Seminars in Diagnostic Pathology 38 (2021) 99–109

Contents lists available at ScienceDirect

Seminars in Diagnostic Pathology

journal homepage: www.elsevier.com/locate/semdp

Review article

Pediatric vulvar malignancies: rare but important to know

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ARTICLE INFO

Keywords:
Pediatric vulvar malignancy
Squamous cell carcinoma
Yolk sac tumors
Primitive neuroectodermal tumor
Melanoma
Rhabdomyosarcoma

ABSTRACT

Malignancies of the vulva in the pediatric population are exceptionally rare, which makes it difficult to gain any insight into their clinicopathologic profile. In this review, we summarize all published cases of a vulva malignancy in pediatric patients (≤21 years) reported in the English language literature for the 50-year period between 1970 and 2020. We estimate that less than 100 malignancies have been reported in total, approximately 50% of which were rhabdomyosarcomas. Invasive squamous cell carcinomas, yolk sac tumors, Ewing sarcoma/primitive neuroectodermal tumors (ES/PNET) and melanomas each represented approximately 10% of reported cases. For rhabdomyosarcoma, the alveolar and embryonal subtypes were reported with equal frequency, with both representing 70% of cases combined. The average patient age was 9.8 years. 48% and 35% were Intergroup Rhabdomyosarcoma Study clinical groupings I and III respectively. Managements were generally multimodal, and overall outcomes for the group were favorable. For invasive squamous cell carcinoma, the patients were all in their teenage years, with an average age at diagnosis of 15.2 years. A small subset of cases were associated with human papillomavirus and immunosuppression, and it is possible that immunosuppression has a role in vulvar squamous carcinogenesis in this population. One case was associated with lichen sclerosus. The patients with yolk sac tumors ranged in age from less than 1 year to 20 years (mean 12) and 67% of cases were stage I at presentation. An insufficient number of cases have been reported to define their prognosis, although some cases were notably aggressive. The few reported cases of melanoma are distinctive only because they were all associated with lichen sclerosus, suggestive of some role for the latter in their pathogenesis. The average age of patients reported with ES/PNET was 15 years (range 3.3 to 20). At least half of the reported cases were advanced stage at presentation, and patient outcomes were notably poor: 62.5% were dead of disease at follow-up. Pediatric vulvar malignancies are rare and are mostly comprised of 5 entities. Their accurate pathologic classification is necessary to facilitate optimal management.

Introduction

Genital tract tumors are uncommon in the pediatric population, and represent 5-10% of all tumors diagnosed in females during the first 2 decades of life.[1] Malignancies of the gynecologic tract in pediatric patients are exceptionally rare, and almost 90% of them originate from the ovary and cervix.[2] Tumoral masses of the adnexa in this population are predominantly benign or non-neoplastic,[3,4] whereas most neoplasms at the other sites of the gynecologic tract are malignant.[1-5] In one analysis from a tumor registry that included 251 females ≤25 years old, the most common histological types at each site were germ cell tumors (35%) for the ovary, squamous cell carcinoma (52%) for the cervix, choriocarcinoma (18%) for the uterus, and squamous cell carcinoma (30%) for the vulva/vagina.[2]

The literature on pediatric vulvar malignancies is composed predominantly of case reports and small case series. Their distinct rarity may also increase the potential for their pathologic mischaracterization, since most practitioners have limited experience with these tumors and any diagnosis of a vulvar malignancy is expected to be non-routine. In this review, we summarize the clinicopathologic features of all reported cases of a vulvar malignancy in patients ≤21 years of age over the past 50 years (1970-2020). Our literature review was restricted to English language publications that were indexed in the PubMed, EMBASE, and Cochrane library databases as of August 2020. We estimate that less than 100 pediatric vulvar malignancies have been reported in total, approximately 50% of which were rhabdomyosarcomas, with invasive squamous cell carcinomas, yolk sac tumors, Ewing sarcoma/primitive neuroectodermal tumors and melanomas each representing

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https://doi.org/10.1053/j.semdp.2020.09.001

Available online 05 September 2020

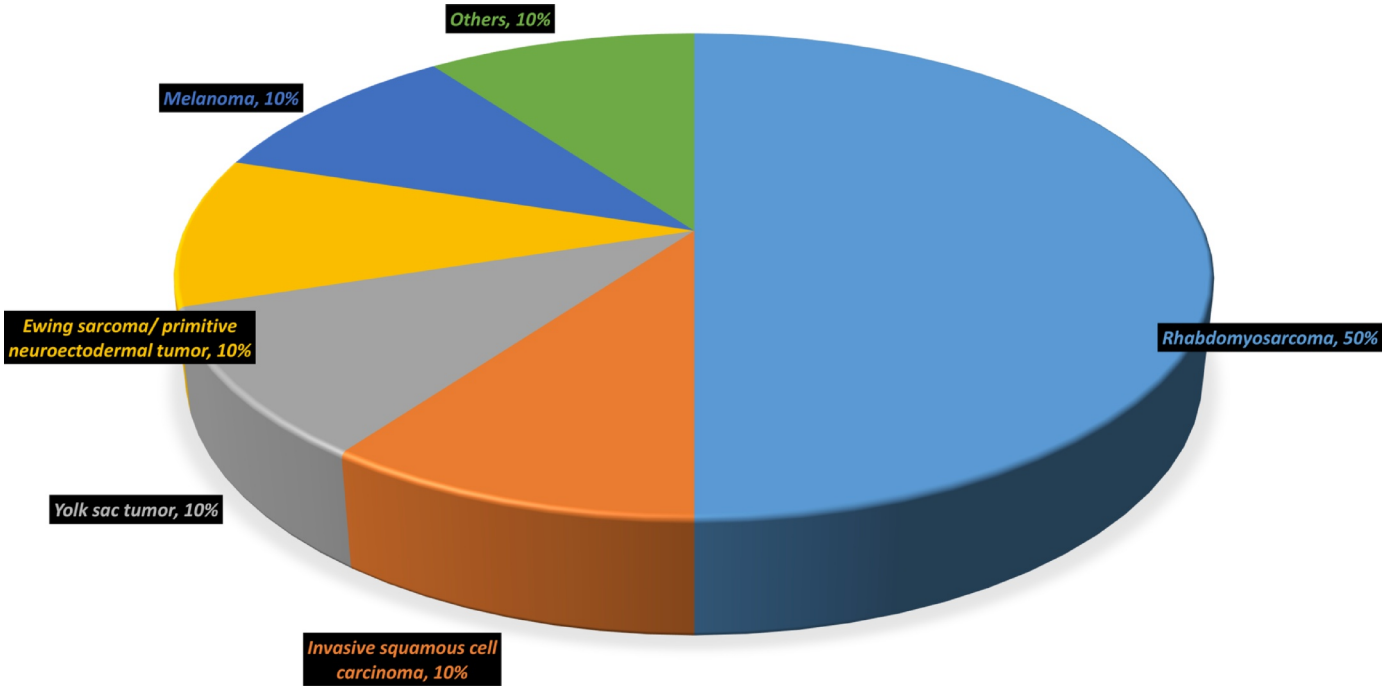

Fig. 1. Estimated distribution of tumor types in reported pediatric vulvar malignancies.

approximately 10% of cases (Fig. 1). However, our specific analyses were restricted to those cases with individual patient-level of data itemization. These are described in more detail below.

Invasive squamous cell carcinoma

Vulvar carcinomas of the young have been described in sporadic reports that go back at least a century. In their 1972 report, Lister and Akinla briefly described the literature up to that point, which consisted of at least 13 cases that had been reported between 1907 and 1965.[6] However, given the variability in the level of histologic documentation in some of the earlier reports, as well as the substantial evolution in the diagnostic approaches to these lesions that has taken place since the earliest of these reports were first published, we restricted our present analysis to those that were reported for the 50 year period between 1970 and mid 2020 (Table 1).[6-14] All cases involved patients in their teenage years, with an average age at diagnosis of 15.2 years (range 14-19); The tumors presented clinically as one or multiple polypoid lesions that were not infrequently ulcerated. All reported cases were squamous cell carcinomas. Where histologic grade was stated, the carcinomas were described as well differentiated, although one was classified as poorly differentiated. The background vulvar epithelium showed conventional high grade squamous intraepithelial lesion in 22%, chronic inflammation in 22%, and lichen sclerosus in 11%. Human papillomavirus (HPV) was reported as positive in 33%, but it was unclear whether HPV testing was performed in the other cases. 2 of the 9 patients showed some evidence of immunosuppression, but this information was often unstated in the remaining reports. Management approaches generally involved excision, with or without additional adjuvant therapies. Follow-up information was available in 6 of the 9 reported cases: 2 deaths were directly or indirectly attributable to their tumors, whereas the remaining 4 patients showed no evidence of disease at follow-up.

