Sex Cord Stromal Tumors in Children and Adolescents: A First Report by The South African Children's Cancer Study Group (1990-2015)

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Abstract

Objectives: *Pediatric sex cord stromal tumors (SCSTs) are extremely rare and there are no reported data from Africa. The authors evaluated the outcomes of children and adolescents with biopsy-proven SCSTs in preparation for the introduction of a national protocol.*

Materials and Methods: *Retrospective data were collated from 9 South African pediatric oncology units from January 1990 to December 2015. Kaplan-Meier analysis was performed to estimate overall survival (OS) and event-free survival.*

Results: *Twenty-three patients were diagnosed with SCSTs, 3 male and 20 female individuals, during the study period. Histologies included 1 thecoma, 9 Sertoli-Leydig cell tumors, and 13 juvenile granulosa cell tumors. Stage I tumors predominated (n=14; 60.9%), with 2 stage II (8.7%), 5 stage III (21.7%), and 2 stage IV tumors (8.7%). The upfront resection rate was 91.3% with no reported surgical morbidity or mortality and an OS of 82.1%. Chemotherapy approaches were not standardized. Most children (81.8%), except 2, had recognized platinum-based regimens. Chemotherapy-related toxicity was minimal and acceptable. Assessment of glomerular filtration rate and audiology assessments were infrequent and not standardized. Three patients were lost to follow-up.*

Conclusions: *Although the numbers in this cohort are small, this study represents the first national cohort in Africa. The 5-year OS of 82.1% was encouraging. Standardized management of rare tumors like SCSTs is critical to improve ensure OS and address potential long-term sequelae.*

Sex cord stromal tumors (SCSTs) are rare.[1] They originate from uncommitted mesenchymal cells below the urogenital ridge and include adult and juvenile granulosa cell tumors (JGCTs), Sertoli-Leydig cells tumors (SLCTs), fibromas, thecomas, and fibrothecomas, and sclerosing stromal tumors, and the much rarer sex cord tumor with annular tubules.[2] These tumors are often hormone-producing. In their benign form, they present histologically as (fibro)thecomas or stromal tumors and in their malignant form as JGCTs or SLCTs; the latter may occur singularly or as mixed cell variants.[3] Like most abdominopelvic tumors, they may present as painful abdominal masses but virilization and precocious puberty are relatively more common in SCSTs.[4] The presence of dark blue or brown macules around the mouth, eyes, nose, anus, or inside the cheeks may suggest the presence of Peutz-Jegher syndrome (melanosis and hamartomatous gastrointestinal polyps),[5] and the presence of thyroid nodules may suggest an association with DICER-1 syndrome.[6] In addition, both ovarian JGCTs and SLCTs have been described in adolescents and adults in conjunction with enchondromatosis (Ollier Disease), where bony disease may masquerade as tumor metastases.[7–9]

Compared with high-income countries, where the frequencies of pediatric SCSTs are reported at ~2% of all gonadal tumors,[10,11] little or no published data from low- and middle-income countries (LMICs) exist.[12] In a large Industrial Injuries Advisory Council report, which reflects age-standardized ratios for gonadal tumors in children from Mali, Nigeria, Zimbabwe, Namibia, and South Africa, SCSTs are described together with germ cell and other gonadal tumors, making any disaggregated assessment of SCSTs, as a specific subgroup impossible.[13] An institutional report from Lahore, Pakistan, described a cohort of 56 adults and children, in which children between the ages of 0 and 19 years comprised only 7.1% (4/56) of all patients reported with ovarian SCSTs.[14] In another clinicopathologic

review from the Aga Khan in Pakistan, cases reported in children similarly comprised 7.6% (39/513) of all tumors that met the inclusion criteria for the review.[15]

Outcomes reported from high-income countries are favorable. The German MAKEI group reported and EFS and OS of 87% and 88%, respectively, in a cohort of 62 patients with nontesticular SCSTs and observed a good response to cisplatin-based regimens in patients with stage 2 and 3 tumors.[16] Similarly, the French have reported equally favorable 5-year EFS and OS of 85% and 94%, respectively, in a mixed cohort of ovarian and testicular SCSTs also using cisplatin-based chemotherapy.[11]

This report aims to describe a small cohort of patients treated nationally across South Africa over a 25-year period. It is the first report of its kind from the African continent.

