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Ovarian tumors in children: how common are lesion recurrence and metachronous disease? A UK CCLG Surgeons Cancer Group nationwide study☆,☆☆,★,★★

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ABSTRACT

Background: Ovarian tumors in children are rare, mature teratoma being the most common histological entity. Robust guidelines to aid patient follow-up after resection are distinctly lacking. Although mature teratoma has a very good prognosis following complete resection, small studies have reported the occurrence of metachronous disease and recurrence to a variable degree (2.5–23% of patients). Nevertheless, there are surgeons who recommend no follow-up is required for these children after primary tumor resection. We investigated the incidence of (i) recurrence and (ii) metachronous disease in pediatric patients following ovarian tumor resection.
Methods: Retrospective multicenter study amongst UK pediatric surgical oncology centers. Females <16 years with diagnosis of ovarian tumor from 2006 to 2016 were included. Functional/neonatal ovarian cysts were excluded.
Results: Three hundred ten patients with ovarian tumors treated at 12 surgical oncology centers were identified. Mean age at surgery was 11 years [IQR 8–14]. Most common diagnosis were mature teratoma (57%, 177 cases), immature teratoma (10.9%, 34 cases) and serous cystadenoma (7.7%, 24 cases). 8.1% (25 cases) of all females were identified with tumor recurrence/ metachronous disease. 5.1% (9 cases) of patients with mature teratoma had recurrent/ metachronous disease. Most of these patients were diagnosed at routine clinic follow-up.
Conclusion: Our study clearly shows that ovarian tumor recurrence(s) and metachronous disease occur, even in "benign" ovarian tumors. We recommend female pediatric patients should have robust follow-up care plans after primary diagnosis and resection of ovarian tumor(s).
Level of Evidence Statement: This is a level II evidence study. It is a retrospective multicentre collaborative study which summarizes data from a national cohort of children.

Ovarian tumors in children are rare. The overall incidence is estimated at 2.6 per 100,000 prepubertal females, but varies depending on patient age and histological diagnosis. [1–3] Mature ovarian teratoma, a slow-growing benign tumor with the potential for malignant transformation constitutes the most common prepubertal ovarian neoplasm. [2] Although this tumor generally is thought to have an excellent outlook following complete resection, synchronous and metachronous disease as well as recurrence have been reported. However, the published studies here are few in number and reported risk(s) for recurrence/ metachronous disease is highly variable (2.5%–23%). [4–6].

Management of germ cell tumors in the United Kingdom (UK) is facilitated by the Children's Cancer and Leukemia Group's (CCLG) Guidelines, which are open to varied interpretation, especially in terms of managing mature teratoma. [7] It is therefore not surprising that a recent national survey amongst UK pediatric surgeons demonstrated highly variable practice and follow-up management of patients after ovarian tumor resection. [8] A number of surgeons who responded to the survey do not routinely arrange clinical follow-up for girls after resection of ovarian teratoma, despite some reports demonstrating a risk for recurrence and metachronous disease. [4–6].

We therefore conducted a nationwide multicenter study in the United Kingdom, in order to better clarify the incidence of

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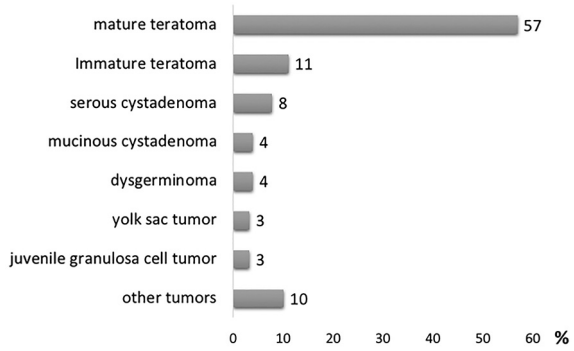

Graph 1. Histology of resected ovarian tumors in the study.

(i) recurrence and (ii) metachronous disease in pediatric patients following ovarian tumor resection.

1. Material and methods

A nationwide study facilitated through the CCLG Surgeons Children's Cancer and Leukemia Group (CCLG) was performed. The study was registered as Audit 7705 with the Royal Manchester Children's Hospital UK as the lead coordinating centre. Participation was open to all pediatric surgical oncology centres in the United Kingdom (UK) on a voluntary basis.

