

# Malignant Ovarian Germ Cell Tumours: Experience in the National University Hospital of Singapore

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## Abstract

*Management of thirteen cases of malignant ovarian germ cell tumours was reported. Of these, 5 (38%) were immature teratoma, 3 (23%) were endodermal sinus tumour, 1 (8%) was dysgerminoma and 4 (31%) were mixed germ cell tumour. Eight (61%) had stage I, 1 (8%) had stage II and 4 (31%) had stage III diseases. Six had unilateral salpingo-oophorectomy, 6 had total abdominal hysterectomy and bilateral salpingo-oophorectomy and 1 had bilateral oophorectomy. Ten (77%) had adjuvant chemotherapy predominantly with bleomycin/etoposide/cisplatin combination. All patients with stage I and stage II tumours were alive with no evidence of disease at ½ year to 5 years followup. Of the 4 patients with stage III diseases, 2 with optimal debulking surgery were alive and disease free at 4 and 7 years after surgery. The other 2 patients with stage III diseases had multiple bulky residual tumours. One of them with a combination of endodermal sinus tumour and embryonal carcinoma died of progressive disease despite chemotherapy 6 months after surgery and the other with mixed endodermal sinus tumour and dysgerminoma was alive with disease at 6 months. Alpha-fetoprotein levels were raised in all 6 patients with endodermal sinus tumour, either pure or combined with other tumours. Regression of alpha-fetoprotein levels was of important prognostic significance in endodermal sinus tumour.*

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*Key words: Adjuvant chemotherapy, Dysgerminoma, Endodermal sinus tumour, Immature teratoma, Tumour markers*

## Introduction

One of the most remarkable advances in the management of gynaecological cancers is in malignant ovarian germ cell tumours. Before the early 70s, some of the malignant ovarian germ cell tumours had a notoriously bad reputation in terms of aggressiveness and poor prognosis. Only about 10% of patients with endodermal sinus tumour survived.<sup>1</sup> Prognosis was extremely poor even in early stage disease.

In the late 70s and early 80s, a potential cure was reported with the use of adjuvant chemotherapy even in metastatic diseases.<sup>2,3</sup> From the mid 80s, combinations containing cisplatin was introduced in the treatment of malignant ovarian germ cell tumours.<sup>4,5</sup>

Malignant ovarian germ cell tumours affect mainly young girls and women. The excellent chemosensitivity of these tumours<sup>6</sup> and the fact that most of these tumours tend to be unilateral makes treatment with conservation of reproductive function possible.<sup>6-9</sup>

As malignant germ cell tumours are relatively rare, accounting for only less than 5% of all ovarian cancers,<sup>8</sup> it is difficult for single institutions to accumulate extensive experience in dealing with such cancers. Continuing experiences reported from various different institutions contribute to the optimal management of this group of rare tumours.

In the Department of Obstetrics and Gynaecology, National University Hospital, Singapore, we have been managing malignant ovarian germ cell tumours in line with the developments that have occurred in the past decade. We therefore aim to report our experience in the management of this group of rare ovarian tumours.

## Materials and Methods

The list of all ovarian malignant germ cell tumours managed between January 1986 and December 1996 in the Department of Obstetrics and Gynaecology, National University Hospital, Singapore was retrieved from

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the computerized data bank of the Department of Pathology, National University Hospital, Singapore. All the patients were managed by or in conjunction with gynaecological oncologists. The age, parity, presenting symptoms, duration of symptoms, associated symptoms, findings on physical examination, ultrasound scan findings, preoperative tumour marker levels (including CA 125, alpha fetoprotein, lactate dehydrogenase and beta human chorionic gonadotrophin), laparotomy and surgical staging findings, types of surgical procedure, size and site of residual diseases, intra and postoperative complications and the histological types including grade in immature teratoma were recorded. When adjuvant chemotherapy was used, the regimes used and complications were also recorded. The clinical, radiological and tumour marker monitoring of the response to treatment were also assessed. All the histological slides were reviewed by one of the authors.