MATERIALS AND METHODS

Retrospective data from children with biopsy-proven SCSTs were reviewed from 9 pediatric oncology units across South Africa. All children with biopsy-proven benign and malignant SCSTs up to the age of 16 years were eligible for inclusion. Given cost constraints, DICER-1 testing was not routinely available to any center. We hypothesized that children with SCSTs would have similar outcomes to those in high-income settings expecting that there may be differences across different centers. Stata Statistical Software V.14 and R Statistical Environment V. 3.5.2 were used to execute statistical analyses. Kaplan-Meier curves were generated to demonstrate overall survival (OS) and event-free survival (EFS) at 12, 24, and 60 months. EFS was calculated from the date of diagnosis until disease progression on chemotherapy, relapse, or death. The Log-rank test was used to identify significant differences between the survival curves across categories defined by age (<36, 36 to 72, >72 mo), socioeconomic status (5 groups identified on the basis of household income and access to private medical insurance), nutritional status (presence/absence of stunting, underweight-for-age [UWFA], and wasting), histology, tumor stage, and type of chemotherapy. A P value of 0.05 was considered to denote statistical significance and 95% confidence intervals (CIs) were calculated to quantify uncertainty in the survival estimates. Ethical approval was obtained from the University of Cape Town's Human Research Ethics Committee (002/2018).

RESULTS

Patient Characteristics

Over the period from January 1, 1990 to December 31, 2015, 23 children were diagnosed with biopsy-proven SCSTs: 3 male individuals (median age, 123 mo; range, 7 to 143 mo) and 20 female individuals (median age, 66 mo; range, 0 to 172 mo), with an M:F ratio of 1:7. Presenting symptoms included abdominopelvic masses (n=6; 26.1%), precocious puberty (n=3; 13.0%), abdominal pain (n=4; 17.3%), abdominal distention (n=4; 17.4%), vaginal bleeding (n=3; 13.0%), gynecomastia (n=2; 8.6%), and virilization in a young girl with an ovarian mass (n=1; 4.3%). Histologically, there was 1 (4.3%) thecoma, 9 (39.1%) SLCTs, and 13 (56.5%) JGCTs. Two SLCTs were testicular, 6 were ovarian, and in 1 male patient, a primary site could not be identified. All JGCTs were ovarian (Table 1).

TABLE 1. Patient Characteristics

No.	Sex	Age (mo)	Histology	Stage	Markers	Outcome
1	M	143	SLCT	1	Testosterone	ADF
2	M	123	SLCT	1	LDH	ADF
3	M	7	SLCT	1	—	ADF
4	F	10	JGCT	1	—	ADF
5	F	8	JGCT	1	—	ADF
6	F	34	JGCT	1	—	ADF
7	F	66	JGCT	1	—	Lost
8	F	0	Thecoma	1	—	ADF
9	F	61	JGCT	1	—	ADF
10	F	47	JGCT	1	Estradiol	ADF
11	F	17	JGCT	1	Estradiol	ADF
12	F	88	SLCT	1	—	ADF
13	F	172	SLCT	3	—	Lost
14	F	87	JGCT	1	LDH	ADF
15	F	105	SLCT	2	—	DD
16	F	132	JGCT	3	—	DD
17	F	146	JGCT	3	—	ADF
18	F	43	SLCT	3	Estradiol	ADF
19	F	55	JGCT	4	Estradiol	ADF
20	F	155	JGCT	1	AFP	ADF
21	F	38	SLCT	3	—	ADF
22	F	162	JGCT	4	LDH	DD
23	F	135	SLCT	2	LDH	ADF

ADF indicates alive, disease free; AFP, alpha fetoprotein; DD, died of disease; F, female; JGCT, juvenile granulosa cell tumor; LDH, lactate dehydrogenase; SLCT, Sertoli-Leydig cell tumor.

