Epidemiological profile and clinico-pathological features of pediatric gynecological cancers at Moi Teaching & Referral Hospital, Kenya

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ABSTRACT

Background: The main pediatric (0–18 years) gynecologic cancers include stromal carcinomas (juvenile granulosa cell tumors and Sertoli-Leydig cell tumors), genital rhabdomyosarcomas and ovarian germ cell. Outcomes depend on time of diagnosis, stage, tumor type and treatment which can have long-term effects on the reproductive career of these patients. This study seeks to analyze the trends in clinical-pathologic presentation, treatment and outcomes in the cases seen at our facility. This is the first paper identifying these cancers published from sub-Saharan Africa.

Method: Retrospective review of clinico-pathologic profiles and treatment outcomes of pediatric gynecologic oncology patients managed at MTRH between 2010 and 2020. Data was abstracted from gynecologic oncology database and medical charts.

Results: Records of 40 patients were analyzed. Most, (92.5%, 37/40) of the patients were between 10 and 18 years. Ovarian germ cell tumors were the leading histological diagnosis in 72.5% (29/40) of the patients; with dysgerminomas being the commonest subtype seen in 12 of the 37 patients (32.4%). The patients received platinum-based chemotherapy in 70% of cases (28/40). There were 14 deaths among the 40 patients (35%).

Conclusion: Surgery remains the main stay of treatment and fertility-sparing surgery with or without adjuvant platinum-based chemotherapy are the standard of care with excellent prognosis following early detection and treatment initiation. LMICs face several challenges in access to quality care and that affects survival of these patients. Due to its commonality, ovarian germ cell cancers warrant a high index of suspicion amongst primary care providers attending to adnexal masses in this age group.

1. Introduction

Pediatric gynecological cancers are uncommon and there is limited data on them particularly in low resource settings. Most quoted data on incidence is from high income countries, for instance, in the United States the incidence is 17 cases per 100,000 individuals per year (Keyser and Berger-Chen, 2018). Few prospective trials such as the GOG-10, 45, 90 and 116 included children and adolescents (0–18 years) with certain gynecologic cancer subtypes and analyses from pediatric oncology cooperative groups that assessed treatment outcome, however there still remains a dearth of epidemiologic data and real-world prognosis (Wohlmuth and Wohlmuth-Wieser, 2021 Feb 12) especially in LMICs.

There are three primary categories of gynecologic cancer that are found in pediatric and adolescent patients. These include stromal carcinomas (juvenile granulosa cell tumors and Sertoli-Leydig cell tumors), rhabdomyosarcomas arising from the vagina and cervix (sarcoma botryoides) and ovarian germ cell tumors (Pommert and Bradley, 2017). Ovarian germ cell tumors (OGCTs) arise primarily in young women between 10 and 30 years of age and they represent approximately 70 percent of ovarian neoplasms in this age group (Zalel et al., 1996; Hubbard and Poynter, 2019). Embryonal rhabdomyosarcoma (eRMS) is the most common soft-tissue sarcoma in the first decade of life (Dehner et al., 2011). Vaginal and vulvar tumors are extremely rare in the pediatric population (Fernandez-Pineda et al., 2011).
Management of pediatric gynecologic cancers has the distinction of being both challenging and complex due to the intricacies of physical and mental health implications requiring a multidisciplinary approach.

With a catchment area of 24 million, the Moi Teaching and Referral Hospital, MTRH in Eldoret, Kenya is strategically placed to receive a variety of the above cases. The hospital has a gynecologic oncology program that started in 2010 and a fellowship training program which started in 2012. This paper is an institutional experience of the clinical-pathological features and treatment outcomes of pediatric gynecologic tumors.

2. Methods

2.1. Study setting

The study was carried out at the MTRH, Cancer Center in Eldoret a referral center that attends to both analytical and non-analytical cases. The hospital receives patients from approximately 14 counties from the region of western Kenya and is the only public hospital in western Kenya that deals with pediatric gynecological cancers. The Gynecologic Oncology Clinic sees approximately one pediatric patient per week. MTRH has four Gynecologic Oncologists with the additional support of 2 oncologists from Toronto, Canada and Michigan, USA under the AMPATH Oncology Institute program.