The rarity of vulvar carcinomas preclude drawing broad conclusions about their clinicopathologic profile. However, they can be understood within the broader context of vulvar squamous cell carcinomas, which are generally classified into two subtypes that display broad clinicopathologic differences. Approximately two-thirds of cases are HPV-independent.[15] These HPV-negative squamous cell carcinomas are typically found among older women, arise in a background of pre-existing conditions such as lichen sclerosus and chronic inflammatory dermatoses, are associated with putative precursors such as differentiated vulvar intraepithelial neoplasia, differentiated exophytic vulvar intraepithelial lesion, and vulvar acanthosis with altered differentiation, frequently display *TP53* mutations, may be less sensitive to radiotherapy, and have a comparatively worse prognosis.[15-17] HPV-positive squamous are less common, are seen in a comparatively younger age group, are associated with conventional high grade squamous intraepithelial lesion (VIN II/III) as its precursor lesion, may be more radiosensitive, and has a generally more favorable prognosis.[15-17] The reported cases of pediatric vulvar squamous cell carcinoma appear to pathogenetically encompass lesions in both groups, with subsets that appear to be HPV-mediated and others that are apparently HPV-independent. Possible risk factors that were discernible, even in our small cohort, include HPV infection, immunosuppression, Fanconi anemia, and lichen sclerosus.

The role of immunosuppression as a possible driver of, or contributor to, vulvar carcinogenesis in this patient population is worthy of additional mention. As was previously noted, 2 of the 9 patients in our review were reported to have immunosuppression, including the case of a 12-year-old girl with vertically acquired HIV infection who developed an invasive squamous cell carcinoma,[7] and the case of the patient with 2 risk factors –Fanconi anemia and immunosuppression – who ultimately died of fungal sepsis.[14] Kim et al.[18] also described the case of a 16-year-old patient that had been on immunosuppressive drugs following a liver transplantation, and who developed vulvar masses that were ultimately diagnosed as high grade squamous intraepithelial lesions. It is well recognized that post-transplant adults have an increased risk for developing vulvar carcinomas,[19] which is probably related, at least in part, to the susceptibility to HPV-mediated carcinogenesis in the setting of immunosuppression. Indeed, one analysis found 100% of the vulvar epithelial neoplasms in post-transplant recipients to be HPV-mediated, as compared to 21-57% in immunocompetent patients.[20] Notably, all of the 3 aforementioned patients with immunosuppression also had HPV-positive vulvar lesions.[7,14,18] In one analysis of 27 patients with vulvar malignancies in young patients (average age 33.3

Table 1
Summary of reported cases of pediatric vulvar invasive squamous cell carcinomas (SCC), (1970-2020)**.

Source, year (reference)	Age, years	Location	Gross/ clinical findings	Histologic features	in situ component	HPV status	Immunologic status	Treatment	Outcome
Lister and Akinla, 1972[6]	14	Entire vulva	Large friable mass	Well differentiated invasive squamous cell carcinoma with hyperkeratosis and marked mitotic activity and numerous keratin pearls; superimposed on chronic vulva granuloma	Absent	Not mentioned	Immunocompetent	Wide excision and lymphadenectomy	Not specified
Cario et al, 1984[8]	18	Left labium majus	Raised ulcerated lesion	Well differentiated invasive squamous cell carcinoma, background of subepithelial chronic inflammation and lichen sclerosus	Absent	Not mentioned	Immunocompetent	Radical vulvectomy, bilateral superficial lymphadenectomy	Uneventful post-operative course, lichen sclerosus returned
Nilsson et al, 1990[9]	16	Left labium majus	Ulceration on majus; enlarged, hard left groin node palpated	Well differentiated squamous cell carcinoma, positive margins, lymph node positive by fine needle aspiration	Not specified	Not mentioned	Not mentioned	External beam radiation, vulvectomy, lymph node dissection, post operative inguinal radiation, chemotherapy, palliative radiation	Died of disease in 2 years
Roman et al, 1991[10]	16	Left labium majus	Inflamed, indurated lesion	Focal invasive squamous cell carcinoma with extensive VIN III	Present	HPV in situ hybridization negative	Immunocompetent	Radical wide excision, left superficial groin node dissection	NED, 8 months
Rabah and Farmer, 1999[11]	12	Not specified	Not specified	Superficially invasive squamous cell carcinoma with VIN III	Present	Not specified	Not specified	Not specified	Not specified
Giaquinto et al, 2000[7]	12	Left labium	Vegetative mass	Well differentiated SCC with very high mitotic index	Present	HPV 16 positive (PCR)	Immunosuppressed (HIV positive)	Left hemivulvectomy, partial resection of right hemivulva, amputation of clitoris, bilateral lymphadenectomy	NED
Carvalho et al, 2002[14]	14	Left labium majus, clitoris, urethra	Ulcerated lesion, enlarged inguinal lymph nodes palpated	Well differentiated squamous cell carcinoma	Not mentioned	HPV 16 positive (PCR)	Immunosuppressed (history of Fanconi's anemia	Neoadjuvant chemotherapy and radiotherapy, left hemicolectomy, partial enterectomy, terminal ileostomy	Died of disease 2 days after last surgery due to systemic infection caused by *Candida tropicalis*
Serkies et al, 2002[12]	16	Right labium minora	Not specified	Poorly differentiated squamous cell carcinoma	Not mentioned	Not mentioned	?Immunocompetent	Local excision, wide local resection, ipsilateral groin dissections of nodal metastases, ipsilateral pelvic lymphadenectomy, external beam irradiation	NED, 6.5 years
Angelico et al, 2019[13]	19	Not specified	Not specified	Squamous cell carcinoma	Not specified	Not specified	Not specified	Wide local excision, bilateral inguinofemoral lymphadenectomy, radiotherapy	Not specified, FIGO stage IIIA

NED: no evidence of disease; HPV: human papillomavirus; PCR: polymerase chain reaction; FIGO: International Federation of Gynecology and Obstetrics; VIN vulvar intraepithelial neoplasia. ** excludes at least one case (reference 21), for not meeting study criteria (lack of individual patient data itemization)

Table 2
Summary of reported cases of pediatric vulvar yolk sac tumors (1970-2020).