Fourteen children had stage 1 tumors (60.9%), 2 had stage 2 tumors (8.7%), 5 had stage 3 tumors (21.7%), and 2 had stage 4 tumors (8.7%).

Tumor Markers

Estradiol was elevated in 4 patients (mean, 11,1134 IU/L; range, 256 to 40,180 IU/L), lactate dehydrogenase in 4 patients, testosterone in 1, and serum alpha-fetoprotein in 1.

Imaging Modalities and Response Assessment

A combination of imaging modalities was used to assess disease in 16 patients at diagnosis and then again at first evaluation, where neoadjuvant treatment was administered after biopsy and before definitive resection. Imaging included chest radiograph and ultrasound (n=2), computerized tomography (CT) only (n=5), magnetic resonance imaging (MRI) and CT (n=7), and MRI only (n=2). Three patients had mixed modality assessments and 5 were undocumented. Imaging modalities were undocumented in 3 patients. In those same patients at first evaluation, 12 patients attained a complete response (CR), 2 a very good partial

response, and 3 a partial response. None of the patients was assessed as having stable disease or disease progression.

Local Control

Surgery

Primary resections were reported in 21 (91.3%) patients. Seventeen patients had CR and 4 incomplete resections. One patient did not undergo surgery because there was no available surgeon. Two patients had neoadjuvant chemotherapy and subsequently came to surgery after their second and sixth course of chemotherapy, respectively. None of the patients received radiotherapy.

Chemotherapy

Twelve patients received no chemotherapy, of whom 11 had International Federation of Obstetrics and Gynaecology (FIGO) stage 1 disease. One patient with stage FIGO 3A, who had no chemotherapy, was a long-term survivor. Six patients received JEb (carboplatin, etoposide, bleomycin), 3 received BEP (bleomycin, etoposide, cisplatin), 1 received PEb (cisplatin, etoposide, bleomycin) (after a change from JEb), 1 received a hybrid of PEb and Jeb, and 1 patient received a nonstandard regimen (MMT8 Protocol 8; vincristine and dactinomycin). Chemotherapy-related toxicity was modest. One patient had severe chemotherapy-induced nausea and vomiting, 1 had febrile neutropenia, 1 had pancytopenia with no fever, 1 had hypomagnesaemia, and 2 suffered hearing loss secondary to cisplatin.

Precisplatin Assessments

Glomerular Filtration Rate Assessments

Four patients received cisplatin chemotherapy: 3 treated with neoadjuvant BEP and 1 changed to PEb after a poor response to JEb. None of the patients, who got upfront BEP, had formal radio-isotope glomerular filtration rate (GFR) testing performed before chemotherapy. The patient who was changed from JEb to PEb had radio-isotope GFR testing done before starting PEb, which was and remained normal throughout therapy. Even in the absence of radio-isotope GFR assessment, no calculated GFRs were documented.

Audiology Assessments

Three of the 5 patients, who received cisplatin-based chemotherapy, had a formal audiology assessment. Of these, only 1 patient had a repeat assessment after the fourth course of chemotherapy and only 2 had an end of treatment audiology assessment. Both of those patients had documented hearing loss, the first who received upfront cisplatin and the second who was changed to a cisplatin-containing regimen. Grading of the hearing deficits and subsequent hearing interventions were not documented.

Follow-Up

Patients were routinely followed-up for 5 years or longer, depending on the institutional practice or until the date of their death. Only 18 of 23 (78.2%) had documented follow-up with a clinical examination, biochemical assessments of markers, and repeat imaging. Two

girls, who were initially treated by adult physicians, were lost to follow-up and were from poor socioeconomic circumstances (household income <7000 USD per annum) 6 and 14 years of age.

Outcomes

Remission was attained in 21 of 23 patients (91.3%). Three patients relapsed and none were salvaged. Of these, 1 patient had a stage 2 SLCT. Another had a stage 3 JGCT, who underwent primary resection and received 6 courses of JEb but relapsed after the end of chemotherapy and the tumor could not be completely resected at relapse. The last patient had a stage 4 JGCT, who had a primary resection and a good initial response to chemotherapy (BEP) but recurred after 6 courses of chemotherapy. The patient died before second-line chemotherapy could be commenced.