The department has a standardized protocol for treating malignant ovarian germ cell tumours. When patients have completed their family, the procedure of choice was a full surgical staging laparotomy with total abdominal hysterectomy and bilateral salpingo-oophorectomy. Optimal cytoreductive surgery was the aim in advanced diseases. In young women where conservation of reproductive potential was a consideration, a full surgical staging procedure and unilateral salpingo-oophorectomy was the treatment of choice in stage 1 disease. In cases where the tumour had spread beyond the involved ovary but the contralateral ovary and uterus were not involved by the tumour, unilateral salpingo-oophorectomy with conservation of the uninvolved ovary and uterus and optimal debulking surgery was the

surgical goal.

Postoperative chemotherapy was given to all patients except for stage 1 A grade 1 immature teratoma or stage 1 A pure dysgerminoma. Particularly in aggressive tumours like endodermal sinus tumour and embryonal carcinoma, chemotherapy was started as soon as the skin sutures were removed. The chemotherapy regime used were cisplatin/vincristine/bleomycin (PVB) combination in the early part of the series and cisplatin/etoposide/bleomycin (BEP) combination in the later part of the series. A total of 6 courses were planned if well tolerated. The chemotherapy regimes used in the department are shown in Table I.

## Results

Table II shows the histological cell type, age, parity, stage, type of surgery, chemotherapy and the current status of the patients. There were 13 cases of malignant

TABLE I: CHEMOTHERAPY REGIMES FOR OVARIAN GERM CELL TUMOURS

Regimen	Drugs	Dose	Schedule
BEP	Bleomycin	10 mg	IV on D 2,9,16 every 3 weeks
	Etoposide	100 mg/m <sup>2</sup>	IV on D 1-3 every 3 weeks
	Cisplatin	100 mg/m <sup>2</sup>	IV on D 1 every 3 weeks
PVB	Cisplatin	100 mg/m <sup>2</sup>	IV D 1 every 3 weeks
	Vinblastine	6 mg/m <sup>2</sup>	IV on D 1 every 3 weeks
	Bleomycin	30 mg	IV on D 1,8,15 every 3 weeks
EP	Etoposide	100 mg/m <sup>2</sup>	IV on D 1-3 every 3 weeks
	Cisplatin	100 mg/m <sup>2</sup>	IV on D 1 every 3 weeks

IV: intravenous; D: day

TABLE II: SUMMARY OF PATIENTS WITH MALIGNANT OVARIAN GERM CELL TUMOURS

No.	Histology	Age	Parity	Stage	Surgery	Chemotherapy	Current status (years)
Immature teratoma							
1	Grade 1	27	0	IC	USO	Nil	Loss F/U
2	Grade 2	36	2	IC	TAHBSO	EP	NED 5
3	Grade 2	22	0	IA	USO	BEP	NED 2
4	Grade 3	34	0	3C	TAHBSO,De	PVB	NED 7
5	Grade 1	13	0	1A	USO	Nil	NED 4
6	EST	45	2	1C	TAHRSO	BEP	NED 3
7	EST	11	0	1C	USO	BEP	NED ½
8	EST	41	2	3C	TAHBSO,De	BEP	NED 4
9	Dysg	33	0	1C	USO	BEP	NED 2
Mixed germ cell tumour							
10	EST + Dysg	37	0	2B	TAHBSO	BEP	NED 2
11	EST+Dysg	45	4	3C	TAHBSO,De	BEP	AWD ½
12	EST +Embryo	24	0	3C	USO,De	BEP	DOD ½
13	Dysg + Gonad	18	0	1B	BSO	Refused	NED ½

EST: endodermal sinus tumour; Dysg: dysgerminoma; Embryo: embryonal carcinoma; Gonad: gonadoblastoma; USO: unilateral salpingo-oophorectomy; BSO: bilateral salpingo-oophorectomy; RSO: right salpingo-oophorectomy; TAH: total abdominal hysterectomy; De: debulking surgery; EP: etoposide/cisplatin; CT: chlorambucil/tamoxifen; BEP: bleomycin/etoposide/cisplatin; NED: no evidence of disease; AWD: alive with disease; DOD: died of disease; F/U: follow up

