Malignant germ cell tumors of the ovary: a review of 41 cases and risk factors for recurrence

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Summary

Objective: To review the outcome of treatment in patients with malignant ovarian germ cell tumors and to define the risk factors for recurrence. *Material and Methods:* Forty-one patients with malignant ovarian germ cell tumors were reviewed retrospectively. Survival time and survival rate were obtained. Risk factors such as stage, histological type, and type of operation were evaluated for reccurrence. *Results:* Twenty-three (56%) had dysgerminomas, eight (19.5%) had mixed germ cell tumors, three (7.3%) had yolk sac tumors, three (7.3%) had immature teratomas, two (4.8%) had squamous cell carcinoma arising from a mature teratoma, one (2.4%) had embryonal carcinoma and one choriocarcinoma. Most of the cases (73%) were in Stage I. Twenty-nine patients (70.7%) underwent conservative surgery and 12 patients (29.3%) had at least bilateral salpingo-oophorectomy. Thirty patients were operated on optimally with surgical staging and 11 suboptimally. Seven patients (17%) had recurrence after remission. The overall survival time was 187 ± 8.43 months for all cases, 195 ± 8.49 for dysgerminoma and 161 ± 10.96 for non-dysgerminoma cases with a median follow-up time of 98.52 (8-204) months. Non-dysgerminoma histologic type, being operated on suboptimally and radically, and advanced tumor stage have been found to be risk factors for recurrence. *Conclusion:* Regardless of histologic types and stages the prognosis of germ cell tumors are satisfactory with current therapeutic strategies.

Key words: Malignant germ cell; Recurrence; Ovary; Risk factors.

Introduction

Malignant ovarian germ cell tumors (MOGCT) are rare tumors of the ovary (2-5%) [1]. Unlike their epithelial counterparts they are usually seen in childbearing age and at an earlier stage. Therefore it is essential to maintain fertility in selected patients [2, 3]. MOGCT are much more curable than epithelial ovarian tumors. The prognosis of these tumors has improved over the past years due to introduction of cisplatin, and the survival rates in patients treated with platinum-containing regimens have been reported to be more than 70% [4-6]. Although not often, recurrences can be seen in MOGCT [2, 7-9] but risk factors for recurrence have not been clearly outlined. In this retrospective study, we review the outcome of treatment in patients with MOGCT and define the risk factors for recurrence.

Material and Methods

Forty-one patients with MOGCT who were operated on in Istanbul University, Istanbul Medical Faculty Department of Obstetrics and Gynecology between 1988 and 2006 were reviewed retrospectively. Clinical, pathological, surgical and postoperative treatment data were collected. Follow-up data were obtained either from patient files or by telephone interviews with the patients or relatives.

Patients were grouped as dysgerminoma and nondysgerminoma cases. Survival time and survival rates were obtained according to this classification. The median follow-up time was 98.52 (8-204) months.

In patients who desired children fertility sparing surgery was performed and radical operations were performed on other patients. Surgical staging was performed according to the guidelines of the International Federation of Gynecology and Obstetrics [10]. Histopathological diagnosis was performed according to the World Health Organization recommendations [11]. Postoperative multiple-agent chemotherapy was given in our medical oncology department. Risk factors such as stage, histology, and type of operation were evaluated for reccurrence.

Kaplan Meier and Cox proportional hazard analysis were used for survival time and survival rate comparision and Fisher's exact test was used for comparision of risk factors in statistical analysis.

Results

Forty-one patients were evaluated. The median age was 25.048 ± 8.4 (11-68). Twenty-three (56%) had dysgerminomas, eight (19.5%) had mixed germ cell tumors, three (7.3%) had yolk sac tumors, three (7.3%) had immature teratomas, two (4.8%) had squamous cell carcinomas arising from mature teratoma, one (2.4%) had embryonal carcinoma and one choriocarcinoma (Table 1). Sixteen women presented with Stage I A, two with Stage IB, 12 with Stage IC, one with Stage IIA, two with Stage IIC, four with Stage IIIB, and four with Stage IIIC disease (Table 2).