Source, year (reference)	Age, years	Location	Size, cm	FIGO stage	Histologic features	Schiller-Duval bodies present
Ungerleider et al, 1978[30]	15	Right labium majus	4	IB	Reticular/ microcystic	Unknown
Castaldo et al, 1980[31]	2	Clitoris	1.5	IB	Reticular/ microcystic	Unknown
Dudley et al, 1983[32]	0.9	Right labium majus	7	IB	Reticular/ microcystic, solid	Present
Flanagan et al, 1997[34]	18	Right labium majus	5	IB	Hepatoid, papillary, glandular	Present
Traen et al, 2004[35]	19	Right labium majus	2.5	IB	Reticular/ microcystic	Present
Chang et al, 2011[36]	14	Left labium majus	5	IIIB	Reticular/microcystic, solid, glandular	Present
Mochizuki et al, 2012[33]	1	Right labium majus	3	IB	Not described	Present
Euscher, 2017[28]	17	Right labium majus	1.2	IIIB	Reticular/ microcystic, solid, glandular	Present
Kishore et al, 2019[37]	20	Suprapubic region	5	Unknown	Solid, reticular, microcystic, pseudopapillary	Present
Source, year (reference)	**Non-YST component**	**IHC**	**Treatment**	**Follow up, months**	**Serum AFP levels**	
Ungerleider et al, 1978[30]	Embryonal carcinoma	Not done	Excision	Died of disease, 23	Unknown	
Castaldo et al, 1980[31]	None	Not done	Excision	No evidence of disease, 42	Within normal limits	
Dudley et al, 1983[32]	None	AFP positive	Neoadjuvant chemoradiation, excision	Died of disease, 6	Unknown	
Flanagan et al, 1997[34]	None	AFP positive	Excision, chemotherapy, radiation	No evidence of disease, 18	29.3 mg/dL	
Traen et al, 2004[35]	Immature teratoma	AFP positive	Excision, chemotherapy	No evidence of disease, 40	Within normal limits	
Chang et al, 2011[36]	Embryonal carcinoma	Not done	Neoadjuvant therapy, excision	No evidence of disease, 26	25.8 ng/mL	
Mochizuki et al, 2012[33]	None	AFP positive	Excision, chemotherapy	No evidence of disease, 99	4986 ng/dL	
Euscher, 2017[28]	None	AFP positive, glypican3 positive, SALL4 positive, CK20 positive, CDX2 positive, CK7 negative	Excision, non-germ cell chemotherapy	Alive with disease, 36	Unknown	
Kishore et al, 2019[37]	None	HCG negative, CA19.9 negative, CEA negative, panCK positive, SALL4 positive	Excision	Not mentioned	99.3 ng/mL	

YST: Yolk sac tumor; AFP: alpha fetoprotein; HCG: human chorionic gonadotropin; IHC: immunohistochemistry; SALL4: Sal-like protein 4; CK: cytokeratin; FIGO: International Federation of Gynecology and Obstetrics

Table 3
Summary of reported cases of vulvar melanoma (1970-2020)**.

Source, year (reference)	Age, years	Location	Gross/ clinical findings	Histology	Background pathology	Breslow depth, mm (Clark level)	Treatment	Outcome
Friedman et al, 1984[55]	14	Two lesion: Left and Right labium minus	Dark brown to black lesion; Dark brown lesion	Malignant melanoma	Lichen sclerosus	0.7 mm	Wide excision Node dissection	No evidence of disease 12 months after excision
Egan et al, 1997[58]	9	Right labium minus	Less than 1 cm irregular pig¬mented dark-brown macule sion; numerous depigmented patches of vitíligo on the left lower extremity	melanoma in situ: "severe junctional melanocytic dysplasia with nuclear pleomorphism and variation in size and shape" effacing¬dermoepidermal junction.	Lichen sclerosus	Not applicable (I)	Wide excision	Not stated
Egan et al, 1997[58]	11	Right labium minus	7-mm hyperpigmented macule that had been progressively increasing in size	"melanocytic dysplasia at the dermoepidermal junction. Individual melanocytes revealed significant nuclear pleomorphism. Some of the atypical melanocytes had migrated individually into the stratum malpighii. Scattered nests of atypical melano¬cytes were seen in the papillary dermis"	Lichen sclerosus	0.47 mm (II)	Wide excision	Not stated
Hassanein et al, 2004[56]	10	Left labium minus	Dark brown pigmented lesion, lichen sclerosus clinically apparent	Atypical melanocytic proliferation along dermo-epidermal junction and in superficial reticular dermis	Lichen sclerosus	0.44 (II)	Wide excision, partial vulvectomy	Alive without disease
Rosamila et al, 2006[57] and Wechter et al, 2004[54]	10	Left	two distinctly separate black lesions with asymmetry and irregular borders; Lymph node metastases;	Melanoma unclassified; no ulceration	Lichen sclerosus	1.0 mm and 0.36 mm	Therapeutic lymphadenectomy; high-dose adjuvant interferon alfa-2b for 1 year	No evidence of disease 32 months after excision
La Spina et al, 2016[59]	11	Right labium majus, left labium majus	"intense vulvar itching without evident lesions. One month later she developed a flat linear hyperpigmented lesion with irregular shape and edges on the right labium majus and a small, roundish, slightly pigmented lesion on the left labium majus associated with diffuse vulvar Lichen sclerosus"	superficial spreading melanoma, no dermal mitotic figures, no ulceration, no lymphovascular vascular infiltration	Lichen sclerosus	0.5 (III)	"complete yet conservative regional excision"	No evidence of disease 1 year after excision

** excludes cases, such as those reported in references 52 and 53, for not meeting study criteria (lack of individual patient data itemization)

years, range 19-40), and which are not included in the present analysis due to a lack of individual patient-level data itemization, the authors noted that smoking and a history of immunosuppressive medical diseases were quite common in their cohort,[21] findings that were confirmatory of prior anecdotal observations by Buscema et al.[22]

Yolk sac tumor/Endodermal sinus tumor

Extragonadal germ cell tumors are very uncommon, with an overall incidence of 1.8 to 3.4/1 million in the United States.[23] The clinicopathologic profiles of extragonal germ cell tumors can differ significantly depending on patient age, location, and histologic type.[24-26] In childhood, extragonadal germ cell tumors represent 46% of all germ cell tumors.[27] The precise etiopathogenesis of extragonadal germ cell tumors is not entirely unclear, although aberrant germ cell migration along the gubernaculum is considered the leading hypothesis.[28] Vulvar yolk sac tumors (YST) are notably rare, and their occurrence in younger patients is exceptional.[28] We identified a total of 9 cases, as outlined in Table 2.[29-37] The patients ranged in age from less than 1 to 20 years (median 15, mean 12), and typically presented with a painless nodular lesion or vulvar enlargement. Serum alpha-fetoprotein levels were elevated where measured. The tumors ranged in size from 1.5 to 7 cm (mean 3.8 cm) and 67% of cases were stage I at presentation. The right labium was the most site of involvement, wherein the tumor originated in 6 of 9 cases. The morphologic features of the reported cases were in keeping with the typically heterogeneous profile of YSTs,[28,38] with the reticular/microcystic pattern predominating in most cases. For the cases where their presence or absence was described, Schiller-Duvall bodies were invariably present. Three cases were associated with a non-YST, germ cell tumor component (immature teratoma in 1 case; embryonal carcinoma in 2). The patients were treated with various combinations of excision and neoadjuvant or adjuvant chemotherapy, and patient outcomes were similarly variable. Patient outcomes in some of the earlier reports suggested that YST is an intrinsically aggressive malignancy.[29,30] However, additional cases that have since been reported suggest that this may be an oversimplification. Too few cases have been reported to know precisely which factors are the primary determinants of patient outcome, although they may display clinically aggressive behavior.

The pathologic differential diagnosis for YST is as broad as the morphologic spectrum for this enigmatic tumor, issues that are discussed in detail elsewhere.[28,38] Well recognized histologic patterns include reticular/microcystic, pseudopapillary, polyvesicular-vitelline, parietal, glandular, hepatoid and solid.[38] Schiller-Duval bodies are characteristic,[25,26,28,38] whereas the typical immunophenotype is positive immunoreactivity for alpha fetoprotein (AFP), Glypican 3, and SALL4; the latter lacks diagnostic specificity within germ cell tumors.[38,39] One site-specific differential diagnostic consideration that is worthy of specific mention is clear cell carcinoma (CCC), which may originate from the vagina in children and may secondarily involve the vulva.[40] YST and CCC may potentially share a variety of pathologic attributes, including clear cells, solid, glandular or papillary units, hyaline globules, immunoreactivity for hepatocyte nuclear factor 1 beta, and lack thereof for the estrogen and progesterone receptors. However, the specific cytoarchitecture of CCC is distinct, as is their immunoreactivity for Napsin A.[41] Although overlap undoubtedly exist in their immunophenotypes, clear cell carcinoma are more likely than YST to show a SALL4-positive, AFP-positive, Glypican 3-positive, CK7-diffusely positive immunoprofile. Furthermore, an elevated serum AFP favors YST.