A standardized data collection form was distributed to participating centres. Female patients <16 years with an index diagnosis of ovarian tumor from 2006 to 2016 were included. Patients with functional cysts and neonatal ovarian cysts were excluded. 'Tumor recurrence(s)' was defined as tumor occurring in the same ovary or adjacent adnexal tissue(s) following primary resection. 'Metachronous disease' was defined as a new tumor occurring in the contralateral ovary after a primary operation.

2. Results

2.1. Demographic data, type of presentation and histology

Twelve of 22 UK CCLG registered pediatric surgical oncology centres participated in the study, resulting in a response rate of 55%. Three-hundred ten patients were identified who underwent resection of an ovarian tumor in the time period under review.

One hundred forty-eight patients presented as surgical emergencies, meaning the child presented to the emergency department with acute symptoms. One hundred sixty cases had elective presentation. Elective presentation was defined as General Practitioner referral to hospital outpatient clinics. Mode of referral was unclear in 2 patients.

Median age at surgery was 11 years [IQR 8–14 years]. Most common diagnoses were mature teratoma (57%, 177 cases), immature teratoma (11%, 34 cases) and serous cystadenoma (7.7%, 24 cases); (Graph 1). Follow-up data was available from all except two centres. Median length of follow-up was 18 months [IQR 6–36.75 months].

2.2. Synchronous tumors

Nine children (2.9% of all cases) had bilateral disease at presentation. The median age here was 14 years [IQR 13–14] at diagnosis. Most common pathologies in these patients were mature teratoma (33%), gonadoblastoma (22%) and dysgerminoma (22%).

Two thirds of patients with bilateral disease at their first presentation underwent bilateral total oopherectomy (Table 1a).

2.3. Metachronous disease

Ten children (3.2% of all cases) were subsequently diagnosed with metachronous tumors. Their median age at initial presentation was 9.25 years [IQR 8.25–12.25 years]. The majority of these patients had undergone open operation(s) with total oopherectomy during the first surgical intervention. In 70% cases initial histology diagnosed mature

Table 1a
Details of patients with ovarian tumors that were diagnosed with synchronous disease at their initial operation. (TO: total oopherectomy, OS: ovary sparing surgery, f/u: Follow-up).

Patient ID	Age at initial resection (years)	laparoscopic/open	Extent of resection	Intraoperative rupture/spillage	Histology
Synch1	6	Laparoscopic	TO, bilateral	No	Sex cord stromal tumor
Synch2	2	Laparoscopic	TO, bilateral	No	Dysgerminoma
Synch3	14	Laparoscopic	TO left, OS right	No	Mature teratoma
Synch4	14	Open	TO, bilateral	No	Mature teratoma
Synch5	15	Open	OS, bilateral	No	Borderline serous epithelial tumor
Synch6	15	Laparoscopic	TO, bilateral	No	Gonadoblastoma
Synch7	13	Open	TO, bilateral	No	Dysgerminoma
Synch8	13	Open	OS, bilateral	No	Mature teratoma
Synch9	14	Open	TO, bilateral	No	Gonadoblastoma

Table 1b
Details of patients with ovarian tumors who developed a metachronous ovarian tumor following the initial tumor resection (TO: total oopherectomy, OS: ovary-sparing surgery, f/u: follow-up).

Patient ID	Age at initial resection (years)	laparoscopic/ open	Extent of resection	Intraoperative rupture/ spillage	Histology	Time to detection (months)	Mode of detection	Further surgery
Meta1	10	Open	TO	No	Mature teratoma	12	Routine f/u	Laparoscopic OS surgery
Meta2	13	Laparoscopic	TO	No	Unidentifiable cystic tumor	17	Routine f/u	Complete resection
Meta3	9	Laparoscopic	TO	No	Mature teratoma	12	Routine f/u	OS cystectomy
Meta4	7	Open	TO	No	Mature teratoma	11	Routine f/u	Laparoscopic OS surgery
Meta5	13	Open	TO	No	Mature teratoma	80	Routine f/u	Laparoscopic OS surgery
Meta6	9	Laparoscopic	OS	No	Mature teratoma	21	Routine f/u	Laparoscopic OS surgery
Meta7	8	Open	TO	No	Malignant neuroectodermal tumor	32	Routine f/u	OS cystectomy
Meta8	4	Open	TO	No	Mature teratoma	15	Routine f/u	Laparoscopic OS surgery
Meta9	15	Open	TO	No	Mature teratoma	79	Routine f/u	n/a
Meta10	10	Laparoscopic	TO	No	Gonadoblastoma	Metachronous at presentation	unclear	Resection of tumor

teratoma. Metachronous disease occurred at a median period of 16.5 months [12–32 months] after the initial operation(s). Mode of detection of metachronous tumors was through routine outpatient clinic follow-up surveillance in 90% cases.