The 5-year OS was 82.1% (95% CI, 65.5%-100%) (Fig. 1) and the 5-year EFS 83.8% (95% CI, 68.6%-100%) (Fig. 2).

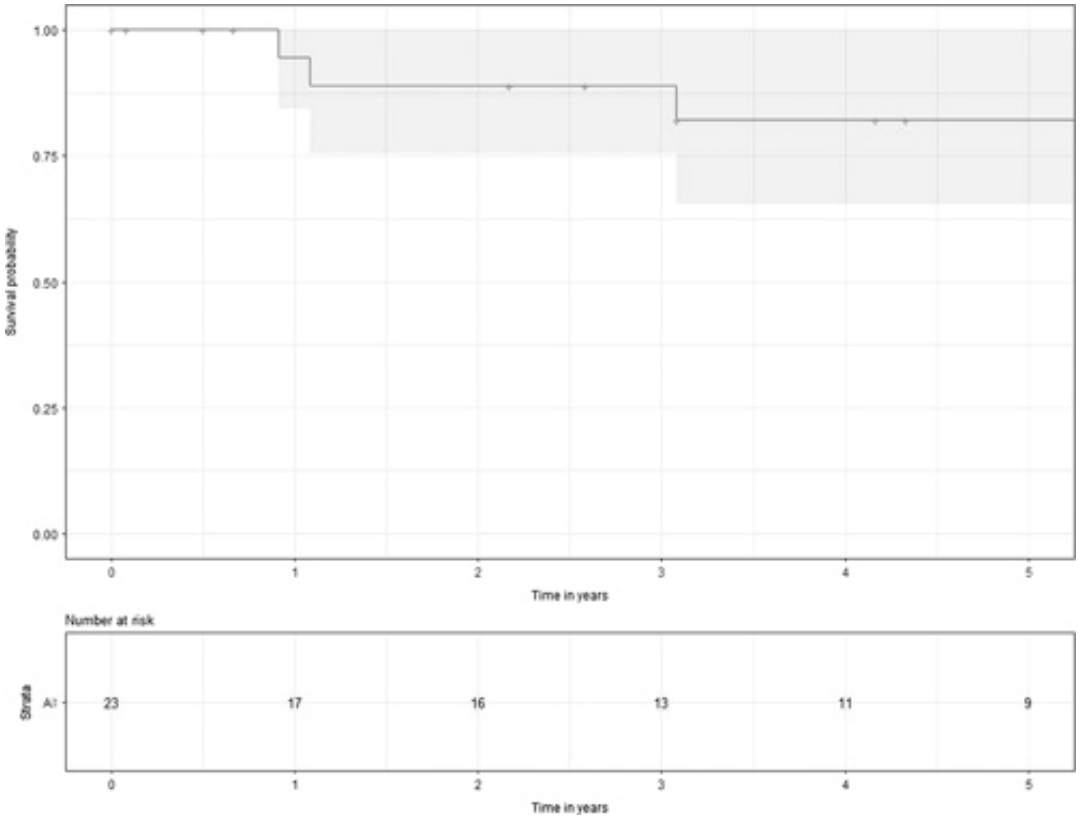

FIGURE 1. Kaplan-Meier curve 5-year overall survival (82.1%) for children with sex cord stromal tumors.

