# Ovarian Sex Cord–Stromal Tumors in Children and Adolescents

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*Ovarian sex cord–stromal tumors (OSCSTs) are a heterogeneous group of tumors that develop from the gonadal non-germ-cell component. Despite recent advances in the clinical and histopathologic diagnosis of OSCSTs, a high degree of uncertainty remains with regard to adequate therapy, particularly in patients presenting with microscopic or macroscopic tumor spread. We review the currently available data on the biology and histology of OSCST in children and adolescents. In addition, we summarize the data from our clinical, histopathologic and genetic analyses of patients that were prospectively reported to the German MAKEI protocols for treatment of nontesticular malignant germ cell tumors. Among these patients, juvenile granulosa cell tumors (JGCTs) constitute the most frequent histologic subtype, followed by Sertoli-Leydig cell tumors (SLCTs) and sclerosing stromal tumors. Patients with JGCT and SLCT show greater mitotic activity than do all those with other histologic types. Furthermore, high mitotic activity is associated with adverse outcome. In addition, prognosis correlates with tumor stage according to the International Federation of Obstetrics and Gynecology. Nevertheless, we observed a favorable response to cisplatin-based chemotherapy in the majority of stage II and III tumors. For the whole cohort of 62 patients, event-free survival was 0.87 ± 0.05 and overall survival 0.88 ± 0.05. Genetic analysis of 27 tumors available for comparative genomic hybridization analysis revealed normal profiles in the majority of tumors and whole chromosomal gain, such as a gain of 12 in single tumors, with no consistent pattern with regard to histology or clinical outcome. This analysis confirmed that most OSCSTs present at a low*

***Our analysis of 64 prospectively documented patients allows the development and prospective evaluation of risk-adapted therapeutic strategies in OSCST based on a standardized clinical and histopathologic assessment.***

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*tumor stage and that prognosis in these patients is excellent. Most important, patients at high risk can be identified through clinical and histopathologic analysis, and the majority can be treated successfully with adjuvant cisplatinum-based chemotherapy. Based on this analysis, a prospective study on OSCST in children and adolescents began recruiting cases in 2004.* (J Reprod Med 2005;50:000–000)

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Ovarian sex cord–stromal tumors (OSCSTs) are rare tumors that develop from the non-germ-cell component of the ovary. Two decades ago, the definition of juvenile granulosa cell tumors (JGCTs) as a distinct histologic entity became a cornerstone of the diagnosis of OSCST in children.[1] In recent years diagnostic accuracy has been increased further by the introduction of immunohistochemical detection of inhibin, which has proven a valuable and specific marker of OSCST. These diagnostic advances have not translated directly into a higher degree of certainty regarding the treatment of OSCST. This dilemma is due mainly to the fact that in the current literature there are no prospectively collected data on OSCST in childhood and adolescence. This therapeutic uncertainty is most pronounced in patients who present with an advanced tumor stage since, until recently, only single patients have been reported who have been treated successfully for advanced OSCST. As a result of this uncertainty, the rare pediatric patients with OSCST use an inappropriate amount of clinical and intellectual resources as compared to other, more frequent ovarian tumors, such as ovarian carcinoma.

Here we summarize the data prospectively collected in the German Germ Cell Tumor *Ma*ligne *Kei*mzelltumoren (MAKEI) study center, at the German Society of Pediatric Oncology and Hematology, German Pediatric Tumor Registry, Kiel. Based on the data reported in this review, the concept of a prospective therapy optimization study on OSCST in children and adolescents is presented; it began registering cases in 2004. It is hoped that the data presented in this review and experience obtained from the prospective trial will help solve some of the most urgent clinical and therapeutic problems in OSCST in children and adolescents.

### *Epidemiology*

Although epidemiologic data on OSCST in children and adolescents are limited, some preliminary data can be obtained from clinical and pathologic registries, such as the German MAKEI database and German Pediatric Tumor Registry. Combining the data on all ovarian tumors (in children and adults), the relative frequency of OSCST is approximately 8%.[2] In the Pediatric Tumor Registry of the German Society of Pediatric Oncology and Hematology, OSCSTs constitute almost 20% of all testicular and ovarian tumors.[3] This indicates that in reports that found lower numbers, the incidence of OSCST may be underestimated, most probably as a result of incomplete tumor registration.