A single patient presented to a UK centre with metachronous disease having previously undergone contralateral resection of an ovarian tumor at a hospital in Switzerland (Table 1b; patient *Meta10*). Table 1b shows further details of the cases with metachronous tumors.

2.4. Tumor recurrence

Recurrence occurred in 15 cases (4.8%). The median age at initial presentation was 12 years [IQR 9.5–14 years]. Most patients had undergone an open oopherectomy with total oopherectomy (Table 1c). The majority of recurrences occurred in malignant tumors, most frequently in immature teratoma (6 cases). Two children with mature teratoma had a recurrence. Both of them underwent ovary-sparing surgery in the initial operation. One of the cases was commenced laparoscopically, and then converted to an open procedure, the other one was performed as open procedure. (Table 1c; patient *Rec5* and *Rec9*).

Recurrence of disease was detected at a median period of 12.5 months [IQR 6–15.5 months]. In the majority of these otherwise 'asymptomatic' patients (N = 12) recurrence was confirmed at routine hospital follow-up appointments by US (ultrasound) surveillance imaging. A single patient presented emergently with acute symptoms of abdominal pain. A further patient's recurrence was detected 'incidentally' during an abdominal CT scan for blunt trauma following a road traffic accident.

Overall, 69 children underwent ovary-sparing surgery, compared to 241 who had a total oopherectomy. 7.2% children with ovary-sparing surgery developed recurrent or metachronous disease, compared to 8.2% of children who had undergone total oopherectomy. This was not statistically significant (p = 1).

3. Discussion

The majority of pediatric ovarian tumors are benign [14]. It is widely believed that these tumors carry an excellent prognosis following resection. More recently, some small study series have suggested that there are risk(s) for recurrence and metachronous disease notably with benign neoplasms [4–6]. Large cohort studies to better clarify 'true' incidence as well as the timeframe during which recurrence and metachronous disease are most likely to occur, however, have been distinctly lacking. The 'poor evidence' currently available is therefore likely reflected by the lack of robust follow-up protocol guidance. This in return has resulted in wide variation(s) in management practice of female patients with benign ovarian tumors by pediatric surgeons. [7]

The few studies which have made effort to examine this subject have been small single-centre studies with reported variable rates of tumor recurrence and metachronous disease. A study from Finland recorded metachronous disease in up to 23% of patients. [6] However, findings should be interpreted here with some caution, due to the very small numbers of patients, i.e., only 22 patients with mature ovarian teratoma over a 30 year time period, out of which 5 patients had metachronous disease. [6] A further study from Paris reported metachronous disease in 13% of patients (4 out of 30) with mature teratoma(s). [9] By contrast, a North American publication reported no single case(s) of recurrence or metachronous disease during their patient follow-up. [5] In another single-centre study reported by Rogers et al., 35 females were followed up with annual US imaging scans following ovary-sparing surgery ("cystectomy") for mature teratoma. More than 50% of patients (19 out of 35 cases) here were detected to have some form of 'cystic lesion' on follow-up imaging. Reportedly, only 2 of 35 cases (5.7%) actually went on to have further surgery with a confirmatory histological diagnosis of recurrent / metachronous teratoma. [10]

Table 1c
Details of patients with ovarian tumors who developed a recurrence of the tumor following initial resection (TO: total oopherectomy, OS: ovary-sparing surgery, f/u: follow-up, n/a: not available).

Patient ID	Age at initial resection (years)	Laparoscopic/ open	Extent of resection	Intraoperative rupture/ spillage	Histology	Time to recurrence (months)	Mode of detection	Further surgery
Rec1	12	Open	TO	No	Malignant mixed germ cell tumor	4	Routine f/u	No further surgery performed
Rec2	13	Open	TO	No	Immature teratoma	4	Routine f/u	Laparoscopic resection, under ongoing follow-up
Rec3	14	Open	TO	No	Dysgerminoma	22	unclear	Further resection
Rec4	12	Open	TO	No	Immature teratoma	14	unclear	Further resection
Rec5	7	Lap converted to open	OS	Yes	Mature teratoma	12	Routine f/u	Completion oopherectomy
Rec6	15	Open	TO	No	Immature teratoma	6	Routine f/u	Resection (retroperitoneal teratoma)
Rec7	15	Laparoscopic	OS	No	Serous cystadenoma	50	Incidental finding	Completion oopherectomy
Rec8	8	Open	TO	No	Malignant mixed germ cell tumor	13	Routine f/u	Further resection
Rec9	14	Open	OS	No	Mature teratoma	8	Routine f/u	Further OS cystectomy
Rec10	13	Open	TO	No	Immature teratoma	25	Routine f/u	n/a
Rec11	11	Open	TO	No	Immature teratoma	14	Routine f/u	Resection (pelvic tumor)
Rec12	6	Open	TO	No	Yolk sac tumor	6	Routine f/u	Further resection (retroperitoneal mass)
Rec13	6	Open	TO	No	Immature teratoma	1	Routine f/u	n/a
Rec14	15	Open	TO	No	Dysgerminoma	16	Routine f/u	Further resection (retroperitoneal mass)
Rec15	11	Laparoscopic	OS	No	Serous cystadenoma	Unclear	representation	Completion oopherectomy