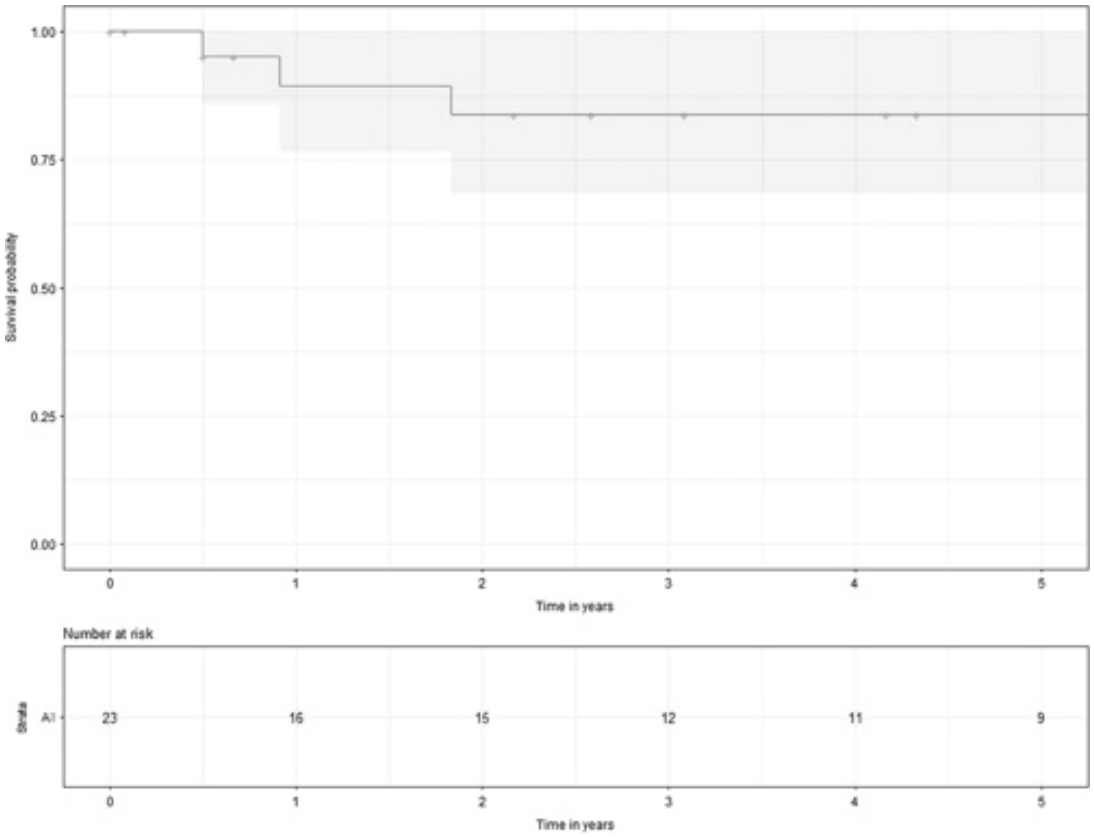

FIGURE 2. Kaplan-Meier curve 5-year event free survival (83.8%) for children with sex cord stromal tumors.

Prognostic Factors Impacting Outcomes

Being UWFA was the only prognostic factor that significantly affected overall (P<0.0001) or EFS (P<0.0001). None of the other parameters (age, stage, histology, socioeconomic status, or type of chemotherapy used) was predictive of outcome.

DISCUSSION

In common with many rare tumors in children, cohorts of patients with SCSTs tend to be small and reports uncommon. Consequently, reports from LMICs tend to be mixed adult-pediatric, institutional, or clinicopathologic [14,15,17] that limits comparisons between reports. Although our numbers are small, it reflects the first national cohort of children with SCSTs. As such, statistical analysis was limited by the small sample size and the limited number of events. Given that the dataset contained only 1 benign SCST, we acknowledge that it is asymptomatic nature compared with malignant SCSTs, may have resulted in its frequency being underreported. Different sites chose different approaches, based almost exclusively on local resource constraints. Where space and bed capacity were limited, outpatient approaches, such as carboplatin-based chemotherapy, were favored over inpatient regimens containing cisplatin. Access to laboratory services was also not standard across sites, limiting the access to and assessment of tumor markers. Radiology services also differed widely especially with respect to access to CT and MRI.