ovarian germ cell tumours in this report (Table II). Almost 40% (5 out of 13) of the patients had immature teratoma, 23% (3 out of 13) had pure endodermal sinus tumour and only 1 (8%) had pure dysgerminoma. Four (31%) had mixed germ cell tumours with endodermal sinus tumour and dysgerminoma accounting for half of the combinations. The median age at presentation was 34 years (range 11 to 45 years). Nine out of 13 patients were nulliparous. The main presenting symptoms are shown in Table III. Abdominal pain and distension were the commonest presenting symptoms. The vast majority (75%) presented within 2 weeks of having symptoms. About half of these patients had no palpable mass on initial examination and one third presented with large pelvi-abdominal mass of more than 16 weeks size.

TABLE III: SYMPTOMS, SIGNS AND ULTRASOUND FEATURES

Symptoms and signs	Cases (%)
Presenting symptoms	
Abdominal pain	4 (31)
Abdominal distension	4 (31)
Fever	2 (15)
Palpable mass	1 (8)
Ambiguous genitalia	1 (8)
Asymptomatic	1 (8)
Duration	
<2 weeks	9 (75)
2 to 4 weeks	1 (8)
>1 month	2 (17)
Pelvi-abdominal mass	
No mass	6 (46)
<16 weeks	2 (15)
>16 weeks	5 (39)
Ascites	
No	10 (77)
Mild	1 (8)
Severe	2 (15)
Ultrasound features (11 cases)	
Normal	1 (9)
Cystic/solid	7 (64)
Solid	3 (27)

Ultrasound scans were done in 11 patients and 7 (64%) of them had solid/cystic features and 3 (27%) had purely solid features. One had normal "ovaries" on ultrasound scan and this occurred in a patient presenting with ambiguous genitalia who had 46 XY chromosomes. The mean resistance index on doppler study was  $0.42 \pm 0.06$  (0.35 to 0.50). Tumour markers were measured in 11 patients. Three of the 4 patients with immature teratoma had negative tumour markers. One patient with grade 3 immature teratoma had raised serum alpha-fetoprotein (8590 ng/ml) and CA125 (151 U/ml) which became negative after treatment. Both cases with mixed germ

cell tumours comprising endodermal sinus tumour and dysgerminoma had markedly raised serum alpha-fetoprotein (19 103 ng/ml and 799 ng/ml) and one of them also had raised CA125 (757 U/ml). The patient in whom the tumour markers became negative after treatment had complete remission. The other had persistently raised alpha-fetoprotein and this patient had persistent tumour despite chemotherapy. The patient with combined endodermal sinus tumour and embryonal carcinoma had very high levels of preoperative alpha-fetoprotein (>35 000 ng/ml), Beta hCG (5760 IU/L) and CA125 (360 U/ml). After surgery, she had multiple bulky residual tumours greater than 2 cm in diameter. The tumour markers did not decrease despite chemotherapy with the BEP regime and she died of progressive disease 6 months after surgery. The patient with combined gonadoblastoma and dysgerminoma had raised serum LDH of 1024 U/L which became negative after surgery. All 3 patients with endodermal sinus tumours had raised preoperative serum alpha-fetoprotein ranging from 1461 ng/ml to 66 600 ng/ml and all became negative after surgery and chemotherapy with no evidence of disease at follow-up.

The tumours were unilateral in 10 cases (76.9%) and the mean tumour size was  $15.69 \pm 10.51$  cm (range 2 to 40 cm). Six of the 9 nulliparous women had conservative unilateral salpingo-oophorectomy, one patient had bilateral oophorectomy and 6 patients had total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAHBSO) (Table II). In 4 of these cases, debulking surgery was necessary. The patient who had bilateral oophorectomy had ambiguous genitalia, absent uterus with 46 XY chromosome. Surgery to prophylactically remove the gonads in view of the 46 XY chromosome incidentally revealed gonadoblastoma and dysgerminoma. Two of the patients presented with acute abdomen due to tumour rupture and haemorrhage and were operated on as emergency cases. The rest had elective surgery. Of the 4 patients who had debulking surgery, 2 had residual tumours of <2 cm in diameter with the remaining 2 having bulky residual tumours. Three of the patients with residual tumours had tumours in the pelvis as well as in the upper abdomen. The other had residual tumour only in the pelvic region. There were no significant intraoperative complications and 1 patient had postoperative wound sepsis. Ten patients had adjuvant chemotherapy and the patient with bilateral gonadoblastoma and dysgerminoma refused chemotherapy. One patient with grade 1 immature teratoma refused to return for follow-up after surgery. Among those who had chemotherapy, the BEP regime was used in 80% of the patients, 1 had PVB combination and 1 patient with grade 2 immature teratoma had the cisplatin/etoposide (PE) regime. The commonest side effect of chemotherapy was grade 4 neutropaenia by