In infants and young children the low incidence of the otherwise-more-frequent ovarian germ cell tumors has to be considered, too. In this age group, OSCSTs constitute a higher percentage of ovarian tumors than in adults. Children <5 years old were registered in the MAKEI studies between 1983 and 2000: there were 18 OSCSTs as compared to 35 ovarian germ cell tumors. OSCSTs, particularly JGCTs, are characteristic of childhood.

### *Biology, Histogenesis and Pathology*

OSCSTs may develop in association with several defined hereditary disorders. In JGCT there is an association with multiple enchondromatosis, or Ollier's disease.[4,5] The pathogenetic mechanism has not been elucidated to date. In the MAKEI study, only 1 patient with Ollier's disease and JGCT was reported.

There is a pronounced association of Peutz-Jeghers syndrome with sex cord–stromal tumors with annular tubules (SCTATs), and approximately one-third of SCTATs appear to develop in the context of Peutz-Jeghers syndrome.[6,7] These tumors usually develop at a younger age than in otherwise-healthy patients and may develop bilaterally. In contrast, predominantly large cell calcifying Sertoli cell tumors can be found in boys with Peutz-Jeghers syndrome.[8] The pathogenetic mechanism is unclear, and it is largely unknown to what extent mutation of the Peutz-Jeghers gene, STK11, is found in sporadic OSCST.

Genetic analysis of sporadic ovarian JGCTs with comparative genomic hybridization has not revealed frequent or characteristic chromosomal imbalances. The majority of tumors show balanced karyotypes, and in about 25% of patients, chromosomal imbalances, such as gain of the whole chromosome 12, can be found. This analysis has not revealed any correlation between karyotype and

**Table I** *Histologic Differentiation of Testicular and Ovarian SCST and Relative Frequencies in the German Society of Pediatric Oncology and Hematology Tumor Registry*[3]

| Histology | n | % |
|---|---|---|
| Juvenile granulosa cell tumor | 48 | 67 |
| Sertoli-Leydig cell tumor | 14 | 19 |
| Sclerosing stroma tumor | 5 | 7 |
| Sex cord tumor with annular tubules | 2 | 3 |
| Steroid tumor | 1 | 1 |
| Thecoma | 2 | 3 |
| Σ | 72 | 100 |

clinical outcome.[9] This finding is in line with a previous DNA ploidy analysis of JGCT. In that study almost half the tumors showed aneuploid DNA indices. However, no correlation with clinical stage was observed.[10]

Morphologically, OSCSTs include granulosa, Sertoli, Leydig and theca cells as well as their respective immature progenitor cells and fibroblasts that are derived from the specialized gonadal stroma. Granulosa and Sertoli cells develop from the sex cords and thus from the coelomic epithelium. During the seventh week of development, the sex cords become apparent as streaks of immature Sertoli cells in the embryonal testis. In the embryonal ovary, comparable structures have not been demonstrated. However, during a more advanced stage of development, conglomerates of pregranulosa cells can be seen that surround the primordial germ cells. In the developing gonads, granulosa and Sertoli cells show sex-specific differentiation. It has been postulated that bisexual developmental potential persists in some undifferentiated sex cord cells of "mature" gonads. This bisexual potential may be reflected in some SCSTs, such as "gynandroblastomas" with simultaneous Sertoli and granulosa cell differentiation.

After malignant transformation of Sertoli or granulosa cells, these are often accompanied by a stromal component. Moreover, some tumors can be found that display pure stromal differentiation. Examples are tumors of the thecoma-fibroma group, Leydig cell tumors and sclerosing stromal tumors.

Pathologically it has proven useful to stage OSCST according to the guidelines for staging ovarian tumors proposed by the International Federation of Gynecology and Obstetrics.[11] This staging system is based on clinical, cytologic and pathologic assessment.

Histologically, OSCSTs have been classified according to the World Health Organization classification of ovarian tumors.[12] Table I shows the relative frequencies of the different histologic types of OSCST in children and adolescents as registered in the Pediatric Tumor Registry of the German Society of Pediatric Oncology and Hematology.