Our patients were predominantly female individuals (M:F 1:7). Comparisons of sex distribution proved to be difficult as most reports focused on ovarian tumors[4,11,15,17] or did not report sex distribution.[18] Histologically, most of the tumors in our cohort were malignant JCGTs and SLCTs (95.8%) with only a single thecoma (4.2%). Two other studies from LMICs reported much higher percentages of benign tumors: the first from Pakistan reported 10 of 39 (25%)[15] and another larger study from India 51 of 158 (32%).[17]
Patients in our cohort presented most commonly with an abdominal mass (29.2%), followed by precocious puberty (20.8%), pain (16.7%), and dysfunctional uterine bleeding (12.5%). In a series from Pakistan, pain was the main presenting complaint (38.4%), followed by comparatively similar rates of abdominopelvic masses (27%), precocious puberty (18%), and dysfunctional uterine bleeding (9%).[15] Similarly, in a series from India, which included both pediatric and adult patients, presentation with pain predominated (51.3%). This was followed by dysfunctional uterine bleeding (31%) with virilization (7.6%) and precocious puberty (1.2%) less frequently encountered.[17] This may be because of the fact that the average age of the cohort in this study was higher because of the inclusion of adults and this may have skewed the rates of precocious puberty as a presenting sign. This hypothesis is supported by a German study which found that patients under 5 years of age presented with significantly higher rates of endocrine symptoms compared with those over 5 years (82.3% vs. 51.6%, respectively, P=0.035) and consequently were also diagnosed earlier.[5] Unsurprisingly all 3 patients in our cohort who presented with precocious puberty were under 5 years at diagnosis.

Imaging modalities varied with respect to disease assessment. Ultrasonography seemed to be underutilized. This is surprising considering that it is recommended as a first-line investigation for adolescents with ovarian masses[18] and is far more accessible in LMIC settings. The use of CT or MRI predominated, consistent with MRI being the favored over CT as the imaging modality of choice for solid-cystic lesions of the pelvis, not only because of its superior anatomic definition but also because of the risk of radiation exposure from CT.

Upfront resection rates were high (91.6%) and this compares favorably with a report from France, where the complete upfront resection rate was 89.4%.[11] The rate of CR was also encouraging at 80.9% (17/21), again comparing favorably with a 53% CR rate reported by the MAKEI group from Germany.[5]

In most patients, chemotherapy was administered for tumors FIGO stage 1C and above in accordance with international recommendations.[5] Six patients received carboplatin-based as opposed to cisplatin-based chemotherapy upfront which is usually preferred. This is likely to be because of a local preference for carboplatin-based regimens as an outpatient chemotherapy instrument. In our setting, cisplatin-based regimens are given to children only as inpatients, given the legitimate concerns about clean, secure water supply in underserviced areas and because adequate posthydration, electrolyte replacement, and delayed emesis can be fastidiously monitored and managed in hospital.

In addition, the lack of access to hearing assessment and formal GFR assessment tools may also have influenced the choice of carboplatin over cisplatin. Only a few patients had precisplatin formal radio-isotope GFR and audiology assessment and hearing assessments thereafter. Even in children with documented hearing deficits, repeat assessments were not performed. This probably reflects the limited access or absence of these services at the time. Routine radio-isotope GFR testing and audiology assessment are only routinely available at large pediatric oncology units in South Africa.

The French TGM-95 study reported a 5-year OS of 94% (EFS 85%),[11] whereas the German MAKEI study reported a 5-year OS of 89% (EFS 86%).[5] Despite varying treatment approaches, outcomes were similar in our cohort with a 5-year OS of 82.1% and EFS of 83.8%. Relapses were not salvaged.

The only factor to significantly impact 5-year OS and EFS was UWFA (P<0.0001). Despite reaching the threshold for statistical significance, the importance of the finding is difficult to interpret given the small sample size and the limited number of events within the sample. Reports in Malawian children with Wilms Tumor have shown a relationship between malnutrition, larger tumors at diagnosis, and altered responses to chemotherapy.[19] Similarly, these children were found to have lower rates of chemotherapy clearance when compared with children with the same diagnosis in high-income settings with normal nutrition.[20] A cohort of Malawian children with Burkitt lymphoma and acute malnutrition were found to have significantly higher rates of profound chemotherapy-induced neutropenia.[21] This finding was more recently validated in a cohort of South African children with Wilms Tumor and malnutrition who were found to have higher rates of treatment-induced neutropenia.[22] A further South African study, however, found no relationship between malnutrition and poorer outcome in children with Wilms Tumor and found that the presence of malnutrition did not predict more advanced disease. They reported that the use of weight and height alone may have underestimated the true rates of malnutrition and recommended more rigorous assessment using mid-upper arm circumference and triceps skin fold measurements as adjuncts of nutritional evaluation. The authors hypothesized that the failure to show a relationship between nutrition and outcome may have been explained by the fact that 84% of the children in their study received aggressive nutritional resuscitation in the first 2 weeks of treatment.[23] Our study used only weight and height at diagnosis to assess nutritional status and this may well have underestimated the rates of wasting. Although the relationship between UWFA and outcome has not previously been reported in children with SCSTs, we feel that the finding in our cohort is tenuous at best and should be regarded with caution. It does not, however, diminish the importance of rigorous nutritional assessment and supplementation in children with cancer on chemotherapy especially in areas where the prevalence of malnutrition is so high.[19]

CONCLUSION

In this cohort of patients with SCSTs, there was good OS despite an inability to salvage relapsed patients. Because of varying access to health care facilities in the different treatment sites, there was a nonstandardized approach to pretreatment imaging modalities, response assessment, GFR and audiology assessment, and follow-up.

Reporting of rare tumors to institutional or national childhood cancer registries is essential to understand the relative frequency of these rare childhood malignancies and to advocate for improvements in access to health care and quality interventions. This can be best achieved in the setting of harmonized national treatment approaches from which children diagnosed with SCSTs would benefit. As national childhood cancer management protocols are being implemented by the South African Children Study Group, we should look to build regional collaborations of health care across all childhood cancer types, especially in relation to rare tumors to improve the outcomes of children with cancer. Barriers to equitable cancer care for children in Africa continue to be pervasive, notably but not exclusively free access to chemotherapy drugs and the availability of sophisticated imaging and laboratory services, which in many African countries continues to fall to individual families to fund.[24] This is a

difficult problem to overcome without a commitment from national health departments to prioritize pediatric cancer care, a difficult task on a continent where malnutrition, malaria, tuberculosis, HIV, and emerging epidemics of hypertension and diabetes[25] are often considered more urgent public health priorities. One way to offset these challenges still exists through funded twinning relationships between pediatric oncology units in developed and developing settings that cover the cost of expensive chemotherapeutics, ensuring uniform access to drugs. The use of graduated management protocols that rely on less sophisticated modalities, like ultrasound as opposed to MRI, for example, may also provide viable alternatives.[26] Although national referral of children with complex or rare tumors does occur regularly within South Africa, continental referral to centers of excellence in this country is again exclusively determined by an individual family's capacity to fund such treatment, rarely with any financial support from their government. Whether a plan of referral to centers of excellence across borders can be agreed upon by member countries around the continent remains as yet purely aspirational. Without significant resource allocation, the improvements in outcome for African children is likely to be small in general and certainly almost unnoticeable for children with rare tumors. As a response to this, regional capacity building through training and collaboration in conjunction with the use of harmonized, not only national but also regional, protocols may provide at least a small opportunity for better care as we move toward 2030.

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REFERENCES

1. Cushing B, Marina NM, Perlman EJ, et al. Pizzo PA, Poplack DG. Principles and Practice of Pediatric Onclogy, 5th ed. In: Pizzo PA, Poplack DG, eds. Germ Cell Tumors. Philadelphia: LIppincott, Williams & WIlkins; 2001:1118–1138.
2. Pratt J. Pathology of the Ovary, 1st ed. Philadelphia, PA: Saunders; 2004:342.
3. Kurman RJ, Carcangiu ML, Herrington CS, et al. Classification of Tumours of the Female Genital Tract, 4th ed. Lyon: IARC; 2014:307.
4. Schneider DT, Calaminus G, Wessalowski R, et al. Ovarian sex cord-stromal tumors in children and adolescents. J Clin Oncol. 2003;21:2357–2363.
5. Schultz KA, Harris AK, Schneider DT, et al. Ovarian Sex Cord-Stromal Tumors. J Oncol Pract. 2016;12:940–946.
6. Heravi-Moussavi A, Anglesio MS, Cheng SW, et al. Recurrent somatic DICER1 mutations in nonepithelial ovarian cancers. N Engl J Med. 2012;366:234–242.
7. Tamimi HK, Bolen JW. Enchondromatosis (Ollier's Disease) and ovarian juvenile granulosa cell tumours. Cancer. 1984;53:1605–1608.
8. Velasco-Oses A, Alonso-Alvaro A, Blanco-Pozo A, et al. Ollier's disease associated with ovarian juvenile granulosa cell tumor. Cancer. 1988;62:222–225.

9. Weyl-Ben Arush A, Oslander L. Ollier's disease associated with ovarian Sertoli-Leydig cell tumor and breast adenoma. Am J Pediatr Hematol Oncol. 1991;13:49–51.
10. Morowitz M, Huff D, von Allmen D. Epithelial ovarian tumors in children: a retrospective analysis. J Pediatr Surg. 2003;38:331–335.
11. Fresneau B, Orbach D, Faure-Conter C, et al. Sex-cord stromal tumors in children and teenagers: results of the TGM-95 study. Pediatr Blood Cancer. 2015;62:2114–2119.
12. Stefan DC, Stones DK, Wainwright RD, et al. Childhood cancer incidence in South Africa, 1987-2007. South Afr Med J. 2015;105:939–947.
13. Parkin DM, Kramárová E, Draper GJ, et al. International Incidence of Childhood Cancer. Lyon: IARC; 1998.
14. Sarwar S, Siddiqui N, Ather S, et al. Outcomes among patients with sex cord stromal tumour of ovary: experience from Pakistan. J Ayub Med Coll Abbottabad. 2014;26:389–392.
15. Haroon S, Idrees R, Zia A, et al. Ovarian sex cord stromal tumours in children and young girls—a more than two decade clinicopathological experience in a developing country, Pakistan. Asian Pac J Cancer Prev. 2014;15:1351–1355.
16. Schneider DT, Calaminus G, Harms D, et al. German Maligne Keimzelltumoren Study G. Ovarian sex cord-stromal tumors in children and adolescents. J Reprod Med. 2005;50:439–446.
17. Bhargava S, Vyas J, Bhargava A. Ovarian sex cord stromal tumours: an instituional experience. Int J Reprod Contracept Obstet Gynaecol. 2017;6:3924–3936.
18. Cecchetto G, Ferrari A, Bernini G, et al. Sex cord stromal tumors of the ovary in children: a clinicopathological report from the Italian TREP project. Pediatr Blood Cancer. 2011;56:1062–1067.
19. Israels T, Borgstein E, Jamali M, et al. Acute malnutrition is common in Malawian patients with a Wilms tumour: a role for peanut butter. Pediatr Blood Cancer. 2009;53:1221–1226.
20. Israels T, Damen CWN, Cole M, et al. Malnourished Malawian patients presenting with large Wilms tumours have a decreased vincristine clearance rate. Eur J Cancer. 2010;46:1841–1847.
21. Israels T, van de Wetering MD, Hesseling P, et al. Malnutrition and neutropenia in children treated for Burkitt lymphoma in Malawi. Pediatr Blood Cancer. 2009;53:47–52.
22. Draper KS, Hadley GP, Pillay K, et al. Relationship between nutritional status and treatment-related neutropenia in children with nephroblastoma. South Afr J Clin Nutr. 2018;31:74–77.
23. Lifson LF, Hadley GP, Wiles NL, et al. Nutritional status of children with Wilms' tumour on admission to a South African hospital and its influence on outcome. Pediatr Blood Cancer. 2017;64:e26382.
24. Kruger M, Hendricks M, Davidson A, et al. Childhood cancer in Africa. Pediatr Blood Cancer. 2014;61:587–592.
25. Oni T, Youngblood E, Boulle A, et al. Patterns of HIV, TB, and non-communicable disease multi-morbidity in peri-urban South Africa—a cross sectional study. BMC Infect Dis. 2015;15:1–8.
26. Hesseling P, McCormick P, Kouya F, et al. Burkitt lymphoma: residual abdominal tumor volume after induction therapy correlates with outcome. Pediatr Blood Cancer. 2010;55:761–762.