

COVER LETTER

08/03/2021

Dear Editor-in-Chief,

Following our recent correspondence with you concerning this article and your agreement to consider publication of this systematic review, we have pleasure in now submitting our original research article entitled “Prevalence of metachronous contralateral mature ovarian teratoma: a systematic review” for consideration by Pediatric Blood & Cancer.

We confirm that this work is original and has not been published elsewhere, nor is it currently under consideration for publication elsewhere.

In this paper, we report on the rates of ipsilateral and contralateral tumor recurrence in patients with ovarian mature teratoma. This is significant because this is an area where there is some uncertainty due to widely varying data.

We believe that this manuscript is appropriate for publication by Pediatric Blood & Cancer because ovarian mature teratomas are a relatively common pediatric tumor and is consequently managed by oncology specialists. Pediatric Blood & Cancer would be an ideal platform to give exposure to this review, ensuring specialists that manage these tumors can access this information and modify their current management.

We believe this article represents the first systematic review to cover this subject matter and we hope can provide some clarity to clinicians who manage patients with this condition. The current approach to follow-up of these patients is clinician-dependent, with many performing surveillance that falls far short of what appears to be necessary based on the findings of this review. This review would hopefully inform current guidelines so that there is a more standardized approach to follow-up, allowing prompt diagnosis and management of patients who have suffered a recurrence. The importance of optimal management of these patients cannot be overstated given the implications for fertility and long-term health if these patients are diagnosed late and thus have oophorectomies.

The reviewers we would recommend based on our review of the literature are: Dr Jonathan Karpelowsky (Sydney, Australia), Dr Fred Rescorla (Riley Hospital, Indianapolis), Dr Jennifer Dietrich (Texas Children’s Hospital).

We have no conflicts of interest to disclose.

Thank you for your consideration of this manuscript.

Yours sincerely,

David Kiely

TITLE PAGE

Complete Title: Prevalence of metachronous contralateral mature ovarian teratoma: a systematic review

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Word count

Abstract: 147

Main Text: 2,855

Number of tables: 1

Number of figures: 3

Short title: Pediatric ovarian mature teratoma recurrence review

Keywords: Ovarian, Mature Teratoma, Recurrence, Pediatric

Data availability statement

Data openly available in a public repository that issues datasets with DOIs

ABSTRACT

There is increasing recognition that contralateral metachronous tumor may occur following treatment of unilateral mature ovarian teratoma. We aimed to define this risk to guide appropriate surveillance strategies. We undertook a systematic review of 3 large medical databases (Ovid Medline, Embase, and Cochrane Controlled Trials Register) to April 2020 using a defined search strategy. From 1831 articles retrieved, 23 were included, reporting 1,101 girls with unilateral mature ovarian teratomas. The intensity and duration of follow-up varied between studies, with only 5 reporting close surveillance. Overall prevalence of metachronous contralateral mature teratoma was 2.1% with a prevalence per study of 0-23% (median 0%). Prevalence was higher (7%) amongst studies with more robust surveillance. These data suggest a small but real risk of metachronous contralateral tumors. Surveillance ultrasonography is proportionate and indicated alongside further prospective data collection to record the natural history and impact of surveillance in greater detail.

INTRODUCTION

Mature teratomas are the most common germ cell tumors in children occurring at both gonadal and extra-gonadal sites, most frequently the sacrococcygeal region in newborn infants, the head and neck region in young children, and the mediastinum of adolescent children. The mainstay of treatment is surgical resection following which local recurrence is a well-recognized phenomenon, most notably for sacrococcygeal tumors resected in the neonatal period, where recurrence rate is approximately 10%.

Beyond local recurrence, there has recently been an increased appreciation of the risk of contralateral metachronous ovarian teratoma in girls who presented with a unilateral ovarian mature teratoma. This is of particular concern since it raises the question of need for surveillance to treat a second tumor, as well as having implications for future fertility. Since many patients will undergo oophorectomy at the time of the initial diagnosis, a need for contralateral ovarian surgery to remove a second tumor carries a risk of infertility and premature menopause, particularly if ovarian sparing surgery is either not considered or impossible.

National guidelines have been updated in light of this increased appreciation to recommend routine surveillance for contralateral disease. For example, the United Kingdom Children's Cancer and Leukaemia Group (UK CCLG) Extra-Cranial Germ Cell Tumour guidelines (1) recommend follow-up for at least 3-years and suggest that radiological follow-up for 10-years following initial diagnosis in this population is reasonable. This has implications for both patients and healthcare resources. Of note, this guidance appears to be based on a single study from 2014 (2) comprising 22 index cases in whom metachronous contralateral disease was seen in 22.7%. Due to the paucity of data there remains some uncertainty around the actual magnitude of risk and hence the validity of this guidance.