2.2. Study design

This is a retrospective descriptive study that reviewed the database for all pediatric (0–18 years) patients seen at MTRH Cancer Center with the final histologic diagnosis of a gynecological cancer between 2010 and 2020. The medical charts were then reviewed and the data analyzed. Patients who had metastases to the reproductive tract or a tumor in the pelvis but not a primary from the reproductive tract were excluded.

2.3. Statistical analysis

This was a retrospective analysis of medical records of all patients under 18 years with histologically confirmed gynecologic cancer seen between 2010 and 2020 at MTRH. Data were analyzed using STATA version 15. Summary statistics were reported with respect to the outcome (dead/alive) for all patient demographic, histological and treatment factors. The Kaplan Meier survival method was used to assess trends in survival for selected covariates.

2.4. Ethical consideration

Ethical clearance was obtained from the Institutional Research and Ethics Committee (IREC) of Moi University/MTRH.

3. Results

A total of 43 pediatric patients were seen between 2010 and 2020 with histologically confirmed gynecologic cancer. Three patient medical charts could not be traced hence 40 medical charts were submitted for data retrieval and analysis.

A large proportion of the patients (92.5%, 37/40) were between 10 and 18 years. Seventy percent (28/40) had both parents alive with at least one parent among 25 pediatric patients had a source of income. Seventy five percent (30/40) of the patients were covered under their parents’ health insurance. Eighty-five per cent (34/40) were tested for HIV infection and were negative. Only 1 patient came from the county MTRH is located in (Table 1).

At the time of admission, 40% (16/40) of the patients had a good performance status (ECOG 0). Clinical presentation features included pain, abdominal distension and abdominal mass. Hormonal manifestation (prepubertal breast development/menstruation, hirsutism etc.) was seen only in one patient with sex cord tumors (Sertoli-Leydig) and a prolapsed vaginal mass was seen in the 2 patients with eRMS.

Germ cell tumor was seen in 29/40 (72.5%) of the patients, 4 had a stromal cell tumor and 4 had an epithelial ovarian cancer. Dysgerminoma was the most common of the germ cell tumors seen in 12/29.

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Table 1

| Variable                        | n (%)  |
|---------------------------------|--------|
| Age (years)                     |        |
| <10                             | 3 (7.5) |
| 10–14                           | 16 (40) |
| 15–18                           | 21 (52.5) |
| Total                           | 40 (100) |
| ECOG performance status*        |        |
| 0, Fully active, able to carry on all pre-disease performance unrestricted | 16 (40) |
| 1, Restricted in physically strenuous activity but ambulatory and able to carry out light work | 12 (30) |
| 2, Ambulatory and capable of all self-care but unable to carry out any work activities | 8 (20) |
| 3, Capable of only limited self-care confined to bed or chair more than 50% of waking hours | 4 (10) |
| Epithelial ovarian cancer       |        |
| Serous adenocarcinoma           | 3 (7.5) |
| Mucinous adenocarcinoma         | 1 (2.5) |
| Ovarian Germ Cell Tumor         |        |
| Dysgerminoma                    | 12 (30) |
| Yolk sac/Endodermal sinus tumor | 8 (20) |
| Immature teratoma               | 5 (12.5) |
| Mixed                           | 4 (10)  |
| Sex cord/Stromal histology      |        |
| Granulosa cell tumor            | 3 (7.5) |
| Sertoli-Leydig cell             | 1 (2.5) |
| Vaginal/Cervical Tumors         |        |
| Rhabdomyosarcoma (sarcoma botryoides) | 2 (5) |
| Squamous cell cancer of cervix  | 1 (2.5) |
| Total                           | 40 (100) |

Notes: *No patient was recorded at ECOG status 4 or 5.
teratoma, 1/3 with granulosa cell tumor and 2/3 with serous epithelial ovarian cancer. One patient with locally advanced cervical cancer received radiotherapy.