All OSCSTs produce inhibin A and B, and in our immunohistochemical analysis, 95% of OSCSTs at least focally stained positive for inhibin. Therefore, the immunohistochemical detection of inhibin constitutes a reliable diagnostic marker that distinguishes SCST from the more frequent germ cell tumors, ovarian carcinoma and other tumors of different cellular origin.[3]

Characteristic histologic samples of JGCT and SLCT are demonstrated in Figure 1. Additional details regarding the histologic morphology of SCST can be obtained from Armed Forces Institute of Pathology atlases[2] and publication by the Kiel study group.[3,13] In addition, coexpression of cytokeratins and vimentin is found frequently in OSCST. This phenomenon indicates that JGCT and SLCT mimic patterns characteristic of immature primordial follicles in the ovary and fetal testis, respectively.

### *Clinical Presentation*

OSCSTs often induce clinical symptoms related to production of sex hormones by the tumor.[14] Characteristically, infants and children present with signs of isosexual precocity, including breast enlargement, pubarche and vaginal bleeding. In postpubertal girls, tumors may lead to primary or secondary amenorrhea and nonspecific signs of virilization, such as pronounced acne.[14]

Like steroid hormone–producing cells, OSCSTs also produce inhibin. Free inhibin can be measured in the serum and may serve as a serologic tumor marker during follow-up. However, the diagnostic value may sometimes be hampered by the physiologically broad normal range in healthy, prepubertal children.[15,16]

In rare patients, SLCT may produce α-fetoprotein (AFP) which can be detected serologically. Histologically, most of these tumors resemble SLCT, with retiform, often hepatoid differentiation and heterologous elements.[17]

### *Differential Diagnosis*

OSCSTs have to be distinguished from ovarian germ cell tumors, epithelial ovarian cancer and gonadal tumors of different histogenesis, such as

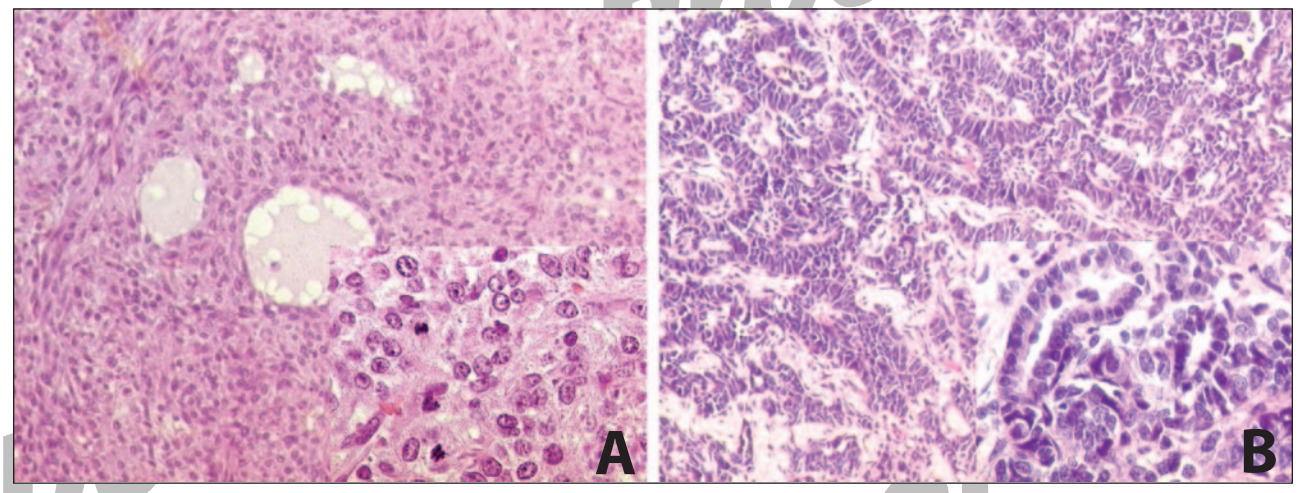


**Figure 1** Histologic appearance of JGCT (A) showing pseudofollicular structures and increased mitotic activity, and (B) Sertoli-Leydig cell tumor with tubular structures. (A and B, ×100; inset, ×500).

leukemia/lymphoma and sarcoma. Tumors presenting with vaginal bleeding in infants must be discriminated from the rare vaginal yolk sac tumors. Clinically, the evaluation of the serologic tumor markers and β–human chorionic gonadotropin helps with regard to the differential diagnosis of secreting malignant germ cell tumors. Therefore, it is mandatory to measure these tumor markers preoperatively.[18]

In some rare patients, the distinction of JGCTs from small cell ovarian carcinoma of the hypercalcemic type may be particularly difficult since the latter may mimic the pseudofollicular growth pattern characteristic of JGCTs.[2] In these situations, the immunohistochemical detection of inhibin constitutes an important diagnostic hallmark of OSCST. We have not observed inhibin positivity in small cell ovarian carcinoma, while virtually all OSCSTs stain positive.[3]

### *Treatment and Prognostic Markers: Literature Review*

The largest series on JGCT published so far analyzed 125 patients, with follow-up data in 831. In this series, only 2 of 80 stage I tumors but all 3 stage II tumors were fatal. Additional clinical and histologic parameters did not contribute to the prognostic assessment. The largest series of SLCT was reported by the same study group and included 207 patients, for whom follow-up information was available on 164.[19] Outcome correlated with both stage and histologic differentiation, and both parameters closely correlated with each other. All well-differentiated SLCTs behaved in a clinically benign fashion, whereas 11% of SLCTs with intermediate differentiation and 59% of poorly differentiated SLCTs (all stage II–III) showed a malignant course. These data correlate with the observation from the MAKEI study that 2 of 3 patients with poorly differentiated SLCT but none with SLCT with intermediate or high differentiation relapsed.

The most recent significant study of JGCT reported on 40 patients treated in France between 1965 and 1990.[4] Comparing our and the French studies, the different staging systems (International Federation of Obstetricians and Gynecologists [FIGO] vs. Wollner classification) must be considered. In the French series, 6 patients treated with chemotherapy were classified as stage III because of tumor rupture (n = 5) or positive ascites (n = 1), and these patients survived. According to FIGO, these would have been stage Ic. In contrast, only 1 of 4 patients with peritoneal or lymph node metastases survived despite chemotherapy (n = 2), radiotherapy (n = 1) or combined chemotherapy and radiotherapy (n = 1).[4]

In contrast to these discouraging data, there are case reports that argue for adjuvant chemotherapy in advanced-stage JGCT. Colombo reported on a girl with a stage III JGCT that achieved complete remission for at least 7 months after PVB chemotherapy.[20] Powell reported on a 13-year-old primigravida with a stage IIIb JGCT that was successfully treated with a combination of methotrexate, actinomycin and chlorambucil.[21] The patient has re-

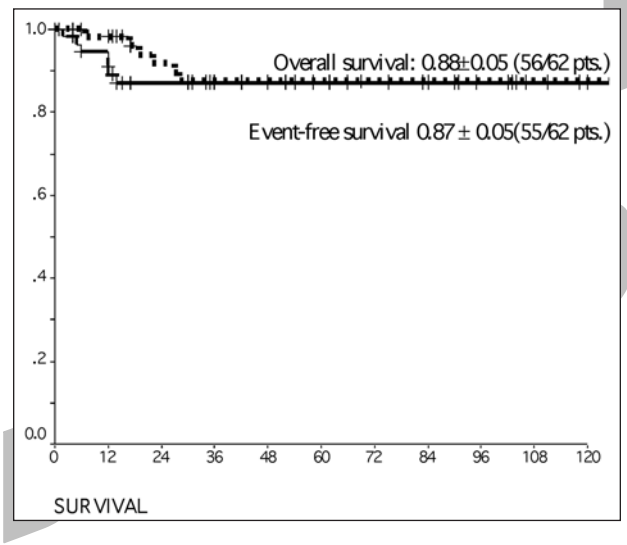


**Figure 2** Event-free and overall survival in 62 children and adolescents with OSCST and follow-up data. pts = Patients.

mained in complete remission for 7 years, during which she gave birth to more children. The same authors reported on 2 stage III tumors successfully treated with surgical debulking and chemotherapy with carboplatin and etoposide and on a recurrent JGCT with liver metastases that achieved complete remission for 44 months after surgery and after 6 cycles of bleomycin and taxol.[22,23]

### *Review of the MAKEI Data*

Although case reports certainly represent a selection of encouraging experience, these reports are in line with the data from the German study group. Between 1980 and 2002, 64 patients with OSCST were enrolled in the MAKEI protocols. For 62 patients, follow-up data have also been reported. In recent years, 10 patients have been registered each year.

The overall clinical and pathologic data obtained in our series correlate well with other series on OSCST.[1,19] However, there appears to be a slight selection toward higher-stage tumors in our series. This holds when an additional 31 tumors reported to the Kiel Pediatric Tumor Registry but not to the MAKEI registry during the same period are included in the analysis of stage[3,14]: 100% of stage II–III tumors, 95% of stage Ic but only 64% of stage Ia tumors diagnosed at the Kiel registry were also reported to MAKEI. These data indicate that the real incidence of OSCST is higher than can be assumed from the data from the clinical MAKEI registries alone.

Considering the whole cohort, the overall prognosis is favorable, and cure rates exceed 80% (Figure 2) and are therefore comparable to those of other studies.[1] Figure 2 also demonstrates that the currently applied strategies for salvage treatment after relapse are insufficient since all but 1 patient with relapse ultimately died as a result of disease progression. This indicates that it is necessary to identify high-risk patients early and to administer intensive treatment to them during primary therapy.

The overall favorable prognosis can be explained by the observation that almost half of all OSCSTs are diagnosed at FIGO stage Ia (Figure 3). Approximately 40% of OSCSTs are classified as stage Ic (microscopic residues—i.e., tumor rupture, malignant ascites, microscopically incomplete resection), and approximately 10% present with peritoneal metastases (stage II–III). Distant metastases have been observed in relapse situations only.

In all patients, tumor resection (tumorovarectomy/tumoradnectomy) constitutes both a diagnostic and therapeutic procedure. The MAKEI data do not indicate that radical retroperitoneal lymph node resection or extended lymph node sampling is mandatory in all OSCSTs because lymph node metastases have been observed only rarely and

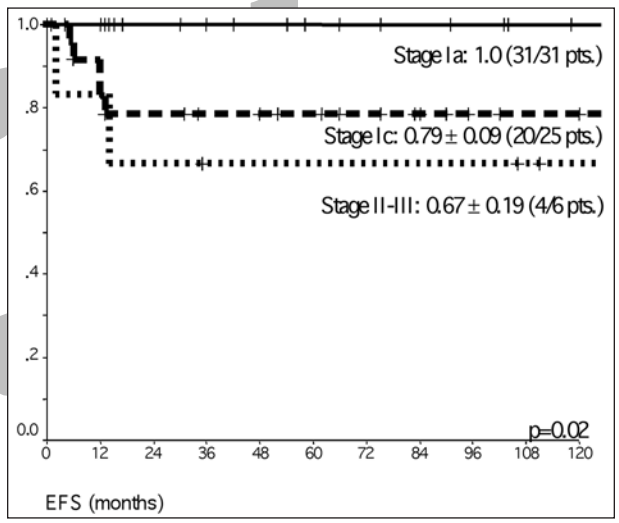


**Figure 3** Event-free survival in 62 children and adolescents with OSCST and follow-up data stratified in accordance with tumor stage. pts = Patients, Cum = cumulative, EFS = event-free survival.

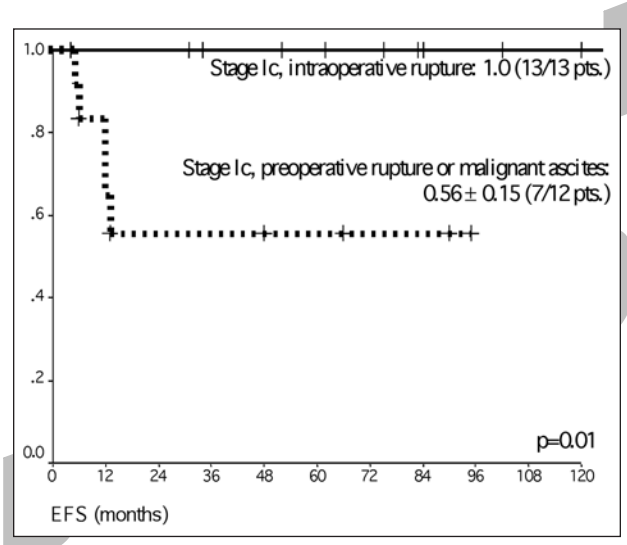


**Figure 4** Event-free survival in 25 patients with stage Ic OSCST stratified by the suspected time of the microscopic tumor spread. Seven patients with preoperative tumor rupture received adjuvant chemotherapy, and among these, 3 relapses occurred. Among 5 patients with preoperative tumor rupture who were not treated with adjuvant chemotherapy, 2 relapses occurred. pts = Patients, Cum = cumulative, EFS = event-free survival.

most commonly in (extended) relapse situations. Our data and the only other published series on JGCT[4] suggest that no adjuvant therapy is necessary in stage Ia tumors.

The data reported by the MAKEI study group represent the first cohort of patients prospectively registered and treated according to a uniform strategy.[14] Based on these data, risk stratification for adjuvant chemotherapy can be proposed for patients with tumors of stage Ic, II or III.

*Stage Ic*

In stage Ic, the decision for or against adjuvant chemotherapy is very difficult. Tumors in which microscopic tumor spread is suspected or proven (but no pathologic evidence of peritoneal metastases) are classified as stage Ic. According to FIGO, tumors may be classified as stage Ic for several reasons. In some patients, preoperative tumor rupture may have occurred, and in others the cytologic analysis of peritoneal washings or ascites provides evidence of malignant tumor cells. In contrast, other tumors may also be classified as stage Ic if the tumor has been punctured or the capsule has otherwise been violated in situ even though the tumor capsule has been intact prior to surgery (intraoperative violation of tumor capsule).

Our previous analysis demonstrated that intraoperative violation of the tumor capsule does not carry an increased risk of recurrence. In contrast, we have seen a high relapse rate (comparable to that in stage II–III) in patients in whom the tumor has been ruptured prior to surgery or in whom ascites contained malignant cells (Figure 4).[14] This observation indicates that thorough documentation and critical evaluation of the clinical and surgical report is mandatory and that cytologic analysis of ascites/peritoneal washings is indispensable. In cases with incomplete documentation or missing cytological evaluation, the assessment of the proliferative activity of the tumors may help with regard to risk assessment (Figure 5), but nevertheless a higher grade of uncertainty remains.

***Stage II–III***

In stage II–III, microscopic or macroscopic spread with peritoneal or lymph node metastases has occurred. It is obvious that surgical treatment alone will not be curative but must be supplemented with adjuvant chemotherapy. In the past, cure of OSCST has been reported in single cases only.[22-24] The MAKEI group was the first to report a series of patients with advanced tumor stage who were treated with adjuvant cisplatin-based combination

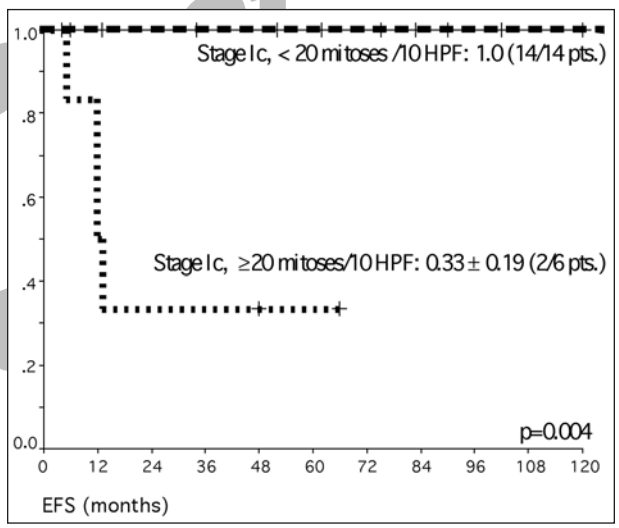


**Figure 5** Event-free survival in 20 patients with stage Ic OSCST and complete data stratified by mitotic activity. pts = Patients, Cum = cumulative, EFS = event-free survival.

chemotherapy.[25,26] In this series, 4 of 6 patients with stage II–III tumors achieved long-lasting remission following surgery and adjuvant chemotherapy.

Both patients who died as a result of tumor progression showed high proliferative activity (≥ 20 mitoses/10 high-power fields), while the 4 remaining patients had a lower mitotic count. This observation is in line with the analysis of the prognostic impact of proliferative activity in stage Ic tumors. Figure 5 demonstrates that in stage Ic tumors, a high mitotic index correlates with impaired outcome. Clearly, high proliferative activity distinguishes patients with poor prognosis.

In addition to proliferative index, age also appears prognostic.[14] We demonstrated that age younger than 10 years correlates with favorable outcome. Therefore, we propose that 2 biologically and clinically distinct types of tumor might exist. One occurs in young children, commonly results in isosexual precocity, is diagnosed at early stages and is prognostically favorable, in line with French data that isosexual precocity correlates with favorable outcome.[4] The other type appears later, causes endocrinologic symptoms less frequently and may present at an advanced stage and is relatively refractory to treatment.

### *Critical Issues*

There are several issues that remain to be addressed critically. The indication for chemotherapy and the minimum amount of chemotherapy necessary in stage Ic tumors are ill defined. Our data suggest that among stage Ic patients, a subgroup of patients at high risk can be identified through histologic assessment. These patients may be suitable for adjuvant chemotherapy. However, the limited data available from our analysis do not allow definition of the required chemotherapy for tumors at stage Ic or higher. In our study, all patients with stage II–III tumors received at least 4 cycles.[14,25] Considering other studies with less favorable outcomes,[1,4,19] we would not advocate less but rather argue for extension to 6 cycles. Although, to a certain extent, chemotherapeutic regimens varied with consecutive MAKEI protocols, all but 1 patient received chemotherapy that included cisplatin and etoposide, mostly as part of 3-agent regimens. Therefore, it appears effective to include these 2 drugs in a 3-agent combination regimen such as cisplatin, etoposide and ifosfamide.

Lastly, alternative strategies must be developed for refractory tumors. In our experience, regional deep hyperthermia has resulted in complete remission in recurrent and refractory OSCST, although experience with this approach is limited, and responses did not translate into durable remissions longer than 2 years.[27]

### *Proposed Concept of the Prospective OSCST 2004 Trial*

In 2004 the first worldwide prospective trial on OSCST in children and adolescents began. This trial aims for a more thorough registration of German patients with OSCST in order to improve our knowledge of the epidemiology of OSCST. In addition, accompanying molecular biologic studies will be performed that will focus on the association of OSCST with hereditary disorders and on biologic markers with potential prognostic significance.

Most important, a risk-stratified therapeutic strategy will be followed based on our previous experience, outlined above. Therapeutic decisions will be made with regard to the parameters histology, tumor stage, completeness of resection and mitotic index. Stage Ia tumors will be followed expectantly. Tumors categorized as stage Ic because of intraoperative tumor violation only will be followed expectantly, too. In contrast, tumors that are classified as stage Ic because of malignant ascites, tumor rupture prior to surgery or microscopic spread beyond the tumor capsule will be treated with cisplatin-based chemotherapy. The same chemotherapy will be administered for stage II and III tumors.

Since outcome is unsatisfactory in advanced tumors with a high mitotic index, therapy must be intensified in them. Therefore, we suggest treating these patients with cisplatin-based chemotherapy in combination with regional deep hyperthermia for first-line treatment.

Since the registration rate of the protocol will be too low, there will be no randomized comparison, but the different groups of patients will be compared to historical controls from MAKEI studies.

### *Conclusion*

Our analysis of 64 prospectively documented patients allows the development and prospective evaluation of risk-adapted therapeutic strategies in OSCST based on a standardized clinical and histopathologic assessment. However, the data presented in this analysis are limited and await validation in a larger, prospective trial. Considering that

the incidence of OSCST is probably underestimated because of incomplete patient recruitment, the studies summarized in this review reveal encouraging perspectives that merit further investigation.

### *Acknowledgments*

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