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Ovarian Sertoli Leydig cell tumours in children and adolescents: An analysis of the European Cooperative Study Group on Pediatric Rare Tumors (EXPeRT)

Dominik T. Schneider [a,*], Daniel Orbach [b], Giovanni Cecchetto [c], Teresa Stachowicz-Stencel [d], Bastian Brummel [a], Ines B. Brecht [e], Gianni Bisogno [f], Andrea Ferrari [g], Yves Reguerre [h], Jan Godzinski [i], Gabriele Calaminus [j], Catherine Patte [k], Ulrich Göbel [l]

[a] *Clinic of Pediatrics, Beurhausstr. 40, D-44137 Dortmund, Germany*
[b] *Department of Paediatric Oncology, Institut Curie, 26 rue d'Ulm, Paris 75231, France*
[c] *Department of Pediatrics, Pediatric Surgery, University of Padua, Via Giustiniani, 3, 35128 Padova, Italy*
[d] *Department of Pediatric Hematology, Oncology and Endocrinology, Medical University Gdansk, 7 Debinki Street, 80-211 Gdansk, Poland*
[e] *Pediatric Oncology and Hematology, University Children's Hospital Erlangen, Loschgestrasse 15, D-91054 Erlangen, Germany*
[f] *Department of Pediatrics, Pediatric Hematology and Oncology, University of Padua, Via Giustiniani, 3, 35128 Padova, Italy*
[g] *Pediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale Tumori, Via G. Venezian 1, Milano 20133, Italy*
[h] *Paediatric Department, Service d'oncologie pédiatrique, Centre hospitalo-universitaire, 4 rue Larrey, 49033 Angers Cedex 1, Angers, France*
[i] *Department of Pediatric Surgery, Marciniak Hospital and Department of Emergency Medicine, Wroclaw Medical University, Poland*
[j] *Clinic of Pediatric Hematology and Oncology, University Hospital Münster, Schweitzerstr. 33, D-48129 Münster, Germany*
[k] *Département d'oncologie pédiatrique, GHU Paris-Sud – CLCC Institut de cancérologie Gustave Roussy, 114 rue Edouard Vaillant, 94805 Villejuif, France*
[l] *Heinrich-Heine-University Düsseldorf, Germany*

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Abstract ***Objective:*** To analyse ovarian Sertoli-Leydig cell tumours (SLCTs) for potential prognostic markers and their use for treatment stratification.
Patients: Forty-four patients were included. Patients were prospectively reported to the German MAKEI (Maligne Keimzelltumoren) studies ($n = 23$), French TGM protocols ($n = 10$), Italian Rare Tumour Project (TREP) registry ($n = 6$), and the Polish Pediatric Rare Tumour Study group ($n = 5$). Tumours were classified according to World Health Organisation (WHO) and staged according to International Federation of Gynecological Oncology (FIGO).

* *Corresponding author:* Tel.: +49 231 953 21680; fax: +49 231 953 21047.
E-mail addresses: dominik.schneider@klinikumdo.de (D.T. Schneider), daniel.orbach@curie.net (D. Orbach), cecchett@pediatria.unipd.it (G. Cecchetto), tsten@gumed.edu.pl (T. Stachowicz-Stencel), ines.brecht@uk-erlangen.de (I.B. Brecht), gianni.bisogno@unipd.it (G. Bisogno), andrea.ferrari@istitutotumori.mi.it (A. Ferrari), yvreguerre@chu-angers.fr (Y. Reguerre), jgodzin@dilnet.wroc.pl (J. Godzinski), gabriele.calaminus@ukmuenster.de (G. Calaminus), Catherine.PATTE@gustaveroussy.fr (C. Patte), U.Gobelgoebelu@arcor.de (U. Göbel).