Melanoma

Although melanomas in pediatric patients represent less than 5% of all cutaneous melanomas, they are the most common skin malignancies among pediatric and adolescent individuals.[42-44] and display a preponderance in females.[45-47] Overall, malignant melanoma of the vulva represent 2.4-10% of all vulvar malignancies, second only to invasive squamous cell carcinomas in frequency.[48,49] However, vulvar melanomas of the young are quite rare, and they are generally not specifically reported even in large-scale population based studies of pediatric melanoma, where they are presumably subsumed in the "other" category of these datasets.[50,51] In three single institutional series of vulva melanoma, approximately 2 to 5% of patients were <21 years of age.[52-54]

In the present analysis, we identified a total of 6 cases that met our search criteria,[54-59] diagnosed in patients that ranged in age from 9 to 14 years (mean 10.8). The cases are therefore better conceptualized as being akin to postpubertal or peri-pubertal cutaneous melanomas, which have been shown to be clinicopathologically distinct from their prepubertal counterparts.[60] The cases included 1 case of melanoma in situ[58] and 5 cases of invasive melanoma.[54-57,59] Their clinicopathologic attributes are summarized in table 3. The observed ratio of in situ to invasive melanoma is consistent with a large scale epidemiologic study on melanomas in the pediatric population that found that 22% of the melanomas in this setting are in situ.[51] Although the patients were caucasian where their race/ethnicity were stated, they were generally devoid of other traditional risk factors that may theoretically predispose them, including large congenital melanocytic nevi, dysplastic nevi, family or personal history of melanoma, increased ultraviolet light exposure and/or a sun-sensitive phenotype, and immunosuppression.[61] Nonetheless, there was a distinctly noteworthy association: all 6 had concurrent lichen sclerosus, a possible association whose mechanistic basis is unclear. Lichen sclerosus in childhood is a rare but firmly established condition, with an estimated prevalence of premenarchal lichen sclerosus of 1 in 900.[62] In one recent meta-analysis of the literature that was comprised of 1707 female patients, the mean age of disease onset was 6.5 years [range 4 months to 14 years) and only rarely did patients present with concurrent extragenital lesions.[63] Lichen sclerosus is not thought to increase the risk of malignancy when diagnosed in prepubertal patients, although truly long term longitudinal follow-up studies are lacking.[64] Melanocytic proliferations are rare in lichen sclerosus, but may encompass the entire spectrum from melanocytic nevi to malignant melanoma, and are accordingly recognized to potentially pose a significant diagnostic challenge.[65,66] This diagnostic conundrum may be further accentuated when they occur in children.[66,67] In one series of 11 vulvar melanocytic proliferations occurring in the setting of lichen sclerosus, 36% were in patients that were less than 21 years old, and all were diagnosed as atypical compound melanocytic nevi.[66]

Atypical genital nevi (AGN), which represent 10% of cutaneous melanocytic proliferations in the genital area,[68] are the principal differential diagnostic considerations for a variety of reasons. AGN is essentially a benign neoplasm that only rarely recurs and when it does recur, does so almost exclusively in the setting of an incomplete primary excision. The median age of occurrence for AGN is 26 years, and they may therefore be identified in pediatric populations.

Histologic features that can be seen in AGN, including a lentiginous and nested junctional component composed of prominent round or fusiform nests (often with a peculiar retraction), cytologic atypia, adnexal involvement, pagetoid spread, and fibrosis in the superficial dermis may also be seen in regressing melanoma and/or melanoma in the setting of lichen sclerosus.[69-71] Carlson et al.[66] found the following features to be useful in distinguishing nevi in the setting of lichen sclerosus from melanoma, as they are more likely to be seen in the former: sharply circumscribed borders, minimal pagetoid scatter if present, concomitant dermal melanocytic nevus, absence of dermal mitotic figures, HMB-45 expression confined to the dermal melanocytes within the sclerosis, and a Ki-67 proliferative index less than 10%. In general, AGN show maturation, and almost half of cases show a large conventional dermal nevus component.[68-71] Some cases may ultimately be impossible to classify in a sampling specimen, and such cases may

Table 4
Summary of reported cases of vulvar rhabdomyosarcoma (1970-2020)**.

Source, year (reference)	Age, years	IRS Clinical group/ Presentation	Location	Tumor size	Tumor type	Gross pathology	Treatment	Follow-up
Copeland et al, 1985[74]	13	I/NS	Adjacent to hymen	NS	ERMS	NS	Excision [TPE), LND; VAC, cyclophosphamide	NED 11 years
Copeland et al, 1985[76]	18	III/NS	Left labium majus	NS	ARMS	NS	Arterial vincristine during XRT	DOD 4 months with widespread metastases
	15	I/NS	NS		ARMS	NS	Excision; VAC	Recurrence 2 moths; living at last follow-up, 12 years after treatment
Hays et al, 1988[81]	16	I/NS	Left labia	NS	ARMS	NS	Excision; ACD + VCN	NED, 7.5 years
	3	I/NS	Left labia	NS	ERMS	NS	Excision; VCN, ACD, local XRT	NED 10 years
	4	IIb/NS	Left labia; inguinofemoral node metastases	NS	ARMS	NS	Excision; Short course of ACD	NED 5 years, LFU
	5	II/NS	Left labia	NS	ERMS	NS	Excision; VAC + XRT	NED 7 years
	19	I/NS	Left labia	NS	"pleomorphic" RMS	NS	Excision; CTX	3 local recurrences at 4,12,56 weeks, excised and radiated; then NED 7 years
	16	IV/NS	Left labia and abdominal mass	NS	"undifferentiated" RMS	NS	CTX	NED 4.5 years
	0.3	III/NS	Left labia	NS	ERMS	NS	Excision; CTX	NED 5.5 years
	0.6	III/NS	Left labia; ?pelvic mass; inguinal nodes positive	NS	ERMS	NS	CTX; inguinal node dissection	NED 4 years
	13	III/NS	Right labia and inguinal node	NS	ERMS	NS	CTX; "partial excision"; node dissection; brachytherapy	AWD at 2.5 years (Pulmonary metastases)
Flamant et al, 1990[78]	14	IV/NS	Labia majora, posterior part	NS	RMS	NS	Brachytherapy; VAC, bleomycin, vinblastine; bleomycin and vinblastine for maintenance	NED 14 years
	13	I/NS	Labia majora, posterior part	NS	RMS	NS	Excision [incomplete); Initially VAC, then VAC-VAD for maintenance; brachytherapy	NED 12 years
	7	I/NS	Labia majora, anterior part	NS	RMS	NS	Excision [incomplete); Initially VAC, then VAC-VAD for maintenance; brachytherapy	NED 11 years
	4	I/NS	Labia majora, anterior part	NS	RMS	NS	Excision (incomplete); brachytherapy; VAC-VAD for maintenance	NED 11 years
Nag, et al, 1993[82]	12	III/NS	Clitoris	3.5 cm	ERMS	NS	Excision (debulking); CTX; high dose remote brachytherapy	NED 22 months
Bond et al, 1994[77]	4	II/slowly growing mass x 4 months	Clitoris	5.5 cm	ARMS	Pale tan, homogeneous and firm	Excision; CTX; XRT	NED 2 years
Andrassy et al, 1995[75]	8	I/localized vulvar mass	NS	NS	ERMS	NS	Excision/dactinomyin, vincristine	NED
	20	I/localized vulvar mass	NS	NS	ARMS	NS	Excision/CTX	NED 4.5 years
	3.5	II/localized vulvar mass	NS	NS	ARMS	NS	Excision/CTX/XRT	NED 7 years
Ghushe and Drugas, 2007[83]	2	NS/firm mobile suprapubic mass increasing in size x 8 months	Clitoris	NS	RMS	NS	NS	NS
Al-Tonbary et al, 2008[79]	3	I/Swelling x 6 months	Clitoris	3.5 cm	"mostly" ERMS	NS	Excision; VAC; XRT	Recurrence at 10 months
Puranik et al, 2010[85]	17	Vulvar mass x 4 months	NS	7 cm	ARMS	"grey-white well circumscribed tumor with a nodular surface"	Excision;	Not stated
Youngstrom & Bartkowski, 2013[80]	2.6	IIA/quickly enlarging mass	Left labia	3 cm	ERMS	NS	Excision; VAC, radiation	Not stated

(*continued on next page*)

require a conservative diagnostic excision. Nevertheless, in general, a diagnosis of vulvar melanoma in the pediatric population should only be rendered if unequivocally diagnostic features are present.