The patients received polychemotherapy with the commonest chemotherapeutic combination used being bleomycin, etoposide and cisplatin (BEP) in 70% of cases (28/40) for germ cell and sex cord-stromal tumors. Vincaistine, Adriamycin (alternating with actinomycin D) and cyclophosphamide (VAC) and carboplatin and paclitaxel (TC) were used in 2 patients each with rhabdomyosarcoma and epithelial ovarian tumors respectively.

Only 7 patients were confirmed to have recurrence during follow up. Tumor markers were not consistently measured thus data was unavailable for most patients at diagnosis and follow up.

By the end of the study period (2010 to 2020), 65% (26/40) of the pediatric patients were still alive (Table 3).

Participants were followed up for a maximum of 8.2 years (median, 0.34 years [0.01–8.16 years]) as per the duration of the study. There were 14 deaths among the 40 patients included in the study. This included 4/12 with dysgerminoma, 4/9 with yolk sac tumor, 1/2 with RMS and all the 3 patients with serious epithelial ovarian cancers. Two patients with ovarian cancer with inconclusive histology also died.

The most critical time for a poor outcome is mostly observed within the first two years of an ovarian cancer diagnosis. During this time, most deaths and recurrences were observed. The remainder of the patients (26/40, 65%) are currently stable, alive with no evidence of disease. One of the patients with embryonal rhabdomyosarcoma (1/2) and the one with cervical cancer (IIIc) is still on follow up, also alive with no evidence of disease at the time of study completion.

The Kaplan-Meier survival curves depict the probabilities of survival by histology (Fig. 1). Patients with immature teratoma, dysgerminoma and yolk sac tumor had better overall survival estimates compared to patients with epithelial ovarian tumors. Stratification of survival estimates by treatment options showed that the patients who underwent a repeat surgery following a sub-optimal surgery from a referring facility as well as the patient who received palliative chemotherapy as first line did very poorly. Fertility-sparing surgery was associated with better survival estimates (Fig. 2).

4. Discussion

4.1. Epidemiological considerations

Pediatric gynecologic cancers are rare but survival rates have increased dramatically in the last 25 years (Trotman and Hoelgen, 2016) with 5-year relative survival rates approaching 85% (Howlader et al., 1975-2012). This retrospective institutional review showed that the majority of pediatric patients seen at MTRH are between 10 and 18 years, which is the age group known to have the highest incidence of these tumors. The relevant findings such as age, clinical characteristics and case distribution are consistent with what was found in other studies (Wohlmuth and Wohlmuth-Wieser, 2021 Feb 12; Pommert and Bradley, 2017). A majority of the patients seen were referred from different counties with only 1 patient seen from the county (Uasin Gishu) where MTRH is located in. MTRH is a referral hospital thus most patients treated here have been referred from different facilities. It is also likely that since this county has several private hospitals where the gynecologic oncologists from MTRH also work and are well known to the community therefore get direct referrals to see these patients.

Rapid diagnosis and treatment initiation is the cornerstone of management of these tumors thus having a majority of parents who had active health insurance helped prevent treatment delays. The Kenyan National Hospital Insurance Fund (NHIF) requires monthly subscriptions and covers most costs related to surgery and chemotherapy. Being the main referral hospital in western Kenya, a majority of patients are referred here due to the availability of a specialized gyn-oncological unit, pediatric oncology unit and radiotherapy allowing for a multi-disciplinary approach to patient management.

