**Manuscript**

**Title**: Ovarian tumors in children: How common are lesion recurrence and metachronous disease? A UK CCLG Surgeons Cancer Group Nationwide Study

**Introduction**

Ovarian tumors in children are rare. The overall incidence is estimated at 2.6 per 100000 prepubertal females, but varies depending on patient age and histological diagnosis. [1,2,3] 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 tumours in the United Kingdom (UK) is facilitated by the Children’s Cancer and Leukaemia 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 tumour 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 (i) recurrence and (ii) metachronous disease in pediatric patients following ovarian tumor resection.

**Material and Methods**

A nationwide study facilitated through the CCLG Surgeons Children’s Cancer and Leukaemia 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 standardised data collection form was distributed to participating centres. Female patients <16 years with an index diagnosis of ovarian tumor from 2006 - 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.

**Results**

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 and ten patients were identified who underwent resection of an ovarian tumor in the time period under review.

One hundred and forty-eight patients presented as surgical emergencies, meaning the child presented to the emergency department with acute symptoms. 160 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].

Synchronous tumours

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).

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 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 tumours.

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 tumours, 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).

**Discussion**

The majority of pediatric ovarian tumors are benign [14]. It is widely believed that these tumours 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 ie. (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]

Accurate data on the incidence of ovarian tumour recurrence and metachronous disease is crucial, not only to provide ‘best practice’ patient follow-up planning, and allow for better informed patient / parent counselling 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 tumours reduces the risk of tumour 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 tumour 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 tumour 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 tumours. Oncological follow-up protocols currently only exist for malignant germ cell tumours. 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 gynaecology specialists. Immediate discharge after operation without any further patient follow-up appears to be not safe practice.

**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.