To inform future clinical practice and potentially surveillance guidelines we aimed to investigate the incidence of metachronous contralateral teratoma in this population through a systematic review of the existing literature.

METHODS

2.1 Protocol Registration

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (3) was performed according to a predefined protocol and was registered this review with PROSPERO (CRD42018108828) in September 3, 2018.

2.2 Study Inclusion Criteria

All articles that reported data on mature ovarian teratomas in female children were eligible for inclusion. We initially intended to limit our review to reports of those aged <16 years, however, in an initial scoping review we identified a number of studies that included cases for children with an upper age cut-off of 18 or 21-years. We therefore included articles that reported cases in the paediatric age range with an upper age cut-off of 21-years, since their omission would have resulted in the exclusion of a significant volume of data of interest. We believe this is a clinically meaningful age for those clinicians who treat children and adolescents.

Articles that did not report data on the primary outcome of interest, namely contralateral metachronous disease were excluded, as were articles reporting a sample size of less than 10 cases to minimise the risk of reporting bias. Conference abstracts were not included in the final dataset unless they had been published in a journal.

2.3 Search sources and parameters

We searched Ovid Medline (from 1946), Embase (from 1974) and the Cochrane Controlled Trials Register (from 1960) for all published articles up to April 22, 2020.

We used a systematic approach to search for all articles. For each database we created different search protocols, which were carefully composed to ensure acquisition of all sentinel articles. Search terms included “teratoma”, “germ cell tumor”, “dermoid cyst”, “follow-up”, “metachronous”, “bilateral”, “multiple” and “recurrence/recurrent”. No language restriction was applied to search criteria.

2.4 Study Selection

Two review authors (DK, CL) independently screened all study titles and abstracts identified in the search against the inclusion criteria. The same two authors assessed full-texts independently against inclusion criteria. Additional studies that had not been captured by the search protocols were retrieved by looking through the references of retrieved and related articles. There were no disagreements regarding the inclusion or exclusion of any studies. The source and the authorship of different studies were not masked during the article selection process. Full texts that met the inclusion criteria and reported outcomes of interest were included.

2.5 Data extraction and synthesis

The primary outcome for this study was incidence of contralateral metachronous mature ovarian teratoma. Secondary outcomes were incidence of other types of contralateral metachronous ovarian tumour, incidence of ipsilateral recurrence or *de novo* ovarian tumours, other relevant clinical details and how cases of contralateral tumour / recurrence were managed. The following data were extracted from each eligible study: study type, study location, patient demographics, follow-up method, primary and secondary outcome data, other relevant clinical

outcomes, and clinical management. Data were extracted by the lead author using an Excel Spreadsheet and reviewed independently for accuracy by a second reviewer (CL). Given the nature of the data available we anticipated that meta-analysis would not be appropriate. Therefore, we performed a qualitative synthesis of the data with a tabulation of the results from all of the included studies.

Subgroup analysis of cases based on initial surgical approach (open versus minimally invasive surgery and oophorectomy versus ovarian sparing surgery) was planned but found impossible due to inability to ascertain method of initial surgical approach in the included studies. Attempts were made to gain further information by contacting the authors, however there has been an inadequate response rate to enable this analysis. Subgroup analysis has been performed based on the surveillance protocol implemented, including only those studies with structured follow-up.

2.6 Risk of bias assessment

The following items were independently assessed by two review authors in each included study, using an adaptation of the Cochrane bias assessment tool (4): selection, detection, reporting and attrition bias. Studies were judged to be at 'high', 'low' or 'unclear' risk for each domain assessed. The bias assessments were then presented in a Risk of Bias Summary Table and Graph using Review Manager v5.3 (The Cochrane Collaboration, 2014).

RESULTS

Article selection and inclusion

Our searches yielded a total of 1826 records and we retrieved 5 additional articles from handsearching (Figure 1). A total of 115 full texts were reviewed of which 92 were excluded, either due to duplication (n=15) or because they did not report data on the age range of interest, they had a sample size of less than 10 cases, they did not report the correct index pathology, did not report the outcomes of interest or were updates on a previously published series. A total of 23 studies met the inclusion criteria and all were included in qualitative data synthesis. These are summarized in Table 1.