Surgical staging is a major challenge in our set up as many patients undergo exploratory laparotomy by general medical doctors or general gynecologists with no staging prior to being referred to our center. Often, a unilateral salpingo-oophorectomy is done or a wedge biopsy of the mass is taken with no details of the appearance of other abdominopelvic organs or sites of metastases. Some patients have also been sterilized (hysterectomy and oophorectomy) by low cadre health care workers. In some patients, significant amount of tumor is left in-situ as the tumor is deemed inoperable hence require repeat surgery which was done in our center. Another delay, has been in getting the histologic diagnosis since our center lacks a gynecologic oncology pathologist and the entire public hospital with patients from the larger western Kenya region relies on 3 anatomic pathologists and 2 general pathologists. These challenges to access to quality health care provision are commonly faced in most African LMICs as seen in studies from Nigeria, Tunisia and Egypt (Ali et al., 2018; Bezdienhout et al., 1997 May; Lucas and Vella, 1983 Sep). Several studies show that early diagnosis and referral to a cancer center improve clinical outcomes (Wohlmuth and Wohlmuth-Wieser, 2021 Feb 12; Pommert and Bradley, 2017; Zalel et al., 1996; Hubbard and Poynter, 2019). At our facility, a patient navigator consistently calls the patient’s parents/guardians to remind them of clinic review dates and due treatments. This has markedly reduced our loss to follow up.

4.2. Malignant ovarian germ cell tumors

Malignant ovarian germ cell tumors (OGCTs) are rare and represent 1–1.5% of all cancers in children and adolescents and account for 60–70% of all gynecologic malignancies in children and adolescents (Ali et al., 2018; Bezdienhout et al., 1997 May; Lucas and Vella, 1983 Sep). Several studies show that early diagnosis and referral to a cancer center improve clinical outcomes (Wohlmuth and Wohlmuth-Wieser, 2021 Feb 12; Pommert and Bradley, 2017; Zalel et al., 1996; Hubbard and Poynter, 2019). At our facility, a patient navigator consistently calls the patient’s parents/guardians to remind them of clinic review dates and due treatments. This has markedly reduced our loss to follow up.

Table 3

| Treatment options and outcomes. | n (%) |
|---------------------------------|-------|
| **Primary surgery** | 6 (15) |
| Fertility sparing surgery (primary surgery) | 8 (20) |
| Neoadjuvant chemotherapy | 1 (2.5) |
| Adjuvant chemotherapy | 15 (37.5) |
| Repeat surgery after suboptimal debulkinga | 5 (12.5) |
| Surgery for recurrence | 2 (5) |
| Emergency surgery | 1 (2.5) |
| Radiotherapy | 1 (2.5) |
| Otherb | 1 (2.5) |
| **Total** | 40 (100) |
| **Chemotherapy used** | |
| Bleomycin, Etoposide and Cisplatin | 28 (70) |
| Carboplatin and Paclitaxel | 2 (5) |
| Vincristine, Adriamycin, Cyclophosphamide | 2 (5) |
| Not indicated | 8 (20) |
| **Total** | 40 (100) |
| **Recurrentec** | |
| Within 6 months | 5 (15.2) |
| 6–12 months | 1 (3) |
| 1–2 years | 1 (3) |
| No recurrence | 26 (78.8) |
| **Total** | 33 (100) |
| **Recurrerentd** | |
| Clinical and chemical | 7 (21.2) |
| No recurrence | 26 (78.8) |
| **Total** | 33 (100) |
| **Dead** | |
| No | 26 (65.0) |
| Yes | 14 (35.0) |
| **Total** | 40 (100) |

Note.

aSub-optimal surgery done at the referring facility.

bOther denotes only a biopsy was taken or nothing was done intra-operatively due to extensive tumor.

cInformation on some patients could not be traced.
et al., 2018). Dysgerminoma was the commonest histology seen in 30.8% of all pediatric gynecologic cancers and 41.4% of all OGCTs in this review, which corresponds to data indicating it constitutes up to 40% of malignant germ cell tumors (Cibas and Ducatman, 2009). In 2009, the Malignant Germ Cell International Collaborative (MaGIC) was established in an international bid to standardize risk factors, staging and treatment approaches. (Olson et al., 2015).

Abdominal mass associated with pain were reported in most of our patients which correlates with other studies (Ali et al., 2018; De Backer et al., 2006). Tumor markers (alpha feto-protein, beta human chorionic gonadotropin and lactate dehydrogenase) common in ovarian germ cell cancers are helpful in the diagnosis and posttreatment surveillance in OGCTs (Terzic et al., 2021). However, most were not routinely done in these patients mostly due to unavailability of the tests and prohibitive costs. Immunohistochemistry has also been uncommonly used, until the last three years, for largely the same reasons.

