleomycin and etoposide, might have played a role in determining an unexpected number of events. Probably due to the small sample size and number of events, leading to underpowered tests, we were unable to identify any prognostic factors nor, in particular, the presence of bone involvement.

In light of the above, the main goal we would like to pursue in our next study is improved EFS. It is extremely important to collect and examine more cases treated with surgery alone in order to improve the definition of prognostic factors for this small group of patients. But in order to gather sufficient data, multicenter intergroup collaboration would be essential.

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AUTHOR CONTRIBUTIONS

Paolo D'Angelo, Maria Debora De Pasquale, Angela Trizzino, Filippo Spreafico, and Monica Terenziani contributed to conception, data collection and analysis, and writing of the manuscript. Maria Carmen Affinita, Massimo Conte, Patrizia Dall'Igna, Andrea Di Cataldo, Alessandro Insera, Massimo Provenzi, Lucia Quaglietta, and Giovanna Riccipetroni contributed to data collection and critical review of the manuscript. Francesco Barretta contributed to statistical analysis and critical review of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not available for publication due to privacy or ethical restrictions.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ORCID

Paolo D'Angelo <https://orcid.org/0000-0002-4021-8472>
 Maria Debora De Pasquale <https://orcid.org/0000-0003-1082-6810>
 Francesco Barretta <https://orcid.org/0000-0002-7797-161X>
 Maria Carmen Affinita <https://orcid.org/0000-0003-1680-0240>
 Massimo Conte <https://orcid.org/0000-0001-9405-7339>
 Patrizia Dall'Igna <https://orcid.org/0000-0002-3822-3272>
 Andrea Di Cataldo <https://orcid.org/0000-0002-4509-3066>
 Alessandro Insera <https://orcid.org/0000-0002-5663-8674>
 Lucia Quaglietta <https://orcid.org/0000-0002-4354-8979>
 Filippo Spreafico <https://orcid.org/0000-0002-5587-3509>
 Monica Terenziani <https://orcid.org/0000-0002-7080-6718>

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