Risk of bias assessment

A summary of the risk of bias assessment is shown in Figures 2 and 3. The principal source of potential bias was detection bias, arising primarily from inconsistent or unclear follow-up regimes. To account for the potential impact of this source of bias, we elected to perform a subgroup analysis for both primary and secondary outcomes including only those studies that employed rigorous follow-up protocols (2, 5-8). Risk of detection bias in other studies was deemed high when follow-up regime was less stringent or for a short period of time (9-17) or unclear where not clearly described (18-26).

Most studies declared no exclusion of participants and so had a low-risk of attrition bias. One study was at high-risk of attrition bias as a large component of their patients (34.6%) were unavailable for follow-up (14). Four studies had an unclear risk of attrition bias as they only had a small proportion (5.4%, 13.3%, 9.7% and 12.5%) of patients lost to follow-up (6, 23, 26, 27). One study had an unclear risk as patients with tumors >10cm diameter were excluded from the study. The risk of bias was felt to be unclear as the impact of tumor size on likelihood of

recurrence / metachronous disease is currently not known (21).

Overall, the risk of reporting bias was determined to be low, as the results reported were generally in keeping with the approach to follow-up, as the studies that monitored patients more closely, generally had higher rates of detected recurrence. The study with a particularly high rate of metachronous disease has an unclear risk of bias, as the rates were in excess of that reported by other units (2). The study that was proposing one port laparoscopic surgery as a technique for surgical management of these patients, was also felt to have an unclear risk of bias, as authors may be less likely to report adverse outcomes, including recurrences, when recommending a new surgical technique (17).

Primary outcome

Overall, the included studies report 1,127 cases of young female patients with mature ovarian teratoma. Of these, 26 cases were bilateral at presentation and were excluded, leaving 1,101 cases of unilateral mature ovarian teratomas. Overall, there were 25 reports of metachronous contralateral tumors, 23 of these were mature teratomas, and 2 were seromucinous cystadenomas. Thus, the overall incidence of contralateral mature teratoma was 2.1% (23/1,101) and the overall incidence of contralateral ovarian tumors was slightly higher (2.3%, 25/1,101). Contralateral metachronous tumors occurred in 8 of the 23 included studies with a median overall incidence per study of 0% (range 0-22.7%, IQR 0-2.5%). There were 13 reports of ipsilateral recurrence (1.2%), and there was 1 additional case of ipsilateral immature teratoma.

Follow-up strategies

A range of follow-up regimes were in place amongst the included articles, with variation in both intensity and duration of follow-up. Five studies utilized a more intensive follow-up

comprising a minimum of at least annual ultrasound scans for at least 3-years (2, 5-8). The remaining studies included did not employ such rigorous surveillance. Follow-up typically comprised review of medical records (11, 12, 14, 15, 20, 28), with additional telephone reviews (10) or clinical follow-up (16, 26). Two studies that we have placed in this category used USS and tumor markers as part of their follow-up, but for shorter duration than the studies mentioned above (17, 18). The remaining studies either had variable follow-up (19, 22, 27) or did not specify their approach (13, 21, 23, 25).

Subgroup analysis

Four studies with low risk of detection bias and more intensive follow-up (annual ultrasound for minimum 3-years) (2, 5-7) as well as a subgroup in one study in which follow-up was by annual clinical assessment and ultrasonography for 5-years (8), were included in subgroup analysis. Overall, amongst these studies, a total of 11 metachronous contralateral mature teratomas, and two contralateral seromucinous cystadenomas were detected in a total of 185 patients (incidence 7%). The median incidence of contralateral metachronous tumor in this subgroup of studies was 6.1% (range 0-22.7%), with the highest rate reported by Taskinen et al (2). In addition, ipsilateral recurrence was reported in 4 of 188 cases (incidence 2.1%).

Timing of second tumor

Many studies did not report the timing of recurrence, however, where time of second tumor detection was reported, it was most commonly within the first five years after initial tumor (2, 5, 6, 10, 11, 20, 26, 28). In the largest study in this review of 177 patients, contralateral metachronous tumors were diagnosed at a mean of 32.86 (range 11-80) months after the initial surgery (19). Of note when considering duration of surveillance, two studies reported metachronous tumors as late as 14-years after initial surgery (2, 6).

DISCUSSION

This systematic review aimed to quantify the magnitude of the risk of both contralateral and ipsilateral tumor development in young girls treated for ovarian mature teratoma. To our knowledge, this is the first systematic review of its type in this population. Through robust search protocols, we have identified and included 23 studies that reported outcomes for 1,127 patients who had undergone surgery for mature ovarian teratomas. Overall, contralateral metachronous tumor was detected in 2.3% of girls although in the subgroup of studies with the most robust surveillance regimes this rose to 7%. The data also highlights a wide variability in the approach to follow-up of these patients after the initial surgical management.