Rhabdomyosarcoma

For the general female population, vulvar sarcomas are rare, and represent 1-3% of vulvar malignancies.[72,73] In one analysis of population based data, the four most commonly diagnosed vulvar sarcomas were dermatofibrosarcoma protuberans (27%), leiomyosarcomas (22.9%), rhabdomyosarcomas (5.7%), liposarcomas (5.1%), and malignant fibrous histiocytomas (5.1%).[72] Vulvar sarcomas reported in pediatric patients have been predominantly rhabdomyosarcomas, and indeed, rhabdomyosarcomas are apparently the most frequently occurring pediatric vulvar malignancy. We estimate that there have been approximately 50 reported cases of pediatric vulvar rhabdomyosarcoma.[74-89] Table 4 outlines data on the 26 cases that met our study criteria. The 26 patients ranged in age from 0.3 to 21 years, with an average of 9.8 years. They presented with a vulvar mass or swelling that was rapidly progressive in some cases and slowly progressive over a several months in others. In 18 [70%] of the 26 cases, the specific vulvar location was stated. There appeared to be a left sided dominance: 10 were centered in the left labia, 2 in the right labia and 4 in clitoris. A plurality of cases was localized at presentation: the Intergroup Rhabdomyosarcoma Study clinical grouping [IRSG] was clearly stated or could easily be inferred in 24 (92%) of the 26 cases, and were as follows: IRSG I [localized disease, completely resected), 11/23; IRSG II (regional disease, grossly resected), 2/23; IRSG III (gross residual disease after surgery), 8/23; IRSG IV (distant metastatic disease at diagnosis) 3/23. In four cases, lymph node metastases were specifically stated to be present. In rhabdomyosarcomas in general, IRS groupings correlate with survival as they represent an iteration of staging and completeness of resection.[90,91] For example, in the IRS-III study, survival rates at 5 years were 93% for patients in group I, 81% in group II, 73% in group III, and 30% in group IV.[91]

The average tumor size in 5 cases where this information was stated was 5.14 cm (range 3 to 7). Gross descriptions of the tumors included "pale tan, homogeneous and firm"[77] and "grey-white well circumscribed tumor with a nodular surface".[85] Regarding histotype, many of the cases preceded contemporary approaches to the classification of rhabdomyosarcomas. Nonetheless, the distribution was as follows: alveolar rhabdomyosarcoma (35%), embryonal rhabdomyosarcoma (35%), rhabdomyosarcoma without further specification (19%), pleomorphic rhabdomyosarcoma (4%), and "undifferentiated" rhabdomyosarcoma (4%). One additional case was described as being "mostly embryonal rhabdomyosarcoma".[79] Managements were generally multimodal, as would be expected for rhabdomyosarcomas, and included combinations of local excisions, hemi-vulvectomies, node dissections where applicable, multi-agent chemotherapy and various radiotherapeutic approaches.[74-85] Overall outcomes for the group were favorable. Of 23 patients with follow-up information, 1 was dead of disease, 1 was alive with the disease, and the remaining were almost entirely without disease, often after many year-intervals. Only 2 patients that were originally thought to be IRSG I recurred. Included in this group was one patient that recurred thrice (at 4, 12 and 56 months) but who then remained free of disease for 7 years after her final recurrence.[81] The second IRSG I patient recurred 10 months after primary management, but about whom additional follow-up information was not reported.[79] Therefore, with an accurate diagnosis and multi-modal management, the prognosis for patients with pediatric vulvar rhabdomyosarcomas appear to be excellent. The reader is referred elsewhere for a detailed examination on the pathologic features for each subtype of rhabdomyosarcoma.[92] However, given the spectrum of reported cases thus far, the principal differential diagnostic consideration from which putative cases of vulvar rhabdomyosarcoma should be distinguished, is Ewing sarcoma/primitive neuroectodermal tumor (ES/

Table 4 (*continued*)

Source, year (reference)	Age, years	IRS Clinical group/ Presentation	Location	Tumor size	Tumor type	Gross pathology	Treatment	Follow-up
Bhattacharyya et al, 2015[84]	21	IV/Progressive vulvar swelling x 7 months	Right labia majora; by imaging, right inguinal and mediastinal lymphadenopathy; lung nodules	6.7 cm	ARMS	NA	VAC, XRT, excision	NED at 6 months

ARMS: alveolar rhabdomyosarcoma; AWD: alive with disease; CTX: chemotherapy; DOD: dead of disease; ERMS: embryonal rhabdomyosarcoma; IRS: The Intergroup Rhabdomyosarcoma Study[90]; NA: not available; NS: not stated; NED: no evidence of disease; RMS rhabdomyosarcoma; VAC: Vincristine, dactinomycin, cyclophosphamide; TPE: total pelvic exenteration; XRT: radiotherapy; VAC-VAD: VAC alternating with vincristine and Adriamycin (VAD); **excludes the cases in references 86-89 for not meeting study criteria (lack of individual patient data itemization or language)

Table 5
Summary of reported cases of pediatric vulvar ewing sarcoma/primitive neuroectodermal tumor (1970-2020).

Source, year (reference)	Age, years	Location	Size, cm	Molecular confirmation	Adjuvant treatment	Outcome
Scherr et al, 1994[93]	10	Left labium major	6.5	no	NA	NA
Lazure et al, 2001[94]	15	NA	20	yes	CT	NED 7 months
McCluggage et al[95]	20	Right labium	6.5	yes	NA	DOD (pulmonary metastases)
	19	NA	4	yes	CT	NA
Tunitsky-Bitton et al, 2015[96]	15	Left labium	5	no	CT	NED 20 months
Xu et al, 2019[97]	3.3	NA	5	yes	CT	DOD 6 months
Halil et al, 2011[98]	14	Left vulva	NA	no	CT, XRT	DOD 9 months
Narayanan et al, 2014[99]	17	Clitoris	3	no	CT, XRT	DOD 6 months
Fong et al, 2008[100]	17	Left vulva	Excisional biopsies: 0.7 × 0.6 × 0.2 and 2.1 × 1.7 × 1.5 cm	yes	CT	NED 48 months
Yang et al, 2012[101]	20	Left labium major	20	yes	None (widely metastatic at presentation; decision not to treat)	DOD 1 month

NA: not available; DOD: dead of disease; NED: no evidence of disease; CT: chemotherapy; XRT: radiotherapy.

PNET), the sporadic occurrence of which has been the subject of several reports.[93-101]

Ewing sarcoma/primitive neuroectodermal tumor

The second most frequently reported sarcoma of the pediatric vulva is ES/PNET, with 10 reported cases.[93-101] Their clinicopathologic features are summarized in Table 5. The average age of the patients was 15 years (range 3.3 to 20). At least half of the reported cases were advanced stage at presentation. The tumors ranged in size from 0.6 to 20 cm, although most tumors were between 3 and 6.5 cm. Patient outcomes were notably poor in the reported cases. Of the 8 with follow-up, 62.5% were dead of disease. Morphologically, ES/PNET are comprised of diffuse sheets of relatively monotonous round cells, often with a high mitotic index, at least focal areas of cytoplasm glycogen, areas of confluent necrosis, and for some tumors, distinct rosette formation. Immunohistochemistry is generally necessary for the pathologic classification of small round blue cells such as ES/PNET. Tumor cells are immunoreactive for CD99 (membranous) and FLI1 (nuclear), and tumors that are more differentiated frequently express neuron specific enolase, synaptophysin and S100 protein.[102] Unlike rhabdomyosarcoma, which is the principal differential diagnostic consideration, they lack immunoreactivity for skeletal muscle-specific markers, such as myogenin and Myo-D1. Extramorphologic studies are often necessary for diagnostic confirmation of ES/PNET at any site, as 85% of cases are associated with the chimeric fusion EWS-FLI1, the product of a t(11;22)(q24;q12) that brings the *EWS* gene on chromosome 22 and the *FLI1* gene on chromosome 11.[101] The diagnoses in 60% of the reported cases of pediatric vulvar ES/PNET were confirmed by molecular studies.