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Results: Median age was 13.9 (0.5–17.4) years. All patients underwent resection by tumour enucleation ($n = 8$), ovariectomy ($n = 17$), adenectomy isolated ($n = 18$) or with hysterectomy ($n = 1$). FIGO-stage: Ia 24 pts., Ic 17 pts., II/III 3 pts. One patient had bilateral tumours. Four patients (stage Ia: 3, stage Ic: 1) developed a metachronous contralateral tumour. Otherwise, all stage Ia patients remained in complete remission. Among 20 patients with incomplete resection or tumour spread (stage Ic–III), eight relapsed, and five patients died. Eleven patients were initially treated with two to six cycles of cisplatin-based chemotherapy. Of these, seven patients are in continuous remission. Poor histological differentiation was associated with higher relapse rate (5/13) compared to intermediate (3/18) and high differentiation (0/4). Tumours with retiform pattern or heterologous elements showed a high relapse rate, too (5/11). After a median follow-up of 62 months, event-free survival is 0.70 ± 0.07, relapse-free survival 0.81 ± 0.06 and overall survival 0.87 ± 0.05.

Conclusions: Prognosis of SLCTs is determined by stage and histopathologic differentiation. Complete resection with careful avoidance of spillage is a prerequisite of cure. The impact of chemotherapy in incompletely resected and advanced stage tumours remains to be evaluated.

1. Introduction

Ovarian sex cord stromal tumours (OSCSTs) represent a heterogeneous group of rare tumours, which account for approximately 10% of all ovarian tumours during childhood and adolescence [15]. They develop from the non-germ cell component of the ovary and may show a variable grade of differentiation [22]. In highly differentiated Sertoli-Leydig cell tumours (SLCTs), tubular structures with Sertoli cells predominate and are accompanied by sheets of Leydig cells. With lower grade of differentiation, the tubular architecture becomes less prominent. Retiform growth pattern is considered a distinct histopathologic pattern that may show specific clinical features such as alpha fetoprotein (AFP) production [4,21]. In some tumours, heterologous elements e.g. with intestinal differentiation may be observed. In adult patients, these pathologic features have been linked to clinical aggressiveness [20].

Recently, the association of SLCTs with mutations of the *DICER*1 gene has been reported [10,16]. These are associated with pleuropulmonary blastoma or familial multinodular goitre or rarely even thyroid cancer, making SLCT a part of a tumour predisposition syndrome [17].

While more has now been learned about the histology and biology of OSCSTs and SLCTs in particular, a great uncertainty remains regarding the optimal clinical management of these tumours, in particular in the paediatric age. This involves all relevant aspects such as diagnostic assessment including potential tumour markers and staging as well as surgical and medical treatment. Previous studies of ovarian sex cord tumours in children and adolescents have primarily focused on juvenile granulosa cell tumours [14]. In these studies, the prognostic relevance of staging including completeness of resection and histological parameters have been reported and introduced for therapy stratification. However, given the biological differences between different OSCST subtypes, the impact of these parameters in SLCTS has still remained unclear. To overcome this uncertainty, the European Cooperative Study Group on Pediatric Rare Tumours (E*X*PeRT) has coordinated the evaluation of an international series of 44 children and adolescents with SLCTs. This series constitutes the largest cohort of SLCTs in children and adolescents reported to date.

2. Patients and methods

2.1. Patients

E*X*PeRT coordinates the activities of the national rare tumour groups in France, Germany, Italy, Poland and the United Kingdom [1]. Among other E*X*PeRT's current activities, a joint analysis of SLCTs has been initiated. For this analysis, SLCTs have been identified among the patients with OSCSTs, who have prospectively been reported to the different national rare tumour groups. In Italy and Poland, the rare tumour groups started registering OSCST patients in 2000 and 2003, respectively [2]. In France, patients were registered within the national TGM 95 protocol for malignant germ cell tumours between 1995 and 2005 [3]. In Germany, OSCSTs have been prospectively reported to the consecutive Maligne Keimzelltumoren (MAKEI 89/96) study since 1993 [13]. Patients older than 18 years have been excluded from this analysis.

2.2. Data collection

The prospectively reported clinical data of the national groups have been validated, pseudonymised and transferred to a uniform E*X*PeRT data sheet by the national coordinators. Follow-up data have been updated until April 2013. This data sheet has then been sent to the coordinator of this analysis (DTS), who

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