Accurate data on the incidence of ovarian tumor recurrence and metachronous disease is crucial, not only to provide 'best practice' patient follow-up planning, and allow for better informed patient / parent counseling but also to help reliably inform and guide the surgeon on the merits of performing ovary-sparing surgery. Although it may seem obvious that routine total oophorectomy for ovarian tumors reduces the risk of tumor recurrence, it may result in infertility if the patient develops metachronous disease necessitating oophorectomy of the only remaining solitary ovary or if the patient suffers contralateral ovarian torsion. [11] It has been shown that total unilateral oophorectomy increases the risk for early menopause in young women. [12] It is believed that this is the result of premature ovarian failure which shortens the reproductive lifespan of the patient even if just one ovary is removed. [12]

To the best of our knowledge this paper highlights the largest nationwide multi-centre study to investigate ovarian tumor recurrence and metachronous disease in pediatric patients. Although whilst it is a retrospective report, the study is strengthened by the fact it did not rely on UK hospital episode statistics (HES) data which is well known for its variable quality and heterogeneity, but was conducted through a robust process of medical case record reviews from each voluntary participating UK pediatric surgical oncology centre. Our study noticeably demonstrates that ovarian tumor recurrence and metachronous disease occurs, however perhaps not as frequently as suggested by other published series referred to previously.

In the current report 9 of 177 patients (5.1%) with mature teratoma had a recurrent or metachronous tumor. In the majority of cases these tumors were detected during routine aftercare follow-up visits with surveillance imaging at a median time period of 12 months [IQR 12–-21 months]. However, we have also shown that metachronous disease can occur as a much later event, with two patients from this survey being diagnosed at 79 and 80 months following initial surgery. We therefore advocate post-operative follow-up with surveillance imaging of all female patients after resection of ovarian tumors. Oncological follow-up protocols currently only exist for malignant germ cell tumors. For children with so-called 'benign ovarian tumors' (i.e. mature teratoma) these protocols are missing. Based on this data survey, we would recommend at least 6 monthly follow-up with clinical review and US. [15] Future research in the form of population based cohort studies - possibly in form of a tumor registry – are required to establish if (and at which timepoint), it is safe to discharge patients from post-operative follow-up. Pediatric surgeons need to be reflective and mindful when considering discharging patients. Patients and carers should be made aware of the possibility of later occurrence of metachronous disease. This risk may be increased further if there is a positive family history of ovarian neoplasms. [13] Establishing the details of the frequency and duration of minimum patient follow-up could be best agreed by consensus with pediatric surgeons, medical oncologists and gynecology specialists. Immediate discharge after operation without any further patient follow-up appears to be not safe practice.

4. Conclusion

This UK nationwide study has demonstrated that ovarian tumor recurrence(s) and metachronous disease occur, even in tumors that were previously deemed as 'benign' lesions with several morbid 'late effects' for patients including infertility and early menopause. We strongly advocate all pediatric patients should undergo follow-up surveillance after resection of an ovarian tumor including benign lesions.

Appendix A. CCLG Collaborators in alphabetical order.