Conclusion

Pediatric vulvar malignancies are exceedingly rare entities. Our review of the literature indicates that less than 100 cases have been reported in total, almost entirely comprised of 5 unrelated entities: rhabdomyosarcomas (50%), invasive squamous cell carcinomas (10%), yolk sac tumors (10%), ES/PNET (10%) and melanomas (10%). The rarity of these malignancies at this site precludes drawing any broad conclusions. Nonetheless, some insights were discernible. Pediatric vulvar rhabdomyosarcoma is associated with favorable outcomes after multimodal management in most cases. Melanomas have a possible association with lichen sclerosus. Care must be taken by the pathologist to avoid mistaking an atypical genital nevus, a benign entity that may be associated with dermal sclerosis, with melanoma (and vice versa), given their morphologic overlap. The small subset of invasive squamous cell carcinomas that were associated with HPV were also associated with immunosuppression, and it is possible that the latter may have a role in carcinogenesis. ES/PNET of the vulva is a clinically aggressive malignancy that is frequently advanced stage at diagnosis and which is associated with a poor prognosis. Yolk sac tumors show clinicopathologic features that are similar to their extra-vulvar counterparts, although too few cases have been reported to truly define their prognosis. Increased awareness and recognition of these entities, and the potential for their occurrence in the pediatric population, is important to optimize management and clinical outcomes.

References

1. Hassan E, Creatsas G, Michalas S. Genital tumors during childhood and adolescence: a clinical and pathological study of 71 cases. *Clin Exp Obstet Gynecol.* 1999;26:20–21.
2. You W, Dainty LA, Rose GS, Krivak T, McHale MT, Olsen CH, et al. Gynecologic malignancies in women aged less than 25 years. *Obstet Gynecol.* 2005;105:1405–1409 Jun.
3. Liu H, Wang X, Lu D, Liu Z, Shi G. Ovarian masses in children and adolescents in China: analysis of 203 cases. *J Ovarian Res.* 2013;6:47.
4. Zhang M, Jiang W, Li G, Xu C. Ovarian masses in children and adolescents - an analysis of 521 clinical cases. *J Pediatr Adolesc Gynecol.* 2014;27(3) e73-7.