Twenty-nine patients (70.7%) underwent conservative surgery and 12 patients (29.3%) had at least bilateral salpingo-oophorectomy. Thirty patients had been operated on optimally with surgical staging, 11 had been operated suboptimally. Seven patients had recurrence after remission (Table 3). Nondysgerminoma histologic

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Table 1. — *Distribution of tumors according to histological types.*

Histology	Number	%
Dysgerminoma	23	56%
Mixed germ cell tumor	8	19.5%
Endodermal sinus tumor	3	7.3%
Immature teratoma	3	7.3%
Choriocarcinoma	1	2.4%
Embryonal carcinoma	1	2.4%
Squamous cell carcinoma derived from mature cystic teratoma	2	4.8%
Total	41	100%

Table 2. — *Stage distribution of the tumors.*

Stage	Number
IA	16
IB	2
IC	12
IIA	1
IIC	2
IIIB	4
IIIC	4

Table 3. — *Risk factors for tumor recurrence.*

		n	%	p
Histology	Nondysgerminoma	6/18	33	$p < 0.05$
	Dysgerminoma	1/23	4	
Operation	Suboptimal	5/11	45	$p < 0.05$
	Optimal	2/30	6	
Operation	Conservative	3/29	13.7	
	Radical	3/12	25	$p < 0.05$
Stage	Stage I	2/30	6.6	$p < 0.05$
	Stage II	5/8	62	

Table 4. — *Survival time in dysgerminoma and non-dysgerminoma cases.*

	n	Survival time (months)
Total	41	187 ± 8.43
Dysgerminoma	23	195 ± 8.49
Non-dysgerminoma	18	161 ± 10.96
		$p < 0.05$

type, suboptimal and radical surgery, and advanced tumor stage were found to be risk factors for recurrence. They have been found to be statistically significant to the parameters of dysgerminoma type, optimal and conservative surgery, and early-stage tumors.

Postoperative multiple-agent chemotherapy was given to 28 patients. Three (7.3%) patients died of malignancy, one with Stage 3B dysgerminoma one with Stage IIIB squamous cell carcinoma arising from a mature teratoma, and one with Stage IB mixed germ cell tumor. The overall survival time was 187 ± 8.43 months for all cases, 195 ± 8.49 for dysgerminoma and 161 ± 10.96 for nondysgerminoma cases with a median follow-up time of 98.52 (8-204) months. The difference in survival time was statistically significant ($p < 0.05$) (Table 4). The survival rate was 88% for dysgerminoma and 68% for nondysgerminoma in the 132nd month ($p < 0.05$).

Discussion

Ovarian germ cell tumors account for 20-25% of all ovarian neoplasms and only about 3% of these are malignant [1]. Unlike their epithelial counterpart, 75% of MOGCT are diagnosed in Stage I. Dysgerminomas are the most common, comprising up to 50% of MOGCT. Mixed component germ cell tumors account for approximately 10% of all germ cell tumors, with dysgerminoma being the most commonly occurring element [7, 12]. In accordance with the literature most of our cases consisted of dysgerminomas (56%); mixed germ cell tumors accounted for 19.5% (Table 1). Regarding stage, 30 of 41 (73%) cases were in Stage I, three of 41 (7.5%) were in Stage II and eight of 41 (19.5%) were in Stage III (Table 2).

