Metachronous benign ovarian tumors are not uncommon in children

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A B S T R A C T

Purpose: To evaluate the risk for metachronous ovarian tumor in pediatric patients with mature ovarian teratoma.

Methods: During 1981–2011, 22 children underwent oophorectomy for mature teratoma at the median age of 11.4 (range 1.5–15.3) years. The patients were followed-up in median 4.4 (range 0.5–25.5) years.

Results: None of the patients had synchronous bilateral tumor at the time of primary operation, but during follow-up five patients (23%) got metachronous contralateral ovarian tumor. The contralateral tumor was observed in median 3.6 (range 1–8.8) years after the primary operation. According to Kaplan–Meier analysis the risk for contralateral tumor was 14% ± 8% (SE) within five years and 66% ± 26% (SE) within 10 years. In this series, the contralateral tumor was operated by ovary preserving surgery. Three of the metachronous tumors were mature teratomas and two were seromucinous infantile cystadenomas. One patient had a second teratoma recurrence 14 years after the first recurrence.

Conclusions: More than one fifth of the children with ovarian mature teratoma get metachronous benign tumor to the contralateral ovary. Therefore a yearly ultrasound follow-up is needed for these patients up to potential pregnancy to enable early diagnosis, ovary preserving surgery and maintenance of fertility in the case of metachronous tumor.

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Ovarian masses are rare in children. Approximately one half of them are neoplastic [1]. The majority of the ovarian neoplastic tumors are benign, the most common diagnosis being a mature teratoma [2–4]. Benign teratomas have been reported to be bilateral in 11%–17% of the adult and pediatric patients occurring most frequently synchronously and only occasionally metachronous appearance has been reported [5–7].

The focus in research and publications concerning patients with benign teratomas has been in mini-invasive and ovary sparing surgery [3,4]. However, the exact risk of recurrence on the contralateral side is unknown, and the role of follow-up after primary surgery has not been investigated in detail [8]. Our clinical follow-up has revealed some metachronous contralateral benign ovarian tumors in children and adolescents operated on mature ovarian teratoma. In this study we wanted to evaluate the frequency of subsequent benign tumors in the contralateral ovary in this patient group to see if follow-up of these patients is really needed. The major clinical implication of follow-up and early diagnosis of recurrence would be the option to ovary preserving surgery.

1. Methods

This retrospective study was performed in the Children’s Hospital of Helsinki University Central Hospital. We identified from the hospital database altogether 46 patients operated for an ovarian neoplastic tumor during 1981–2011. Twenty-two (48%) of them had mature teratoma.

The clinical data of the diagnostic and operative procedures as well as follow-up data were collected from the hospital medical and surgical records. The ovarian tissue samples were re-evaluated by one of the researchers (JL). During the last 20 years the patients have been followed up yearly with abdominal ultrasonography and tumor markers (serum alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG) and CA-125) for five years after the primary operation. After five years the follow-up had not been so systematic.

Kaplan–Meier analysis was performed to evaluate the development of metachronous tumors (Statview® 5.0.1, SAS Institute Inc.). The study was approved by the institutional Ethical Review Committee.

2. Results

The median age of the 22 patients with mature teratoma was 11.4 (range 1.5–15.3) years at primary surgery. Preoperative diagnostic evaluation was done with ultrasonography for all 22 patients, with confirmation by magnetic resonance imaging for 11 patients and with
computed tomography for 4 patients. None of the patients had tumor on the contralateral ovary either in preoperative imaging or in peroperative examination. Contralateral ovarian biopsy was performed in one patient during the primary operation due to multiple cysts with negative results, but the patient was later diagnosed with a tumor also in the contralateral tumor. All the patients were primarily treated with oophorectomy. The histology of the primary tumor was mature teratoma in all 22 cases also in the re-examination [IL].

The median follow-up time was 4.5 (range 1.0–25.5) years. Five out of the 22 patients (23%) were observed to have a neoplastic tumor in the contralateral ovary in median of 3.6 (range 1–8.8) years after the primary surgery. At the time of re-operation all the measured tumor markers were normal (s-CA-125 in all five patients, s-AFP and -hCG in four patients). The primary operation was done at the median age of 11.3 (range 1.5–14.6) years for the 17 patients without metachronous tumor and at the age of 13.7 years (range 3.6–15.3) for the five patients with metachronous tumor (p = 0.531). Two patients were detected to have preoperative tumor rupture during the primary operation. The other of them got contralateral recidive after one year follow-up. The estimated risk for contralateral ovarian tumor was 14% ± 8% (SE) at 5 years and 66% ± 26% (SE) at 10 years in Kaplan–Meier analysis (Fig. 1).

The recurrent tumors were operated by ovariectomy preserving surgery. One patient was detected to have second mature teratoma recurrence in the remaining ovary during pregnancy, 14 years after the first recurrence. The second recurrence was treated with oophorectomy at the time of caesarean section.