5. PDQ® Pediatric Treatment Editorial Board. PDQ Childhood Cervical and Vaginal Cancer Treatment. Bethesda, MD: National Cancer Institute. Updated <12/12/2019>. Available at: https://www.cancer.gov/types/cervical/hp/child-cervical-vaginal-treatment-pdq. Accessed <08/13/2020>.
6. Lister UM, Akinla O. Carcinoma of the vulva in childhood. *J Obstet Gynaecol Br Commonw.* 1972;79:470–473.
7. Giaquinto C, Del Mistro A, De Rossi A, Bertorelle R, Giacomet V, Ruga E, et al. Vulvar carcinoma in a 12-year-old girl with vertically acquired human immunodeficiency virus infection. *Pediatrics.* 2000;106:E57.
8. Cario GM, House MJ, Paradinas FJ. Squamous cell carcinoma of the vulva in association with mixed vulvar dystrophy in an 18-year-old girl. Case report. *Br J Obstet Gynaecol.* 1984;91:87–90.
9. Nilsson T, Alm P, Malmström H, Simonsen E, Tropé C. A 16-year-old girl with invasive carcinoma of the vulva. *Acta Obstet Gynecol Scand.* 1990;69:541–542.
10. Roman LD, Mitchell MF, Burke TW, Silva EG. Unsuspected invasive squamous cell carcinoma of the vulva in young women. *Gynecol Oncol.* 1991;41(2):182–185.
11. Rabah R, Farmer D. Squamous cell carcinoma of the vulva in a child. *J Lower Genit Tract Dis.* 1999;3:204–206.
12. Serkies K, Wysocka B, Emerich J, Hrabowska M, Jassem J. Salvage hemipelvis radiotherapy with fertility preservation in an adolescent with recurrent vulvar carcinoma. *Gynecol Oncol.* 2002;85(2) 381-3.
13. Angelico G, Santoro A, Inzani F, Spadola S, Fiorentino V, Cianfrini F, et al. Ultrasound-guided FNA cytology of groin lymph nodes improves the management of squamous cell carcinoma of the vulva: results from a comparative cytohistological study. *Cancer Cytopathol.* 2019;127(8):514–520.
14. Carvalho JP, Nogueira Dias ML, Carvalho FM, Del Pilar Estevez Diz M, Petito JW. Squamous cell vulvar carcinoma associated with Fanconi's anemia: a case report. *Int J Gynecol Cancer.* 2002;12:220–222.
15. Allo G, Yap ML, Cuartero J, Milosevic M, Ferguson S, Mackay H, et al. HPV-independent vulvar squamous cell carcinoma is associated with significantly worse prognosis compared with HPV-associated tumors. *Int J Gynecol Pathol.* 2020;39(4):391–399 Jul.
16. Singh N, Gilks CB. Vulval squamous cell carcinoma and its precursors. *Histopathology.* 2020;76(1):128–138.
17. Sand FL, Nielsen DMB, Frederiksen MH, Rasmussen CL, Kjaer SK. The prognostic value of p16 and p53 expression for survival after vulvar cancer: a systematic review and meta-analysis. *Gynecol Oncol.* 2019;152:208–217.
18. Kim N, Lim S, Cho HY. Pediatric vulvar squamous cell carcinoma in a liver transplantation recipient: a case report. *J Gynecol Oncol.* 2011;22(3) 207-10.
19. Vajdic CM, McDonald SP, McCredie MR, van Leeuwen MT, Stewart JH, Law M, et al. Cancer incidence before and after kidney transplantation. *JAMA.* 2006;296:2823–2831.
20. Brown MR, Noffsinger A, First MR, Penn I, Husseinzadeh N. HPV subtype analysis in lower genital tract neoplasms of female renal transplant recipients. *Gynecol Oncol.* 2000;79:220–224.
21. Carter J, Carlson J, Fowler J, Hartenbach E, Adcock L, Carson L, et al. Invasive vulvar tumors in young women–a disease of the immunosuppressed? *Gynecol Oncol.* 1993;51(3) https://doi.org/10.1006/gyno.1993.1295 Dec307-10.
22. Buscema J, Woodruff JD, Parmley TH, Genadry R. Carcinoma in situ of the vulva. *Obstet Gynecol.* 1980;55(2) Feb225-30.
23. Stang A, Trabert B, Wentzensen N, et al. Gonadal and extragonadal germ cell tumours in the United States, 1973-2007. *Int J Androl.* 2012;35:616-625.
24. Ronchi A, Cozzolino I, Montella M, Panarese I, Zito Marino F, Rossetti S, et al. Extragonadal germ cell tumors: not just a matter of location. A review about clinical, molecular and pathological features. *Cancer Med.* 2019;8(16):6832–6840 Nov.
25. McKenney JK, Heerema-McKenney A, Rouse RV. Extragonadal germ cell tumors: a review with emphasis on pathologic features, clinical prognostic variables, and differential diagnostic considerations. *Adv Anat Pathol.* 2007;14(2):69–92.
26. Clement PB, Young RH, Scully RE. Extraovarian pelvic yolk sac tumors. *Cancer.* 1988;62(3) 620-6.
27. Harms D, Jänig U. Germ cell tumours of childhood. Report of 170 cases including 59 pure and partial yolk-sac tumours. *Virchows Arch A.* 1986;409(2) 223-39.
28. Euscher ED. Unusual presentations of gynecologic tumors: extragonadal yolk sac tumor of the vulva. *Arch Pathol Lab Med.* 2017;141(2) 293-297.
29. Dudley AG, Young RH, Lawrence WD, Scully RE. Endodermal sinus tumor of the vulva in an infant. *Obstet Gynecol.* 1983;61(3 Suppl):76S–79S.
30. Ungerleider RS, et al. Endodermal sinus tumor: the Stanford experience and the first reported case arising in the vulva. *Cancer.* 1978;41(4):1627–1634.
31. Castaldo TW, et al. Endodermal sinus tumor of the clitoris. *Gynecol Oncol.* 1980;9(3):376–380.
32. Dudley AG, et al. Endodermal sinus tumor of the vulva in an infant. *Obstet Gynecol.* 1983;61(3 Suppl):76S–79S.
33. Mochizuki K, et al. Yolk sac tumor of the vulva: a case report with recurrence after long-term follow-up. *Pediatr Surg Int.* 2012;28(9):931–934.
34. Flanagan CW, et al. Primary endodermal sinus tumor of the vulva: a case report and review of the literature. *Gynecol Oncol.* 1997;66(3):515–518.
35. Traen K, et al. Endodermal sinus tumor of the vulva: successfully treated with high-dose chemotherapy. *Int J Gynecol Cancer.* 2004;14(5):998–1003.
36. Yin-Yi Chang C, et al. Vulvar yolk sac tumor mixed with embryonal carcinoma in a peri-pubertal girl: a case report. *Taiwan J Obstet Gynecol.* 2011;50(4):503–505.
37. Kishore M, Malhotra P, Kaushal M, Singh P, Kapur N. Fine needle aspiration (FNA) of subcutaneous lesion: a diagnostic dilemma on cytology. *Cyto J.* 2019;16:17.
38. Nogales FF, Preda O, Nicolae A. Yolk sac tumours revisited. A review of their many faces and names. *Histopathology.* 2012;60(7):1023–1033.
39. Fadare O, Shaker N, Alghamdi A, Ganesan R, Hanley KZ, Hoang LN, et al. Endometrial tumors with yolk sac tumor-like morphologic patterns or immunophenotypes: an expanded appraisal. *Mod Pathol.* 2019;32(12):1847–1860.
40. Fernandez-Pineda I, Spunt SL, Parida L, Krasin MJ, Davidoff AM, Rao BN. Vaginal tumors in childhood: the experience of St. Jude Children's Research Hospital. . *J Pediatr Surg.* 2011;46(11):2071–2075.
41. Fadare O, Parkash V. Pathology of endometrioid and clear cell carcinoma of the ovary. *Surg Pathol Clin.* 2019;12(2):529–564.
42. Paulson KG, Gupta D, Kim TS, Veatch JR, Byrd DR, Bhatia S, et al. Age-specific incidence of melanoma in the United States. *JAMA Dermatol.* 2019;156(1):57–64.
43. Campbell LB, Kreicher KL, Gittleman HR, Strodtbeck K, Barnholtz-Sloan J, Bordeaux JS. Melanoma incidence in children and adolescents: decreasing trends in the United States. *J Pediatr.* 2015;166(6):1505–1513.
44. Siegel DA, King J, Tai E, Buchanan N, Ajani UA, Li J. Cancer incidence rates and trends among children and adolescents in the United States, 2001-2009. *Pediatrics.* 2014;134(4) e945–955.
45. Strouse JJ, Fears TR, Tucker MA, et al. Pediatric melanoma: risk factor and survival analysis of the surveillance, epidemiology and end results database. *J Clin Oncol.* 2005;23:4735–4741.
46. Pappo AS. Melanoma in children and adolescents. *Eur J Cancer.* 2003;39:2651–2661.
47. Conti EM, Cercato MC, Gatta G, et al. Childhood melanoma in Europe since 1978: a population-based survival study. *Eur J Cancer.* 2001;37:780–784.
48. Sugiyama VE, Chan JK, Shin JY, Berek JS, Osann K, Kapp DS. Vulvar melanoma: a multivariable analysis of 644 patients. *Obstet Gynecol.* 2007;110(2 Pt 1):296–301.
49. Zapardiel I, Iacoponi S, Coronado PJ, Zalewski K, Chen F, Fotopoulou C, et al. VULCAN Study coinvestigators. Prognostic factors in patients with vulvar cancer: the VULCAN study. *Int J Gynecol Cancer.* 2020. https://doi.org/10.1136/ijgc-2019-000526.
50. Lorimer PD, White RL, Walsh K, Han Y, Kirks RC, Symanowski J, et al. Pediatric and adolescent melanoma: a national cancer data base update. *Ann Surg Oncol.* 2016;23(12):4058–4066.
51. Austin MT, Xing Y, Hayes-Jordan AA, Lally KP, Cormier JN. Melanoma incidence rises for children and adolescents: an epidemiologic review of pediatric melanoma in the United States. *J Pediatr Surg.* 2013;48(11):2207–2213.
52. Verschraegen CF, Benjapibal M, Supakarapongkul W, Levy LB, Ross M, Atkinson EN, et al. Vulvar melanoma at the M. D. anderson cancer center: 25 years later. *Int J Gynecol Cancer.* 2001;11(5):359–364.
53. Chung AF, Woodruff JM, Lewis Jr JL. Malignant melanoma of the vulva: a report of 44 cases. *Obstet Gynecol.* 1975;45(6):638–646.
54. Wechter ME, Gruber SB, Haefner HK, Lowe L, Schwartz JL, Reynolds KR, et al. Vulvar melanoma: a report of 20 cases and review of the literature. *J Am Acad Dermatol.* 2004;50(4):554–562.
55. Friedman RJ, Kopf AW, Jones WB. Malignant melanoma in association with lichen sclerosus on the vulva of a 14-year-old. *Am J Dermatopathol.* 1984;6(Suppl):253–256 Summer.
56. Hassanein AM, Mrstik ME, Hardt NS, Morgan LA, Wilkinson EJ. Malignant melanoma associated with lichen sclerosus in the vulva of a 10-year-old. *Pediatr Dermatol.* 2004;21(4):473–476.
57. Rosamilia LL, Schwartz JL, Lowe L, Gruber SB, Quint EH, Johnson TM, et al. Vulvar melanoma in a 10-year-old girl in association with lichen sclerosus. *J Am Acad Dermatol.* 2006;54(2 Suppl):S52–S53.
58. Egan CA, Bradley RR, Logsdon VK, Summers BK, Hunter GR, Vanderhooft SL. Vulvar melanoma in childhood. *Arch Dermatol.* 1997;133(3):345–348.
59. La Spina M, Meli MC, De Pasquale R, Perrotta RE, Lanzafame S, Caltabiano R, et al. Vulvar melanoma associated with lichen sclerosus in a child: case report and literature review. *Pediatr Dermatol.* 2016;33(3):e190–e194.
60. Bahrami A, Barnhill RL. Pathology and genomics of pediatric melanoma: a critical reexamination and new insights. *Pediatr Blood Cancer.* 2018;65(2) https://doi.org/10.1002/pbc.26792.
61. Stefanaki C, Chardalias L, Soura E, Katsarou A, Stratigos A. Paediatric melanoma. *J Eur Acad Dermatol Venereol.* 2017;31(10):1604–1615.
62. Powell J, Wojnarowska F. Childhood vulvar lichen sclerosus: an increasingly common problem. *J Am Acad Dermatol.* 2001;44(5):803–806.
63. Balakirski G, Grothaus J, Altengarten J, Ott H. Paediatric lichen sclerosus: a systematic review of 4516 cases. *Br J Dermatol.* 2020;182(1):231–233.
64. Mashayekhi S, Flohr C, Lewis FM. The treatment of vulval lichen sclerosus in prepubertal girls: a critically appraised topic. *Br J Dermatol.* 2017;176(2):307–316.
65. El Shabrawi-Caelen L, Soyer HP, Schaeppi H, Cerroni L, Schirren CG, Rudolph C, et al. Genital lentigines and melanocytic nevi with superimposed lichen sclerosus: a diagnostic challenge. *J Am Acad Dermatol.* 2004;50(5):690–694.
66. Carlson JA, Mu XC, Slominski A, Weismann K, Crowson AN, Malfetano J, et al. Melanocytic proliferations associated with lichen sclerosus. *Arch Dermatol.* 2002;138(1):77–87.
67. Pinto A, Mclaren SH, Poppas DP, Magro CM. Genital melanocytic nevus arising in a background of lichen sclerosus in a 7-year-old female: the diagnostic pitfall with malignant melanoma. A literature review. *Am J Dermatopathol.* 2012;34(8):838–843.
68. Ribé A. Melanocytic lesions of the genital area with attention given to atypical genital nevi. *J Cutan Pathol.* 2008;35(Suppl 2):24–27.
69. Gleason BC, Hirsch MS, Nucci MR, Schmidt BA, Zembowicz A, Mihm Jr MC, et al. Atypical genital nevi. A clinicopathologic analysis of 56 cases. *Am J Surg Pathol.* 2008;32(1):51–57.
70. Clark Jr WH, Hood AF, Tucker MA, et al. Atypical melanocytic nevi of the genital type with a discussion of reciprocal parenchymal-stromal interactions in the biology of neoplasia. *Hum Pathol.* 1998;29(1 Suppl 1) S1–24.
71. Brenn T. Atypical genital nevus. *Arch Pathol Lab Med.* 2011;135(3):317–320.
72. Johnson S, Renz M, Wheeler L, Diver E, Dorigo O, Litkouhi B, et al. Vulvar sarcoma