Germ cell tumors are broadly classified as dysgerminomas and non-dysgerminomas. This is important because their natural history and response to treatment, prognosis and survival times are very different [13, 14]. The largest series in literature about MOGCT belong to Zhang *et al.* [9] with 233 cases. They reported that 5-year survival rate differed between dysgerminoma and non-dysgerminomatous tumors being 84.2% for the former and 44.6% for the latter. In patients with non-dysgerminomatous tumors, chemotherapy with PVB and BEP regimens gave a 5-year survival rate of 66.0% and 73.3%, respectively. We found similar results with the findings of Zhang *et al.* [9]. In our series, we also classified the patients as dysgerminomas and non-dysgerminomas and compared their survival time and survival rate. The survival time was 195 ± 8.49 months for dysgerminoma and 161 ± 10.96 for nondysgerminoma cases with a median follow-up time 98.52 (8-204) months. The difference in survival time was statistically significant ($p < 0.05$) (Table 4). The survival rate was 88% for dysgerminoma and 68% for nondysgerminoma in the 132nd month ($p < 0.05$). In our series dysgerminomas were diagnosed at earlier stages, had low recurrence rates, and better survival time and rates. The survival rate of girls with malignant germ cell tumors of the ovary was excellent in Billmire *et al's* study with an incidence of only 3% (4 of 131) of primary tumor-related mortality [6].

MOGCT affect women of childbearing age and are much more curable than their epithelial counterparts [15]. Fertility-preserving surgery followed by combination chemotherapy is equally effective in terms of survival when compared with more radical surgery [16-19].

We performed fertility-preserving surgery in 29 patients. Eighteen have attempted conception and 12 (8 in natural cycles, 4 with assisted reproductive techniques) have achieved pregnancy (66.6%). In Tangir *et al's* series [20] out of 116 patients fertility-preserving surgery was performed in 64 patients. Thirty-eight have attempted conception and 29 have achieved at least one pregnancy (76%). Low *et al.* [2] reported 14 healthy live births in 74 patients treated for malignant germ cell tumors of the ovary and the majority of these patients who received combination chemotherapy resumed normal ovarian function, and could expect a normal fertility rate and healthy offspring.

We concluded that for young women who wish to preserve childbearing capacity, regardless of the stage of the tumor, fertility-preserving surgery with complete surgical staging followed chemotherapy is an appropriate and definitive treatment. For patients in whom childbearing capacity is not an issue, surgery should include total abdominal hysterectomy and bilateral salpingo-oophorectomy with complete staging.

In the literature there has not been data about the risk factors for recurrence. Peccatori *et al.* [7] found recurrence in ten out of 129 patients (7.7%). Recurrence was observed in three out of 66 patients in De Backer *et al.'s* series [8], seven recurrences out of 74 patients (9.5%) in Low *et al.'s* series [9], and 43 out of 233 (18.4%) in Zhang *et al.'s* series [10]. However none of them discussed the risk factors. Our study mainly focused on the risk factors for tumor recurrence. We evaluated whether histologic type (dysgerminoma/non-dysgerminoma), stage of disease (early/late), and type of operation (optimal/subotimal, radical/conservative) have any effect on recurrence rate. Out of 41 patients, seven (17%) had recurrences. While only one patient (Stage IIIB) out of 23 dysgerminoma cases (4%) had recurrence, six patients out of 18 nondysgermima cases (33%) had recurrence ($p < 0.005$). Patients with dysgerminoma had lower recurrence rates as compared with nondysgerminoma types. In patients operated on optimally the recurrence rate was 6% (2 patients out of 30). In contrast, in 11 of the suboptimally operated patients five had recurrences (45%) ($p < 0.005$). These findings support the fact that optimal staging surgery is essential in managing malignant germ cell tumors. As the relation between the stage of tumor and recurrence was compared, we found higher recurrence rates in advanced stage of tumors. In 30 patients with Stage I disease, only two patients (6.6%) had recurrence. On the contrary, in eight patients with higher than Stage I, five patients (62%) had recurrence. Higher recurrence rate in advanced stage is an expected finding. Interestingly, the patients operated on conservatively had lower recurrence rates as compared with those operated on radically (at least bilateral salpingo-oophorectomy) (3/29 13.7% vs 3/12 25%, respectively). However when keeping in mind that the patients operated on radically were in higher stages this finding seems reasonable.

In conclusion, we observed that histology of the tumor (being nondysgerminoma), advanced stage, suboptimal operations, radical operations (due to advanced stage) carried higher risk factors for recurrence in malignant germ cell tumors of the ovary. These patients should be followed with high attention. More studies with more cases are needed to define the risk factors for recurrence of MOGCT.

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