In three cases the recurrent contralateral tumor was also mature teratoma, but in two cases it was infantile seromucinous cystadenoma (Table 1). One additional patient was operated because of metachronous non-neoplastic polycystic ovary.

### 3. Discussion

In this retrospective study, we observed that the patients operated for ovarian mature teratomas during childhood are in a substantial risk of having benign neoplastic tumors in the contralateral ovary later in life.

Ovarian neoplasms are rare in children. In our 30 years’ material, 46 patients with ovarian neoplasms were diagnosed in a population of about 18,000 newborns yearly. Almost half of the primary tumors were mature teratomas, fitting to the previous observations [9,10]. In our study, 23% of the patients with ovarian mature teratoma had a neoplastic tumor in the contralateral ovary during a median follow-up time of 4 years. None of them had had any signs or findings of neoplasm in the contralateral ovary at the time of the primary surgery.

Bilateral simultaneous ovarian teratomas have been reported in adult patients with a prevalence of 10.8%–13.2% [5,6,11]. However, in adults we did not succeed to find proper follow-up series evaluating the risk for metachronous tumors.

In children the reported patient series have been small and usually no follow-up information has been provided. In the study of Al Jama et al. [4] one out of 28 pediatric ovarian teratoma patients was operated because of synchronous mature teratoma in the contralateral ovary, but no follow-up data were given. In another study of 30 patients with mature teratoma, two developed multiple recurrent cysts and lesions to the remaining ovary resulting in removal of the ovary because of severe pain [3]. Unfortunately, neither the histology, nor the length of the follow-up was reported. In the study of DeBacker et al. three out of nine patients with immature teratoma were diagnosed with contralateral tumor after 3–6 months’ follow-up [12]. However, no metachronous tumors were reported in the 45 patients with mature teratoma [12]. In a recent study from Paris, 5 out of the 30 (17%) pediatric patients with (mature) ovarian teratoma had bilateral tumor [7]. One patient had a synchronous bilateral tumor and four patients developed metachronous tumor after a median follow-up of 3 (range 1–14) years. This is in line with our findings.

Multifocal origin of ovarian teratomas has previously been reported [13]. In adult patients, bilateral tumors have usually been macroscopically evident, but some patients have had covert tumors identified only by a peroperative biopsy of the contralateral ovary [5,6]. A Chinese study suggests that metachronous appearance of benign ovarian tumors could be a particular feature in young females [14]. The 20 patients with a subsequent tumor in the contralateral ovary were younger than the 40 patients without tumor in the remaining ovary (26 vs. 30 years, p < 0.05). Our hypothesis is that in adult patients with bilateral ovarian teratomas, the neoplasm has had time to develop into a macroscopic tumor on both sides. In contrast, in pediatric patients the niche of the neoplasm may be covert in the other ovary at the time of primary surgery, and more time is needed for the tumor to become macroscopically detectable on the contralateral side.

Tumor spillage before or during the primary operation is a potential but unlikely explanation for metachronous appearance of ovarian tumors. In our material, two patients were detected to have preoperative tumor ruptures and the other was detected to have contralateral tumor at follow-up. However, the role of tumor spillage in the development of contralateral ovarian tumors is not supported by the observation that none of the 27 patients with mature cystic teratoma and tumor spillage had tumor recurrence or tumor in the contralateral ovary [8].

In our material two out of the five patients with metachronous tumor developed infantile seromucinous cystadenoma to the contralateral ovary. In adults mucinous epithelial neoplasms have rarely been reported in association with mature teratomas [15]. Recently one pediatric patient has been reported to have a metachronous ipsilateral mucinous cystadenoma three years after ovari-sparing surgery of mature teratoma [16]. In a study of Massicot et al. [10] 7 out of 31 patients with infantile seromucinous cystadenoma had bilateral involvement. In their series one patient had also bilateral mature

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**Table 1**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Primary operation age (year)</th>
<th>Metachronous contralateral tumor Diagnosis</th>
<th>Operation age (year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>Seromucinous cystadenoma</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>Mature teratoma</td>
<td>14; 28</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
<td>Seromucinous cystadenoma</td>
<td>17</td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>Mature teratoma</td>
<td>22</td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>Mature teratoma</td>
<td>16</td>
</tr>
</tbody>
</table>

* The patients had two teratoma recurrences in the remaining ovary.

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**Fig. 1.** Appearance of contralateral benign ovarian tumor after oophorectomy because of mature teratoma.
ovarian teratoma and unilateral cystadenoma. It was discussed that the epithelial tumour could also originate from the differentiation of potentially totipotent teratoma cells.

In this series one fifth of the young females with mature ovarian teratoma developed contralateral tumor during follow-up. We conclude that yearly ultrasound follow-up of pediatric patients with ovarian teratoma is justified to enable the early detection of the contralateral or ipsilateral tumor, and consequently giving the option to ovary sparing surgery and preserving fertility. The length of follow-up should probably be continued up to the first pregnancy.

References