outcomes by histologic subtype: a surveillance, epidemiology, and end results (SEER) database review. *Int J Gynecol Cancer.* 2020;30(8):1118–1123.
73. DiSaia PJ, Rutledge F, Smith JP. Sarcoma of the vulva. Report of 12 patients. *Obstet Gynecol.* 1971;38(2):180–184.
74. Copeland LJ, Gershenson DM, Saul PB, Sneige N, Stringer CA, Edwards CL. Sarcoma botryoides of the female genital tract. *Obstet Gynecol.* 1985;66(2):262–266.
75. Andrassy RJ, Hays DM, Raney RB, Wiener ES, Lawrence W, Lobe TE, et al. Conservative surgical management of vaginal and vulvar pediatric rhabdomyosarcoma: a report from the Intergroup Rhabdomyosarcoma Study III. *J Pediatr Surg.* 1995;30(7) 1034-6; discussion 1036-7.
76. Copeland LJ, Sneige N, Stringer CA, Gershenson DM, Saul B, Kavanagh JJ. Alveolar rhabdomyosarcoma of the female genitalia. *Cancer.* 1985;56(4):849–855.
77. Bond SJ, Seibel N, Kapur S, Newman KD. Rhabdomyosarcoma of the clitoris. *Cancer.* 1994;73(7):1984–1986.
78. Flamant F, Gerbaulet A, Nihoul-Fekete C, Valteau-Couanet D, Chassagne D, Lemerle J. Long-term sequelae of conservative treatment by surgery, brachytherapy, and chemotherapy for vulval and vaginal rhabdomyosarcoma in children. *J Clin Oncol.* 1990;8(11):1847–1853.
79. Al-Tonbary Y, Zalata K, Sarhan M, El-Ashery R, Fouda A. Rhabdomyosarcoma of the clitoris. *Hematol Oncol Stem Cell Ther.* 2008;1(2):133–135.
80. Youngstrom EA, Bartkowski DP. Vulvar embryonal rhabdomyosarcoma: a case report. *J Pediatr Urol.* 2013;9(4) e144-6.
81. Hays DM, Shimada H, Raney Jr RB, Tefft M, Newton W, Crist WM, et al. Clinical staging and treatment results in rhabdomyosarcoma of the female genital tract among children and adolescents. *Cancer.* 1988;61(9):1893–1903.
82. Nag S, Grecula J, Ruymann FB. Aggressive chemotherapy, organ-preserving surgery, and high-dose-rate remote brachytherapy in the treatment of rhabdomyosarcoma in infants and young children. *Cancer.* 1993;72(9):2769–2776.
83. Ghushe ND, Drugas GT. Rhabdomyosarcoma of the clitoris. *Pediatr Radiol.* 2007;37(11):1179.
84. Bhattacharyya T, Patel FD, Srinivasan R, Rai B, Saha P, Nijhawan R. Rhabdomyosarcoma of vulva in a young lady: a rare case report with review of literature. *J Cancer Res Ther.* 2015;11(3):650.
85. Puranik RB, Naik S, Kulkarni S, Kulkarni MH. Alveolar rhabdomyosarcoma of vulva. *Indian J Pathol Microbiol.* 2010;53(1):167–168. https://doi.org/10.4103/0377-4929.59218.
86. Martelli H, Oberlin O, Rey A, Godzinski J, Spicer RD, Bouvet N, et al. Conservative treatment for girls with nonmetastatic rhabdomyosarcoma of the genital tract: a report from the Study Committee of the International Society of Pediatric Oncology. *J Clin Oncol.* 1999;17(7):2117–2122.
87. Magné N, Oberlin O, Martelli H, Gerbaulet A, Chassagne D, Haie-Meder C. Vulval and vaginal rhabdomyosarcoma in children: update and reappraisal of Institut Gustave Roussy brachytherapy experience. *Int J Radiat Oncol Biol Phys.* 2008;72(3):878–883.
88. Kirsch CH, Goodman M, Esiashvili N. Outcome of female pediatric patients diagnosed with genital tract rhabdomyosarcoma based on analysis of cases registered in SEER database between 1973 and 2006. *Am J Clin Oncol.* 2014;37(1):47–50.
89. Fábregues A, Colmenero I, Torrelo A, Azorín D, de Prada I, Contra T, et al. Congenital botryoid rhabdomyosarcoma of the vulva. *Actas Dermosifiliogr.* 2005;96(3):188–190.
90. Maurer HH, Beltangady M, Gehan EA, Crist W, Hammond D, Hays DM, et al. The intergroup rhabdomyosarcoma study-I. A final report. *Cancer.* 1988;61(2):209–220.
91. Crist W, Gehan EA, Ragab AH, et al. The third intergroup rhabdomyosarcoma study. *J Clin Oncol.* 1995;13:610–630.
92. Leiner J, Le Loarer F. The current landscape of rhabdomyosarcomas: an update. *Virchows Arch.* 2020;476(1):97–108.
93. Scherr G R, d'Ablaing G, 3rd, Ouzounian JG. Peripheral primitive neuroectodermal tumor of the vulva. *Gynecol Oncol.* 1994;54:254–258.
94. Lazure T, Alsamad I A, Meuric S. al Primary uterine and vulvar Ewing's sarcoma/peripheral neuroectodermal tumors in children: two unusual locations. *Ann Pathol.* 2001;21:263–266.
95. McCluggage WG, Sumathi VP, Nucci MR, Hirsch M, Dal Cin P, Wells M, et al. Ewing family of tumours involving the vulva and vagina: report of a series of four cases. *J Clin Pathol.* 2007;60(6):674–680.
96. Tunitsky-Bitton E, Uy-Kroh MJS, Michener C, Tarr ME. Primary ewing sarcoma presenting as a vulvar mass in an adolescent: case report and review of literature. *J Pediatr Adolesc Gynecol.* 2015;28(6) e179-83.
97. Xu QQ, Xing WW, Chen G, Dang YW, Luo YG, Chen P, et al. Primitive neuroectodermal tumors of the abdominal wall and vulva in children: report of two cases and review of the literature. *World J Clin Cases.* 2019;7(21):3671–3682.
98. Halil S, Kucuk M, Arvas M, Aydin O, Calay ZZ. Peripheral primitive neuroectodermal tumor (PNET) of the vulva: a case report. *Eur J Gynaecol Oncol.* 2011;32(1):117–118.
99. Narayanan G, Rajan V, Puthusseri J, Kattoor J, Soman LV. Primitive neuroectodermal tumor of the vulva in an adolescent girl. *World J Oncol.* 2014;5(5-6):220–222.
100. Fong YE, López-Terrada D, Zhai QJ. Primary Ewing sarcoma/peripheral primitive neuroectodermal tumor of the vulva. *Hum Pathol.* 2008;39(10):1535–1539.
101. Yang J, Guo Q, Yang Y, Zhang J, Lang J, et al. Primary vulvar Ewing sarcoma/primitive neuroectodermal tumor: a report of one case and review of the literature. *J Pediatr Adolesc Gynecol.* 2012;25 e93-97.
102. Desai SS, Jambhekar NA. Pathology of Ewing's sarcoma/PNET: current opinion and emerging concepts. *Indian J Orthop.* 2010;44(4):363–368.