Surgery is the cornerstone in definitive management of OGCT and even in advanced cases; with conservative surgery and platinum-based chemotherapy (Mangili et al., 2017; Gershenson and Frazier, 2016), prognosis is excellent (Duhil de Bénazé et al., 2018), however, as seen in
our analysis, 4 out of 12 patients died which is considerably high by high income country standards. This is the practice employed in our center. However, as most patients are not in the domicile of MTRH, and either have to travel long distance (4–8 h drive) and look for accommodation in the area or have been seen by low cadre medical professionals with low index of suspicion for gynecologic malignancy, these patients suffer diagnostic delays and thus come to us while in advanced stages of the disease. There may be additional delays in optimizing the patients for surgery chiefly due to a high demand of blood and blood products.

Since OGCTs are very chemosensitive, the exploration of feasibility of neoadjuvant chemotherapy (NACT) has been done by small institution-based studies which have shown that in patients with advanced/metastatic disease, NACT may be warranted. A notable study to evaluate this, utilized four cycles of BEP followed by fertility-sparing surgery in 23 patients with bulky disease compared with 43 patients who underwent primary debulking surgery with FIGO stage III or IV disease. In this study by Talukdar et al., 21 patients in the NACT arm showed a response to treatment with 16 achieving a complete response and five with a partial response. Of note, 18 of the 21 patients in the NACT group underwent fertility-sparing surgery, and those with residual disease were given an additional two cycles of BEP. From this arm, 21 survived with a median disease-free survival period of 17.6 years. (Talukdar et al., 2014) The same principle was applied to yolk sac tumors by Lu et al., who also discovered that in 53 patients with yolk sac tumor, those who got NACT had a better progression free survival and that residual tumor of greater than 2 cm was an independent risk factor for relapse. (Lu et al., 2014).

This may improve the survival of patients with advanced ovarian germ cell tumors especially in LMICs where extensive surgical support is lacking in terms of equipment and personnel. It will also be of benefit in morbidity reduction (Olson et al., 2015) as patients need not undergo extensive surgery and may only require fertility-sparing surgery.

Based on several studies, most ovarian immature teratomas occur in the 12–15 age group. However, in our study, only 1 of the 5 patients was between 10 and 14 years while the rest were aged between 15 and 18 years (Bezuidenhout et al., 1997 May). Malignant ovarian immature teratomas from several analyses in Africa have described a low incidence and good outcomes particularly for low grade tumors (Terzic et al., 2021; Bezuidenhout et al., 1997 May; Akang et al., 1994 Mar) which was consistent to data from high income countries (Shinkai et al., 2020). Prognosis is largely influenced by the grade of the tumor (O’Connor and Norris, 1994). In our study we had 5 cases and all were still alive by the end of the study period. However, due to inconsistent pathological reporting, the grades of the tumor were not universally indicated in our cases. Treatment offered was the same as for other OGCTs.

4.3. Sex cord - stromal ovarian cancer

These tumors have similar clinico-pathological features in the testes and ovary. Granulosa cell tumors are much more common in females and are divided into adult and juvenile forms (Young, 2005 Feb) with the latter seen in pediatric patients. Surgery is the main therapeutic option since 70% of the patients present with stage I tumors, due to the indolent nature of these neoplasms and the overall good prognosis. The overall response rate is 63% to 80% (Ray-Coquard et al., 2014 Nov; Schneider et al., 2003 Oct). Out of the 4 patients seen at our facility, 2 had confirmed stage 1 disease. These patients are on long-term follow up due to the long natural history of the disease in case of relapse hence need for repeated surgical procedure. Two of the patients received adjuvant chemotherapy with a platinum-based protocol which is usually recommended for patients with advanced stage GCSTs or recurrent disease.

4.4. Rare gynecologic tumors in pediatric patients

Vaginal and cervical tumors were the least common in our setting with 2 cases of embryonal rhabdomyosarcoma and one case of a 16-year-old HIV-uninfected with stage IIIc1, squamous cell carcinoma of the cervix. The latter patient underwent chemoradiation and is currently alive with no evidence of disease however has developed a vesicovaginal fistula.

Vaginal tumors are extremely rare in the pediatric population. Early recognition of symptoms like bleeding and a protruding vaginal mass may prevent morbidity and mortality. Studies have shown a good prognosis of early vaginal RMS (Fernandez-Pineda et al., 2011). Of the 2 patients included in this study, one was diagnosed early and surgery was sufficient to cure her while the other had advanced disease with massive blood loss resulting in her demise. Treatment of RMS includes prognostic stratification based on tumor inter-grouping and fusion status. Therapy can be multimodal including surgery and polychemotherapy (vinクリンスト、다기능모음성, 클로프호사미드) with or without radiotherapy (Walterhouse et al., 2014; Beverly Raney et al., 2011).

It is highly infrequent to find cervical cancer in a teenager as was our patient, more so since it was HIV-unrelated. The 16-year-old patient encompassed the common risk factors for cervical cancer including early age at sexual debut (11 years), multiple sexual partners and multiparity (delivered her second child 5 months prior to diagnosis). Her treatment was standardized to her stage in accordance to the FIGO 2018 guidelines (Bharla et al., 2018 Oct).

This study’s main limitation was its retrospective nature. Some patients’ medical charts could not be traced and several information such as clinical staging, tumor grading and adverse events were not captured. Recurrence/death was not reported as actuarial at 2 or 5 years due to missing follow up data.

5. Conclusion

Pediatric gynecologic cancers have similar relevant findings in age and case distribution globally. Ovarian germ cell cancers are the commonest and thus a high index of suspicion should be encouraged in primary care providers attending to adnexal masses in this age group.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Keyser, E., & Berger-Chen, S. (2018). Gynecologic Issues in Children and Adolescent Cancer Patients and Survivors, ACOG Committee Opinion No. 747 Summary. Obstetrics & Gynecology, 132(2), 535-536. doi:10.1097/Aog.0000000000002764.

Wohlmuth, C., Wohlmuth-Wieser, I., 2021. Gynecologic Malignancies in Children and Adolescents: How Common is the Uncommon? J. Clinical Medicine. 10 (4), 722.

Pommerit, L., Bradley, W., 2017. Pediatric Gynecologic Cancers. Current Oncology Reports 19 (7). https://doi.org/10.1007/s11912-017-0604-7.

Zaleh, Y., Piura, B., Elchalal, U., Czermobilsky, B., Antebi, S., Dgani, R., 1996. Diagnosis and management of malignant germ cell ovarian tumors in young females. Int. J. Gynecology Obstetrics 55 (1), 1-10. https://doi.org/10.1016/0020-7292(96)02719-1.

Hubbard, A., Poynter, J., 2019. Global incidence comparisons and trends in ovarian germ cell tumors by geographic region in girls, adolescents and young women: 1988–2012. Gynecol. Oncol. 154 (3), 608–615. https://doi.org/10.1016/j.ygyno.2019.06.025.

Dehner, L., Jarzembski, J., Hill, D., 2011. Embryonal rhabdomyosarcoma of the uterine cervix: a report of 14 cases and a discussion of its unusual clinicopathological
associations. Mod. Pathol. 25 (4), 602–614. https://doi.org/10.1038/modpathol.2011.185.

Fernandez-Pineda, I., Spunt, S., Parida, L., Krasin, M., Davidoff, A., Rao, B., 2011. Vaginal tumors in childhood: the experience of St Jude Children’s Research Hospital. J. Pediatric Surgery 46 (11), 2071–2075. https://doi.org/10.1016/j.jpedsurg.2011.05.003.

Trotman, G.E., Horfen, H., 2016. Gynecologic issues in the Pediatric and Adolescent Patient with Cancer. Curr Treat Options Peds 2 (3), 196–208. https://doi.org/10.1007/s40746-016-0059-3.

Howlader N, Noone AM, Krapcho M, Garshell et.al. (eds). SEER Cancer Statistics Review, 1975–2012, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975-2012/..

Cibas E, DuCauzman B. Diagnostic Principles and Clinical Correlates, Expert Consult. 3rd ed. Philadelphia, PA: Saunders/Elsevier, ISBN: 9781416053293; 2009.

Trotman, G.E., Hoefgen, H., 2016. Gynecologic Issues in the Pediatric and Adolescent Patient with Cancer. J. Pediatric Surgery 53 (4), 837–840. https://doi.org/10.1016/j.jpedsurg.2011.05.003.

Drake DD, Lin M, Krasin M, et al. (eds). SEER Cancer Statistics Review, 1975–2012, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975-2012/..

Gershenson, D.M., Frazier, A.L., 2016. Conundrums in the management of malignant ovarian germ cell tumors: the road to collaboration. J. Clin. Oncol. 33 (27), 3018–3024. https://doi.org/10.1007/s40746-016-0059-3.

Lu, Y., Yang, J., Wu, M., You, M., You, Y., Chen, J., Lang, J., Shen, K., 2014. Tumor Registry. Virchows Arch. 443 (4), 549–560. https://doi.org/10.1007/s00428-003-0869-0. Epub 2003 Aug 9 PMID: 12910419.

Fernandez-Pineda, I., Spunt, S.L., Parida, L., Krasin, M.J., Davidoff, A.M., Rao, B.N., 2011. Vaginal tumors in childhood: the experience of St Jude Children’s Research Hospital. J. Pediatric Surgery 46 (11), 2071–2075.

Walterhouse, D.O., Pappo, A.S., Meza, J.L., Brennan, J.C., Hayes-Jordan, A.A., Parkham, D.M., Crine, T.P., Anderson, J.R., Meyer, W.H., Hawkins, D.S., 2014. Shorter-Duration Therapy Using Vinristine, Dacinomycin, and Lower-Dose Cyclophosphamide With or Without Radiotherapy for Patients With Newly Diagnosed Low-Risk Rhabdomyosarcoma: A Report From the Soft Tissue Sarcoma Committee of the Children’s Oncology Group. JCO 32 (31), 3547–3552.

Beverly Raney, R., Walterhouse, D.O., Meza, J.L., Andraszy, R.J., Brennan, J.C., Crist, W.M., Maurer, H.M., Meyer, W.H., Parham, D.M., Anderson, J.R., 2011. Results of the Intergroup Rhabdomyosarcoma Study Group D9602 Protocol, Using Vincristine and Dacinomycin With or Without Cyclophosphamide and Radiation Therapy, for Newly Diagnosed Patients With Low-Risk Embryonal Rhabdomyosarcoma: A Report From the Soft Tissue Sarcoma Committee of the Children’s Oncology Group. JCO 29 (10), 1312–1318.

Bhatia, N., Aoki, D., Sharma, D.N., Sankaranarayanan, R., 2018. Cancer of the cervix uteri. Int. J. Gynecology & Obstetrics. 143, 22–36. O’Connor, D.M., Norris, H.J., 1994. The Influence of Grade on the Outcome of Stage I Ovarian Immature (Malignant) Teratomas and the Reproducibility of Grading. International Journal of gynecological Pathology. 13 (4), 283–289.

Shinkai, T., Masutomo, K., Chiha, F., Shirane, K., Tanaka, Y., Aiyoshi, T., Sasaki, T., Ono, K., Gotoh, C., Urita, Y., Takayasu, H., Suzuki, R., Sakashita, S., 2020. Pediatric ovarian immature teratoma: Histological grading and clinical characteristics. J. Pediatric Surgery. 55 (4), 707–710.

Diagnostic work-up in paediatric and adolescent patients with adnexal masses: an evidence-based approach. J. Obstet. Gynaecol. 41 (4), 503–515.

Bezniedenho, J., Schneider, J.W., Hugo, F., Wessels, G., 1997. Teratomas in infancy and childhood at Tygerberg Hospital, South Africa, 1973 to 1992. Arch. Pathol. Lab. Med. 121 (5), 499–502. PMID: 9167604.

Lucas, S.B., Vella, E.J., 1983. Ovarian tumors in Malawi – a histopathological study. J Obstet Gynaecol East Cent Africa. 2 (3), 97–101. PMID: 12340193.

Akgan, E.E., Odnufa, A.O., Agbadigiu, P.U., 1994. A review of teratomas in Ibadan. Afr. J. Med. Med. Sci. 23 (1), 53–60. PMID: 7839947.

Young, R.H., 2005. Sex cord-stromal tumors of the ovary and testis: their similarities and differences with consideration of selected problems. Mod. Pathol. 18 (Suppl 2), S81–S98. https://doi.org/10.1038/modpathol.3800311. PMID: 15502809.

Ray-Coquard, I., Brown, J., Harter, P., Provencher, D.M., Fong, P.C., Maenpaa, J., Ledermann, J.A., Emms, G., Bignall, D.B., Glasgow, R.M., Mezzanzanica, D., Colombo, M., 2014. Gynecologic Cancer Intergroup (GCIG) consensus review for ovarian sex cord stromal tumors. Int J Gynecol Cancer. 24 (9 Suppl 3), S42–S47. https://doi.org/10.1007/IGGC.0000000000000249. PMID: 23541179.

Schneider, D.T., Janig, U., Calaminus, G., Gebel, U., Harms, D., 2003. Ovarian sex cord-stromal tumors—a clinicopathological study of 72 cases from the Kiel Pediatric Tumor Registry. Virchows Arch. 443 (4), 549–560. https://doi.org/10.1007/s00428-003-0869-0. Epub 2003 Aug 9 PMID: 12910419.

Fernandez-Pineda, I., Spunt, S.L., Parida, L., Krasin, M.J., Davidoff, A.M., Rao, B.N., 2011. Vaginal tumors in childhood: the experience of St Jude Children’s Research Hospital. J. Pediatric Surgery. 46 (11), 2071–2075.

Walterhouse, D.O., Pappo, A.S., Meza, J.L., Brennan, J.C., Hayes-Jordan, A.A., Parkham, D.M., Crine, T.P., Anderson, J.R., Meyer, W.H., Hawkins, D.S., 2014. Shorter-Duration Therapy Using Vinristine, Dacinomycin, and Lower-Dose Cyclophosphamide With or Without Radiotherapy for Patients With Newly Diagnosed Low-Risk Rhabdomyosarcoma: A Report From the Soft Tissue Sarcoma Committee of the Children’s Oncology Group. JCO 32 (31), 3547–3552.

Beverly Raney, R., Walterhouse, D.O., Meza, J.L., Andraszy, R.J., Brennan, J.C., Crist, W.M., Maurer, H.M., Meyer, W.H., Parham, D.M., Anderson, J.R., 2011. Results of the Intergroup Rhabdomyosarcoma Study Group D9602 Protocol, Using Vincristine and Dacinomycin With or Without Cyclophosphamide and Radiation Therapy, for Newly Diagnosed Patients With Low-Risk Embryonal Rhabdomyosarcoma: A Report From the Soft Tissue Sarcoma Committee of the Children’s Oncology Group. JCO 29 (10), 1312–1318.

Bhatia, N., Aoki, D., Sharma, D.N., Sankaranarayanan, R., 2018. Cancer of the cervix uteri. Int. J. Gynecology & Obstetrics. 143, 22–36. O’Connor, D.M., Norris, H.J., 1994. The Influence of Grade on the Outcome of Stage I Ovarian Immature (Malignant) Teratomas and the Reproducibility of Grading. International Journal of gynecological Pathology. 13 (4), 283–289.

Shinkai, T., Masutomo, K., Chiha, F., Shirane, K., Tanaka, Y., Aiyoshi, T., Sasaki, T., Ono, K., Gotoh, C., Urita, Y., Takayasu, H., Suzuki, R., Sakashita, S., 2020. Pediatric ovarian immature teratoma: Histological grading and clinical characteristics. J. Pediatric Surgery. 55 (4), 707–710.