The principal limitation of our review is the risk of including studies with significant detection and attrition bias. The wide range of reported recurrence rates (0-22.7%) is most likely attributed to the varying approaches to follow-up. To mitigate against these sources of bias we have performed a subgroup analysis including only those studies with lower risk of bias on account of their robust follow-up regimes. Whilst our search strategy was robust, it is possible that some studies (e.g. unpublished data due to low recurrence rates) were not identified. Indeed we are unable to completely exclude the influence of reporting bias on our overall results; it is possible that series of particularly low recurrence rate are not reported as they were considered less valuable and equally that detection of a recurrence may have prompted reporting of a series of cases. Of note however several series reporting a zero recurrence rate were identified and are included in this review. One final limitation of our review is that for the majority, follow-up was relatively short. As a consequence, the long-term natural history of this condition remains uncertain.

The strengths of our study are our systematic approach to identification of articles, our detailed

assessment of each report and our risk of bias assessment to identify appropriate studies for inclusion in subgroup analysis. Furthermore, through this review we are able to report on outcomes of over 1000 cases; this size of cohort has not been studied previously with regards to this condition.

The findings of our review should be taken in context of the existing literature. Whilst the cumulative recurrence rate is lower than the 22.7% reported by Taskinen et al - notable rates of metachronous disease were reported by others (5, 6) and the overall rate in studies with most robust follow-up (7%) should not be dismissed. The implications of our findings are that routine surveillance of girls who present with a unilateral mature ovarian teratoma should certainly be considered since 1 in 14 will develop contralateral disease. We believe such surveillance is justified given the low burden of surveillance (annual clinical review and zero radiation burden). Such surveillance will likely result in identification of contralateral tumors before they become clinically apparent resulting in lower risk of malignant transformation and higher ovarian salvage rates. Our data suggest it may also result in detection of a smaller number of ipsilateral recurrences. In parallel, we recommend that studies on the impact of such surveillance be undertaken so that we can fully understand, with time, whether routine surveillance does indeed improve early detection and outcomes, and whether these benefits outweigh cost and other potential disadvantages such as patient/parental anxiety.

When determining appropriate long-term surveillance for these patients, we have considered the time taken to develop recurrence. Most recurrences in the studies included here have been diagnosed within 5-years, although several reports included patients with metachronous disease outside of this window (2, 5, 6, 29), with two reports of metachronous disease diagnosed 14-years later (2, 6). Follow-up regimes recommended by these two reports are

annual ultrasound scan until first pregnancy (2), or menopause (6). This may not be practical in many countries, and clearly has resource and cost implications. Whilst beyond the scope of this review, we would consider that annual ultrasound examination for the first 5-years at least, is likely achievable, and since ultrasonography is a useful imaging modality in the identification of ovarian masses, the addition of routine tumor marker monitoring is probably unnecessary, particularly given that most mature teratomas are non-secretory.

In recent years, the increasing awareness of the long-term implications of early oophorectomy on later health and the possibility of metachronous contralateral disease has led to increased proportion of these patients having ovarian sparing surgery as opposed to oophorectomy. Whilst this approach likely maximises ovarian salvage, fertility and avoids premature menopause, these benefits must be balanced against the potential for higher ipsilateral recurrence. As ovarian sparing surgery becomes more commonplace, monitoring of ipsilateral recurrence must take place and higher rates of ipsilateral recurrence may be anticipated in the future. This further supports the need for close surveillance of this population.

Overall, the findings of this review support the need for surveillance in this population and will, we hope, inform modification of guidelines across jurisdictions, to ensure closer post-operative follow-up. Existing data support a minimum surveillance period of 5-years, but ideally surveillance should continue beyond this. Whether lifelong surveillance can truly be justified remains debatable and will depend on a number of local factors. In order to establish the optimal surveillance strategy with certainty, we call for a greater understanding of the natural history of these cases through prospective longer-term surveillance and epidemiological studies. With such a strategy it may be possible to enhance our understanding

of the pathophysiology of these tumors, and hopefully give insight into patients at greatest risk of recurrences (30). Subsequently, we may be able to tailor our approach to surveillance based on these factors targeting those at highest risk. Whilst the pathogenesis is not universally agreed on or understood (11), monitoring all patients with these tumors by the above means appears the most appropriate approach.

Acknowledgements

The authors would like to thank their families for their continued love and support.

Conflict of Interest

The authors declare that there is no conflict of interest.

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Figure legends

Figure 1: Article selection flowchart

Figure 2: Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Figure 3: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies