Clinical review of 63 cases of sex cord stromal tumors

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Summary

Purpose of investigation: A retrospective analysis of 63 cases of sex cord stromal tumors treated in a 22-year period to evaluate the prognostic impact of different clinical parameters.

Methods: Sixty-three cases of sex cord stromal tumors were studied. These neoplasms are characteristically detected at an early stage and may recur locally years after the initial diagnosis. The most frequent cell type was adult granulosa cell tumor (75%); a total of 37 patients (62%) had Stage IA lesions.

Results: The cornerstone of treatment is surgery. Conservative surgical treatment was performed in 11 out of 47 cases (23%) of early stage tumor and in one of 13 patients affected by advanced neoplasm. Five of these 12 patients became pregnant after the treatment. Endometrial hyperplasia and uterine adenocarcinoma were diagnosed in 26.5% and 8.8% of the cases, respectively. Twenty-one patients (35%) received adjuvant therapy: 20 chemotherapy and one chemo-radiation treatment. Eight patients (13%) either progressed or recurred. All the recurrent patients but one had been treated with adjuvant chemotherapy (VAC and/or PVB). Overall survival by stage was 88.2% for Stage I and 30% for Stage III-IV.

Conclusion: Tumor stage is the most important clinical parameter of prognostic relevance. Tumor size and laterality significantly affected prognosis in terms of overall survival; survival rate did not seem to be affected either by the age of the patients or by the modality of surgical treatment.

Key words: Sex cord stromal tumors; Granulosa cell tumors; Surgical treatment; Chemotherapy.

Introduction

Sex cord stromal tumors (SCSTs) are rare neoplasms that account approximately for 3 to 5% of ovarian malignancies and the majority are functioning tumors with clinical manifestations [1]. They are characterized by 86 to 100% long-term survival rates for Stage IA tumors, and they have a propensity for late recurrences [1, 2].

The most common histotype is represented by granulosa cell tumors which account for 70% of all ovarian stromal tumors [3-6]. Other histotypes are: Sertoli-Leydig cell tumors, gynandroblastoma and lipid cell tumors.

Two distinct types of granulosa cell tumors have been described based on clinical presentation and histological characteristics: the juvenile and the adult form [3, 7-9].

Adult granulosa cell tumors (AGCTs) are the most common and generally present in the peri- or post-menopausal female with a median age at presentation of 50-57 years [3, 4, 10-13]. AGCTs have been considered to be of low-grade malignancy with a favorable prognosis [4, 6, 10, 13]. The majority of cases (60-95%) are in Stage I at the time of diagnosis and unilateral with a 5-year survival of 90% [2-4, 12]. However, the natural history is characterized by slow growth tending toward late recurrence even 37 years after the initial diagnosis [6, 10, 13, 14]. After surgery for localized disease, recurrence in the pelvic or abdomino-pelvic areas, which account for more than 10% of cases, represents an ominous sign; patients with advanced disease have a 5-year survival ranging from 0 to 22% [4, 15].

Juvenile granulosa cell tumors (JGCTs) are rare forms with distinctive microscopic features which in 97% of cases occur before the age of 30 and are often associated with precocious puberty. Almost all tumors present at Stage I [9, 12].

Several serum markers have been evaluated in the past few decades, such as gonadotropins, follicle regulatory proteins and inhibin. Inhibin has been shown to be a product of granulosa cells and in a few case reports has been shown to parallel the course of the disease. However its sensitivity and specificity are still unknown [3, 16, 17].

Sertoli-Leydig cell tumors (SLCTs) account for less than 0.5% of all ovarian tumors. Almost all cases present at Stage I and most of them are virilizing. Prognosis is usually favorable, except for those poorly differentiated or with heterologous elements [12, 18].

The rarity of these tumors and their somewhat unpredictable biologic behavior preclude any definitive statements about their optimal management [15, 19]. However, surgery remains the cornerstone of treatment; conservative surgery seems to be the appropriate approach to young patients with Stage IA disease while for older women or those with more advanced-stage disease, abdominal hysterectomy, bilateral salpingo-oophorectomy and tumor debulking are usually indicated.

The selection of early-stage patients for any post-operative treatment is controversial [15]. At the present the relative benefit of adjuvant chemotherapy has still not been demonstrated, and it would be difficult to assess given the long natural history of these tumors coupled with the current toxicity of the chemotherapy regimens

employed [20, 21]. In patients with advanced disease adjuvant therapy should be considered. In those patients with recurrent or metastatic disease, treatment has not been standardized yet [15].

In order to select those patients who should receive postoperative therapy, an understanding of prognostic factors is essential. Unfortunately, other than advanced clinical stage, prognostically significant variables predictive of recurrence have yet to be defined. Other possible prognostic factors such as tumor size, laterality, histotype, cellular atypia, mitotic rate, preoperative capsule rupture, age and lymphatic space involvement emerge in some studies but not in others [6, 10, 21, 23]. The aim of this study was to present a retrospective analysis of 63 cases of sex cord stromal tumors treated at the Department of Obstetrics and Gynecology, University of Brescia, in a 22-year period, and to evaluate the prognostic impact of different clinical parameters.

Materials and Methods

During the period June 1980 to September 2002, 63 patients with SCSTs were diagnosed and treated at the Department of Obstetrics and Gynecology, University of Brescia.

All clinical records were retrospectively reviewed and the necessary clinical data obtained. The following parameters were evaluated: patient age, parity, histotype, stage, tumor size, laterality, grading, mitotic index, endocrine manifestations, surgical treatment, adjuvant therapy, second look, recurrences rate, site of relapse, type of treatment at relapse and survival, and pregnancies after conservative treatment. Histopathological sections were reviewed.

Tumor stage was assigned according to the criteria of the International Federation of Gynecology and Obstetrics (FIGO). Criteria defined by the World Health Organization (WHO) were employed for histologic diagnosis.

Three patients who first came under observation with recurrent disease were excluded from the study.

All patients were treated with primary surgery. Patients with Stage I disease and under 37 years old underwent unilateral salpingo-oophorectomy (USO) or simple cystectomy; patients who did not require preservation of fertility underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH-BSO), patients with advanced disease underwent debulking surgery involving at least TAH-BSO, omentectomy, and pelvic±paraaortic lymphadenectomy.

Adjuvant therapy was administered based on the following criteria: Stage > IA tumors of any histologic subtype and Stage I SLCTs that are poorly differentiated or that contain heterologous elements.

The treatment consisted of chemotherapy. In most cases combination regimens of vincristine, actinomycin, and cyclophosphamide (VAC) or cisplatin, vinblastin or etoposide, and bleomycin (PVB or PEB), for six cycles, were employed. Only one case was treated with a combination of chemo-radiation therapy.

Follow-up was performed until September 2002. Depending on the stage, patients were examined every four months for the first two years, every six months for the following five years and yearly thereafter for advanced disease, every six months for the first three years and yearly thereafter for early disease.

Statistical analysis of the data was carried out with chi-square test. Survival curves were generated according to the method of Kaplan and Meier. The log-rank test was used to compare the homogeneity of survival functions across strata defined by categories of prognostic variables. A p value of less than 0.05 was considered significant.

Results

The study included 60 patients with sex cord stromal tumors: 45 cases of AGCTs (75%), five cases of JGCTs (8.3%), nine cases of SLCTs (15%), and one case of gynandroblastoma (17%).

The mean age at diagnosis was 45 years (range: 7-81). Twenty-one (35%) patients were postmenopausal and 39 (65%) women were premenopausal. The mean age of Stage I patients was 47 years (47 cases) and 39.5 years for advanced-stage subjects (13 cases). Mean age by histotype was 48 years for adult granulosa cell tumors, 19 years for juvenile granulosa cell tumors and 45 years for Sertoli-Leydig cell tumors; the only patient affected by gynandroblastoma was 37 years old. Forty-seven patients were pluriparous (78.3%) and 13 patients were nulliparous (21.7%).

The symptoms were similar in most cases and often related to hormonal activity. Symptoms and/or signs related to endocrine activity were present in 33 patients (55%). Most commonly patients presented with bleeding disturbances in premenopause (12/39: 31%) or postmenopause (13/21: 62%). Three premenopausal subjects (8%) and two postmenopausal patients (10%) presented with evidence of virilization.

Forty-eight endometrial samples were available for histology: 31 (65%) presented normal endometrium, endometrial hyperplasia was described in 13 patients (27%) and endometrial adenocarcinoma was diagnosed in four subjects (8%). The distribution of cases by stage and histotype is shown in Table 1. Forty-seven women (78%) were Stage I (37 Stage IA, 10 Stage IC). Twenty-eight patients with granoulosa cell tumors (25 AGCTs and 3 JGCTs) were Stage IA (56%) and ten (9 AGCTs and 1 JGCT) Stage IC (20%). All patients with SLCTs were Stage IA. The only one case of gynandroblastoma was Stage IV.

Tumor size was available in 48 cases (80%): 11 of them had lesions < 5 cm (23%) in diameter; 20 cases were characterized by lesions ranging from 5 to 10 cm (42%), and 17 patients were affected by tumors larger than 10 cm (35%).

Neoplasms were unilateral in 54 cases (90%) and bilateral in six cases (10%). Only one of 47 patients with early stage tumor was affected by a bilateral neoplasm (2%),

Table 1. — *Distribution of cases by stage and histotype.*

Stage	Adult Granulosa	Juvenile Granulosa	Sertoli-Leydig	Gynandro-blastoma	Total cases
IA	25	3	9	–	37
IC	9	1	–	–	10
II	2	–	–	–	2
III	5	–	–	–	5
IV	4	1	–	1	6
Total cases	45	5	9	1	60

while five out of 13 cases (38%) with advanced stage tumor were bilateral (p < 0.0001).

Distribution by grade was: 27 G1, 24 G2, and 9 G3; by mitotic index: 24 showed more than 5 mitotic figures per high power field and 34 less than 5.

Conservative surgical treatment was performed in 11 out of 47 cases (23%) of Stage I tumors and in one of 13 patients affected by advanced neoplasm (8%): this was the case of a 7-year-old girl affected by JGCT in Stage IV (Table 2). Conservative treatment was performed in 11 out of 39 premenopausal women (28%) and in one out of 21 postmenopausal patients (5%). Five of these 12 patients become pregnant after the treatment. A definitive approach was employed in 48 patients (80%): in 40 out of 45 patients with AGCT (89%), only in one of the five cases of JGCT (20%) and in six out of nine patients affected by SLCT (66%).

Table 2. — *Distribution of cases by stage and type of surgery.*

Stage	Type of surgery		Total cases
	Definitive	Conservative	
Ia	29	8	37
Ic	7	3	10
II	2	–	2
III	5	–	5
IV	5	1	6
Total cases	48	12	60

Lymphoadenectomy was performed in 24 out of 60 (40%) patients. Positive nodes were diagnosed only in one patient affected by AGCT in Stage IV and with a tumor size of 8 cm.

Twenty-one patients (35%) received adjuvant therapy: 20 chemotherapy and one chemo-radiation treatment. One subject was Stage IA, ten were Stage IC, two Stage II, four Stage III and four Stage IV, while the remaining advanced stage cases (1 Stage III and 2 Stage IV) did not receive chemotherapy due to poor medical conditions and were treated hormonally. Distribution by histotype showed 17 cases of AGCTs, two cases of JGCTs, one case of SLCT and the only case of gynandroblastoma that had undergone chemo-radiation treatment.

Nine women underwent procedure second-look which was positive in two cases who were Stage III at the time of the diagnosis.

Median time of follow-up was 91 months (4-264 months). Eight patients (13%) either progressed (5 cases) or recurred (3 cases) and all developed a pelvic progression/recurrence. Recurring subjects had undergone definitive primary surgery for Stage IC (1 case), III (3 cases) and IV (2 cases) AGCTs, one case was a Stage IV JGCT who had undergone conservative surgery given the age of the patient (7-year-old girl), and one was Stage IV gynandoblastoma. All the recurrent patients but one, (who declined treatment), had been treated with adjuvant chemotherapy (VAC, PVB or PEB). Median time to recurrence was 86 months (0-137 months).

Progression/recurrence was not treated in four cases due to poor medical conditions, three patients underwent chemotherapy, one was treated with surgery and

chemotherapy and another one with surgery alone. Only one (13%) recurrent patient survived: she was a 31-year-old woman with Stage IIIC, monolateral, AGCT, grade 1, who did not receive adjuvant chemotherapy. She presented with an abdomino-pelvic recurrence 11 months after diagnosis and was treated surgically. This woman is still alive with no evidence of disease 28 months after primary treatment.

Recurrence rate by stage was 2% for Stage I (1/47 cases) and 54% for advanced tumors (7/13 cases) (p < 0.001); by tumor diameter it was 0% in cases of tumor < 5 cm and 5-10 cm (0/11 cases and 0/20 cases, respectively) and 29% for tumors larger than 10 cm (5/17 cases) (p = 0.004). No statistically significant difference in recurrence rate was seen by age (< or > 40 yrs), histotype and type of surgery (conservative vs definitive). Overall survival rate was 82.1%. At the time of the analysis 46 patients were alive with no evidence of disease, seven died due to the malignant disease, two died due to intercurrent diseases and four were lost to follow-up after 28, 36, 42 and 65 months, respectively.

In our study clinical and pathological factors were analyzed in terms of overall survival. Stage (Figure 1), laterality (Figure 2), and tumor size (Figure 3) significantly (p < 0.01) affected prognosis in terms of overall survival. Survival rates by histotype were not comparable given the uneven number of patients among the subtypes of SCSTs and the very small number of some of the subgroups. Overall survival by histotype was 80% for AGCTs, 75% for JGCTs, 100% for SLCTs and the only case of gynandroblastoma died of malignant disease.

Survival rate did not seem to be affected by the age of the patients (> or < 40 years old), by grading, mitotic activity or by the modality of surgical treatment (conservative vs definitive).
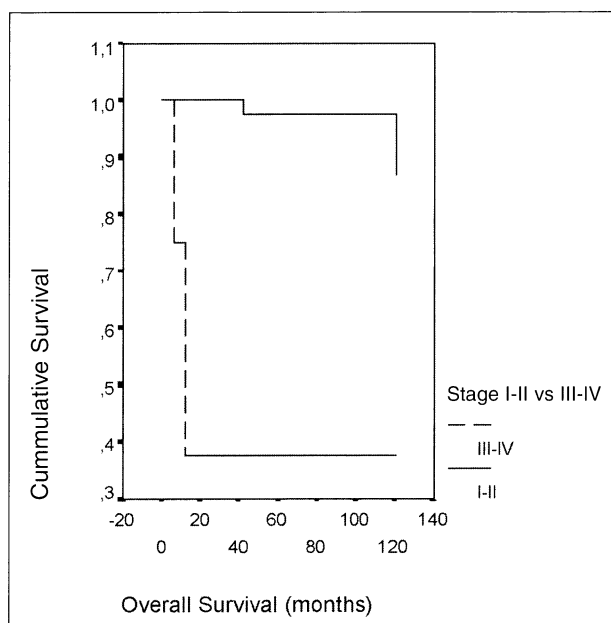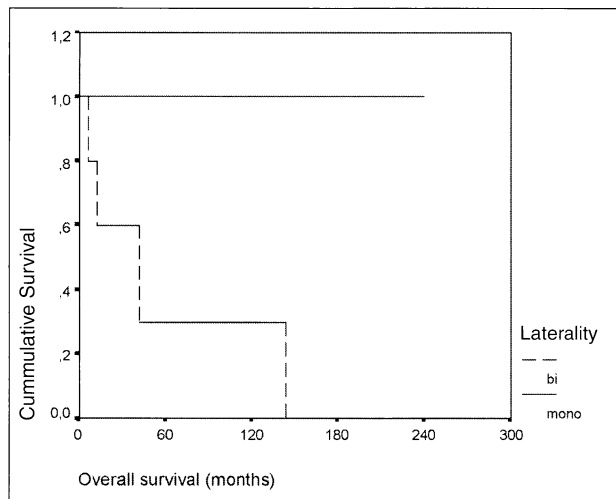

Figure 1. — Overall survival by stage.
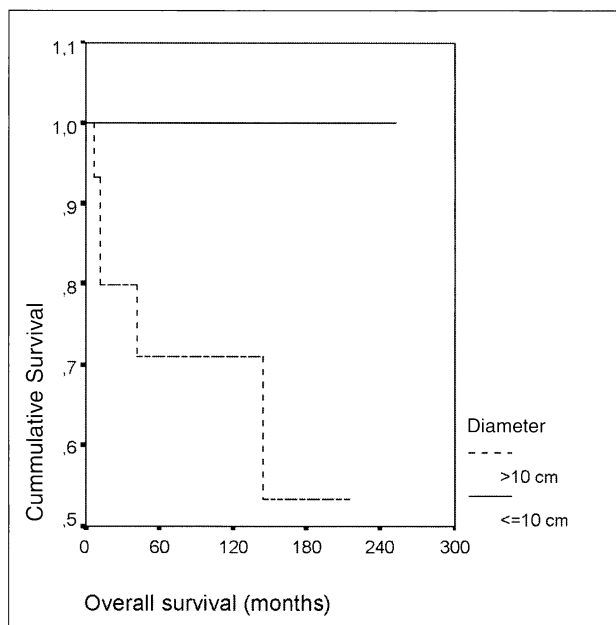
Figure 2. — Overall survival by laterality.

Figure 3. — Overall survival by tumor size.

Discussion

The results of this study confirm that SCSTs are uncommon gynecological tumors with a peak incidence around the first postmenopausal decade (mean age at diagnosis 45 years) with the exception of JGCTs (19 years).

Although relatively rare, recognition and knowledge of the distinctive clinical behavior of these subtypes are essential for adequate management. Some patients present with nonspecific symptoms, but most cases have endocrine manifestations as a direct consequence of hormone secretion by the tumor and an association with endometrial hyperplasia and adenocarcinoma has been documented [3-8, 10, 11]. In our series symptoms and/or signs related to endocrine activity were present in 55% of the patients. Endometrial hyperplasia and endometrial adenocarcinoma were described in 27% and in 8% of the cases, respectively. Endometrial proliferation/hyperplasia is an effect of prolonged unopposed estrogen production by these tumors and this correlation has been widely accepted in the literature [3, 4, 13].

Due to the hormonal activity of these tumors and the resultant symptoms, the majority of patients are diagnosed with Stage I disease as opposed to epithelial ovarian carcinoma patients who are usually diagnosed with Stage III tumor. In agreement with this statement, in our series 78% of the patients had Stage I disease at the time of the diagnosis.

The therapy for SCSTs is surgical. Given the long natural history and low incidence of bilaterality of 3-5% [3-5] in patients with Stage I disease, less than 40 years old and those wishing to preserve fertility, conservative therapy seems to be an adequate treatment. Cases who do not require preservation of fertility or patients with advanced disease should be treated with radical surgery [3, 6, 12].

A review of the literature revealed that few large series address this aspect of the primary treatment of SCSTs. Pankratz et al. [10] reviewed 61 Stage I patients. The recurrence rates were 57% in patients treated with conservative surgery, but only 26% in those undergoing definitive surgery. However, a review of the data shows that 10/19 cases that underwent USO, and 4/9 that had a BSO had either Stage II or III disease and therefore were at obvious risk for recurrence with conservative treatment as opposed to only 8/21 of patients who had undergone more extensive surgery. Evans et al. [5] published a series of 118 patients of whom 89 were retrospectively assigned to Stage I. Their analysis showed that 17% of the subjects who underwent definitive surgery developed a recurrence, whereas those having a less extensive procedure had a recurrence rate of 26%. However, details relating the surgical procedure to the stage of disease are lacking, and the analysis included patients whose stage was unknown. Ohel et al. [11] reviewed 165 patients: 77 were Stage I, 20 Stage II, and 46 Stage III-IV; 34 were treated conservatively and had an overall 5-year survival rate of 75%, while 94 underwent extensive surgery and their overall 5-year survival rate was 59%. It is likely that the improved results in the group treated with the conservative procedure reflect the earlier stage of disease at the time of presentation, but details to clarify this aspect are not available.

In a more recent population-based study of 37 patients with Stage I disease, by Lauszus et al. [24], the actual survival rate after ten years was 40% in postmenopausal women operated on conservatively and more than 90% for the radically treated patients. They observed a relapse rate of 35% in Stage I, which is similar to that of other studies [25, 26], but differs from other studies where relapse rates range from 2 to 9% [13, 27]. The possible explanations for this difference are short follow-up time, variation in selection, and retrospective design, which increase the risk of recall bias. Moreover the paper

remains inconclusive with respect to whether pre-menopausal women should have conservative surgery.

Therefore, based on the data from the literature, conclusions about the relative value of conservative versus more extensive surgery cannot be made. Since the majority of patients present with early-stage disease and that recurrences, if they occur, do so many years later, consideration for preservation of the apparently uninvolved remaining organs needs to be given. In the present paper a conservative surgical treatment was performed in 23% of early stage tumors, none of them recurred and five of these 11 patients become pregnant after treatment.

The role for adjuvant therapy in Stage I-II or completely resected Stage III disease has not yet been defined [3, 6, 12, 28, 29]. Currently platinum-based combination chemotherapy appears to be the most used postoperative treatment. The value of radiotherapy and its appropriate role in the treatment of SCSTs is unclear. Hormonal therapy as well could play a role in the treatment of metastatic SCSTs, but its efficacy has not been defined yet.

Radiotherapy has been used in both adjuvant and recurrent settings with clinically described responses and palliation of symptoms. Initially postoperative radiotherapy was used in the adjuvant setting, and several studies suggested that it improved survival in these patients [3, 10, 21, 30]. Pankratz *et al.* [10], often quoted in the literature, published a review of 61 cases, 48 of whom received adjuvant radiation therapy. The authors state that the group of patients receiving radiotherapy had a lower mortality than those who received no radiation; however the data are not adequate to allow a comparison of these two groups to determine whether the observed differences were due to therapy. On the contrary other studies suggest no survival benefit for adjuvant radiotherapy [3, 5, 6, 11]. A series of 200 patients was published by Evans *et al.* [5] and 43 of those, received radiotherapy. The impact of radiation therapy on recurrence rate was negligible. In fact 15% of the patients treated with surgery alone recurred compared to 20% of the subjects who received combined treatment. Again, the data are not sufficient to verify whether the two groups are comparable with respect to other prognostic factors. Stenwig *et al.* [31] reported on 64 Stage I cases who received adjuvant radiotherapy to the pelvic area that did not appear to have improved survival with adjuvant treatment.

The role of radiotherapy is further complicated by the fact that the volume that requires treatment has not been defined yet, and furthermore the dose required to treat patients varies considerably and in some of the published series was not reported. In summary there are no convincing data to support the concept that radiotherapy should be used in the adjuvant setting. The use of radiotherapy in the matastatic and recurrent setting is largely anecdotal, and in the literature there are case reports of patients with excellent response to this treatment, however the responses have been short, within months [3, 10, 30]. Therefore the role of radiotherapy in the palliative setting could be for symptomatic disease and for those patients who are unsuitable for surgical debulking or other forms of therapy.

Chemotherapy has also been shown to induce responses in SCSTs. There are no adequate data of early-stage patients treated in the adjuvant setting. Moreover the relative impact of adjuvant chemotherapy is still difficult to assess, mainly in early stage tumors that have poor prognostic features, given the long natural history of these tumors coupled with the toxicity of some of the combination regimes employed. Advances in this area may be made only through cooperative trials, although late recurrences for GCTs would make it difficult to interpret data collected from any adjuvant prospective clinical trial and pose serious questions about their need.

In the present study 11 early-stage patients (2 in Stage IA and 9 in Stage IC) received postoperative chemotherapy, and of those only one (9%) recurred, but the lack of a comparable control group and the limited number of patients make impossible to draw any conclusion about the role of adjuvant chemotherapy in high-risk early-stage patients.

Chemotherapy has mainly been considered for those patients with advanced, recurrent or metastatic disease. A variety of chemotherapy regimes have been used, but have been considered palliative only.

Cisplatin-based regimens, most commonly with etoposide, bleomycin, doxorubicin or cyclophosphamide, produce an overall response rate of 63-80% but responses are not durable [2, 12, 20, 21, 32]. Colombo *et al.* [2] first reported the use of the combination regimen consisting of cisplatinum, vinblastine, and bleomycin (PVB) in the treatment of 11 recurrent and/or metastatic granulosa cell tumors. The overall response rate was 74%. All the six complete responses except one were alive and free of disease at a median follow-up time of 14 months. Of the three partial responders, two died of drug-related toxicity while one was alive and without evidence of disease at 34 months.

Zambetti *et al.* [20] treated seven patients with the same regimen used by Colombo *et al.* Three of them obtained a complete response and one a partial response. Two complete responders were without evidence of disease at seven and 36 months, and a third relapsed at 15 months. Again toxicity was significant.

Gershenson *et al.* [32] published a study on the use of the combination of cisplatin, etoposide, and bleomycin (PEB) for the treatment of metastatic ovarian SCSTs (7 cases) and poorly differentiated SLCTs confined to the ovary (2 cases). The overall response rate was 83%. Of the three patients with non-measurable disease, one relapsed, one developed progressive disease and one remained in remission at the time of analysis. Of the seven patients with metastatic disease only one (14%) had a durable remission. Median progression-free survival was 14 months and median survival time was 28 months. Their conclusion was that although the overall response rate to the combination chemotherapy was high, the regimen apparently lacked durable activity in this group of tumors.

Pecorelli *et al.* [15] in 1999 published the results of the EORTC study on cisplatin, vinblastine and bleomycin (PVB) combination chemotherapy in 38 recurrent or advanced ovarian GCTs. In the group of 25 patients who had received prior surgery only, seven and six had complete and partial responses, respectively, for an overall response rate of 52%. At a median follow-up of 39 months, six patients were alive with no evidence of disease, six were alive with disease, 12 died due to malignant disease and one died due to intercurrent disease. The median time to progression was 13.9 months, the median survival was 25.4 months and 3-year survival was 49%. In the group of 13 patients who had received postoperative radiotherapy or other prior chemotherapy, five complete and five partial responses were described for an overall response rate of 77%. At a median follow-up of 50 months, six patients were still alive, only one with no evidence of disease, six died due to malignant disease and one died due to intercurrent disease. The median time to progression was 19.3 months and the median survival was 41.1 months. Although response rates to combination chemotherapy are high, the impact on both disease-free and overall long-term survival is currently unknown. Related toxicity is significant and its impact has to be considered in the use of different regimens. Some authors have reported the responsiveness of GCTs to paclitaxel therapy, thus the combination of paclitaxel and a platinum drug seems to be a reasonable regimen for future trials both in adjuvant and palliative settings [21, 32].

Whenever patients are unable or unwilling to accept systemic combination chemotherapy, hormonal therapies such as progestins, antiestrogens, or gonadotropin-releasing hormone agonists with low side-effect profiles and transient responses of a few months duration have been used [3, 33-35].

Tumor stage is the only well recognized clinical parameter of prognostic importance in the literature. Bjorkholm *et al.* [6] reported survival rates for Stage I tumors in excess of 95% at five and ten years. Comparatively, the 5-year survival for Stage II and III tumors was 55% and 25%, respectively. Miller *et al.* [36] in their study on 70 patients with AGCTs concluded that, after logistic regression analysis, only tumor stage remains significant as a clinical prognostic factor. Malmstrom and co-workers [13] published survival rates of 94% and 88% in Stage I patients after five and ten years, respectively, and in Stage II-III of 44% after five and ten years. Bridgewater [12] reported that true Stage IA tumors have a 10-year survival of 100%, whereas Stage II-IV tumors have a survival of less than 50%.

In the present study the overall survival rate was 94.1% for Stage I tumors and 30% for Stage III-IV neoplasms; in our series there was only one patient with Stage IIB disease and only one with Stage IIC and both survived.

Bilaterality, tumor size, cellular atypia, mitotic rate, preoperative capsule rupture, age and lymphatic space involvement are factors that have been inconsistently reported and overall less convincing as being important for prognosis [3, 6, 12, 13, 36, 37].

Bilaterality, given its low incidence in this group of tumors, appears related to a more advanced stage which, as a consequence, leads to a worse prognosis. In fact in our series only 2% of patients with early stage tumor were affected by bilateral neoplasms. Cronjè *et al.* [37] presented a retrospective study of 454 patients and they observed that bilateral presence of the tumor seemed to be the most important factor indicating malignancy. Accordingly in the present study overall survival by laterality was 88.0% for monolateral tumors and 16.7% for bilateral tumors.

In the study published by Fox *et al.* [4] the prognosis was worse for those women with larger tumors; 5-year survival rate was 100% for patients with tumors less than 5 cm, 64% for patients with tumors between 6 and 15 cm and 61% for patients with tumors more than 15 cm in diameter. Stenwig *et al.* [31] claimed that tumor size had no significant influence on prognosis for tumor diameters less than 15 cm: 5-year survival rate was 73% for patients with tumors less than 5 cm, 63% for patients with tumors between 6 and 15 cm and 34% for patients with tumors more than 15 cm in diameter. Bjorkholm *et al.* [6] reported a 100% 10-year survival for Stage I ovarian SCSTs less than 5 cm in diameter in contrast to 92% for tumors with a diameter between 5 and 15 cm. Miller *et al.* [36] performed a logistic regression analysis of clinical parameters in ovarian GCTs and identified tumor stage as the most important variable predicting recurrent disease and tumor size as "less" important. Malmstrom *et al.* [13] when looking at survival according to tumor size in Stage I patients concluded that there was no obvious relationship between tumor size and survival.

In the present paper overall survival by size was 100% for a tumor diameter less than 5 cm, 85.0% for a tumor diameter between 5 and 10 cm and 52.9% for a tumor diameter more than 10 cm in diameter.

Fox *et al.* [4] in their series described a relationship between the degree of mitotic activity within the tumor and the patient's chance of survival, but the degree of cellular atypia within the neoplam appeared to be of less prognostic impact. Bjorkholm *et al.* [6] reported a 80% relative 25-year survival rate in cases with mild atypia, in contrast with a 60% survival in those with moderate atypia, but differences in mitotic rate did not have a statistically significant effect on the prognosis of Stage I tumors. Zaloudek and Norris [38] found a high mitotic rate in two neoplasms that recurred, whereas in the other 11 tumors with lower mitotic rates none recurred. In the same series they did not find any correlation between clinical behavior and degree of cytologic atypia. Bartl *et al.* [39] investigated 27 patients with GCTs and found that five of the women had polymorphic tumors and a high mitotic rate in the preparations, all died of the disease. Malmstrom and co-workers [13] in a study on 54 granulosa cell tumors concluded that mitotic rate is a well defined parameter and influences survival significantly. In fact, although the overall survival was 90%, those patients with a mitotic frequency of $\geq$ 10/10 HPF had a significantly poorer survival (longest survival: 4 years)

than that of patients in the intermediate group with 5-9/10 HPF (80% 5-year survival rate) and those patients with a less or equal 4/10 HPF (100% 5-year survival rate). It confirms the prognostic importance of mitotic rate revealed in previous studies, but evidence remains inconclusive [4, 35, 40, 41].

Determination of the above-mentioned factors of possible prognostic significance has been based on retrospective reviews, in which only univariant analyses were performed. Therefore the importance of individual factors, beside stage, remains uncertain. Newer diagnostic methods, such as flow cytometry of DNA content, ploidy, and morphometry have been applied with, again, no clear conclusions [24, 42, 43].

In conclusion, SCSTs are relatively uncommon neoplasms that are characterized by their long natural history. The primary treatment is surgery in order to obtain an appropriate staging as well. Conservative procedures seem to be indicated in patients with disease localized to one ovary and those wishing to preserve fertility. Unfortunately, other than clinical stage, prognostically significant variables predictive of recurrence are still uncertain. The role of adjuvant chemo- or radiotherapy in Stage I-II or completely debulked Stage III disease has not yet been defined. Chemotherapy should be considered in those patients with advanced or metastatic disease, but more clinical trials are needed to identify a standard of treatment for these settings, and to quantify the real impact on both disease-free and overall survival, given the significant toxicity of the presently employed regimens. Thus, awaiting more conclusive data, treatment of patients with either recurrent or metastatic disease should be individualized based on the size and location of the lesion, its resectability, and the patient's medical condition.

Given the low incidence of these tumors and their long natural history, classical randomized clinical studies to assess the impact of different prognostic factors on prognosis and to evaluate the relative benefits of different therapies have not been possible. Moreover it is unlikely that they will be realized as methods to define better modalities of treatment in the near future.

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