James Andrews, Royal Hospital for Children Glasgow.
Katherine Burnand, Great Ormond Street Hospital.
Alison Campbell, Sheffield Children's Hospital.
David Colvin, Royal Belfast Hospital for Sick Children.
Kate Cross, Great Ormond Street Hospital.
Fiona Dawson, St George's Hospital London.
Alistair Dick, Royal Belfast Hospital for Sick Children.
Evelyn Ervine, Royal Belfast Hospital for Sick Children.
Ross Fisher, Sheffield Children's Hospital.
Hany Gabra, Newcastle Children's Hospital.
Philip Hammond, Royal Hospital for Sick Children Edinburgh.
Kamal Kuti, Royal Hospital for Sick Children Edinburgh.
Michael Jacovides, Royal Hospital for Children, Glasgow.
Claire Jackson, Addenbrookes Hospital Cambridge.
Khokila Lakoo, Oxford Children's Hospital.
Ahmed Mohamed, Newcastle Children's Hospital.
Mohamed Mostafa, Bristol Children's Hospital.
Bruce Okoye, St George's Hospital London.
Mark Powis, Leeds Children's Hospital.
Timothy Rogers, Bristol Children's Hospital.
Andrew Ross, Oxford Children's Hospital.
Gillian Winter, Aberdeen Royal Infirmary.

References

[1] Skinner MA, Schlatter MG, Heifetz SA, et al. Ovarian neoplasms in children. Arch Surg 1993;128:849–53.
[2] Amies Oelschlager AM, Gow KW, Morse CB, et al. Management of Large Ovarian Neoplasms in pediatric and adolescent females. J Pediatr Adolesc Gynecol 2016; 29:88–94. https://doi.org/10.1016/j.jpag.2014.07.018.
[3] Lindfors O. Primary ovarian neoplasms in infants and children. A study of 81 cases diagnosed in Finland and Sweden. Annales chirurgiae et gynaecologiae Fenniae. Suppl 1971;177:1–66.
[4] Templeman CL, Hertweck SP, Scheetz JP, et al. The management of mature cystic teratomas in children and adolescents: a retrospective analysis. Hum Reprod 2000;15: 2669–72. https://doi.org/10.1093/humrep/15.12.2669.
[5] Mangili G, Sigismondi C, Gadducci A, et al. Outcome and risk factors for recurrence in malignant ovarian germ cell tumors: a MITO-9 retrospective study. Int J Gynecol Cancer 2011;21(8):1414–21. https://doi.org/10.1097/IGC.0b013e3182236582.
[6] Taskinen S, Urtane A, Fagerholm R. Metachronous benign ovarian tumors are not uncommon in children. J Pediatr Surg 2014;49:543–5. https://doi.org/10.1016/j.jpedsurg.2013.09.019.
[7] Childrens' Cancer and Leukaemia Group. Interim guideline for the treatment of extracranial germ cell tumours in children and adolescents. Brougham J et al. 2018.
[8] Braungart S, Craigie RJ, Losty PD. Controversies in the management of ovarian tumours in prepubertal children – a BAPS and UK CCLG Surgeons Cancer Group national survey. J Pediatr Surg 2018;53(11):2231–4. https://doi.org/10.1016/j.jpedsurg.2017.11.068.
[9] Chabaud-Williamson M, Netchine I, Fasola S, et al. Ovarian-sparing surgery for ovarian teratoma in children. Pediatr Blood Cancer 2011;57:429–34. https://doi.org/10.1002/pbc.23070.
[10] Rogers EM, Allen L, Kives S. The recurrence rate of ovarian dermoid cysts in pediatric and adolescent girls. J Pediatr Adolesc Gynecol 2014;27(4):222–6. https://doi.org/10.1016/j.jpag.2013.11.006.
[11] Renaud EJ, Sømme S, Islam S, et al. Ovarian masses in the child and adolescent: An American Pediatric Surgical Association Outcomes and Evidence-Based Practice Committee systematic review. J Pediatr Surg 2019;54(3):369–77. https://doi.org/10.1016/j.jpedsurg.2018.08.058.
[12] Cramer D, Xu H, Harlow BL. Does "incessant" ovulation increase risk for early menopause? Am J Obstet Gynecol 1995;172:568.
[13] Braungart S, McCullagh M. Management of familial ovarian teratoma: the need for guidance. Eur J Pediatr Surg Rep 2016;4:31–3. https://doi.org/10.1055/s-0036-1593832.
[14] Hermans AJ, Kluivers KB, Janssen LM, et al. Adnexal masses in children, adolescents and women of reproductive age in the Netherlands: a nationwide population-based cohort study. Gynecol Oncol 2016;143:93–7. https://doi.org/10.1016/j.ygyno.2016.07.096.
[15] Yazbek J, Raju SK, Ben-Nagi J, et al. Effect of quality of gynaecological ultrasonography on management of patients with suspected ovarian cancer: a randomised controlled trial. Lancet Oncol 2008;9:124–31.