WHO criteria in 4 out of 10 patients who had cisplatin combinations. No serious renal or pulmonary toxicity was encountered in patients who had the BEP or PVB regimes. Two of the patients had peripheral neuropathy and one had persistent tinnitus.

All 9 patients who had stage I and II tumours including the 4 cases who had conservative surgery were alive with no clinical, biochemical and radiological evidence of recurrence. The period of follow-up ranged from ½ year to 7 years with a median of 2 years. Both stage IIIC patients who had optimal debulking surgery were free of tumour at 4 and 7 years of follow-up. Of the 2 patients with suboptimally debulked stage IIIC disease, 1 with combined endodermal sinus tumour and embryonal carcinoma died of progressive disease within 6 months of surgery and the other who had combined endodermal sinus tumour and dysgerminoma was alive at 6 months but with disease despite chemotherapy.

Two of the patients who had unilateral oophorectomy followed by chemotherapy became pregnant followed by full term delivery of a normal baby each.

## Discussion

The incidence of malignant ovarian germ cell tumours ranges from 1% to 6% as reported in the West<sup>10</sup> and from 8% to 19% as reported in Asia.<sup>11,12</sup> Fifty-four per cent of our patients were in their 30s and 40s with 38% being below the age of 24 years.<sup>9</sup>

In most Western reports, pure dysgerminoma is the most common malignant ovarian germ cell tumour type, accounting for 35% to 54% of the cases.<sup>6,9</sup> However, there was only one case (8%) of pure dysgerminoma in our study. On the other hand, immature teratoma accounted for 38% of our cases and endodermal sinus tumour accounted for 23%, compared to incidences of only 15% and 10% of these lesions respectively reported by Piura et al.<sup>9</sup> Our findings were more consistent with those reported from China with 7% dysgerminoma,<sup>7</sup> 57% immature teratoma and 25% endodermal sinus tumour;<sup>12</sup> but bias from the small sample size of our series could not be excluded.

Although abdominal pain was the commonest presenting symptom (31%) in our patients, it is not as high as the figure (87%) reported by Gershenson and Wharton.<sup>13</sup> Only 1 (8%) patient presented because of palpable mass in contrast to 85% in another study.<sup>13</sup> Most of our patients (61%) presented with stage I cancer. Other authors similarly reported a high proportion of patients, 57% to 85%, presenting as stage I tumours.<sup>7,9</sup>

We found that tumour markers were useful in the management of ovarian germ cell tumours. All 6 of our patients (100%) with endodermal sinus tumour component, either pure or mixed with other histological types, had raised alpha-fetoprotein levels. All those with sub-

sequent clinical and radiological complete remission had negative alpha-fetoprotein levels. This finding is supported by another study where there was 100% positive rate for alpha-fetoprotein in endodermal sinus tumour.<sup>14</sup> The patients with residual tumours had lower levels of serum tumour markers on follow up and those which became negative had no evidence of recurrence or persistent tumour. Of the 2 cases with persistently raised alpha-fetoprotein, one died 6 months after treatment and the other was alive with disease. Regression of alpha-fetoprotein is therefore a good predictor of prognosis. In immature teratoma however, tumour markers were not as useful as only 1 of the 4 (25%) had raised tumour markers. Kawai et al<sup>14</sup> reported 62% positive rate for alpha-fetoprotein in immature teratoma.

As malignant germ cell tumours tend to affect younger women, conservation of reproductive potential is of great concern. Various reports have demonstrated the safety of unilateral oophorectomy in the treatment of early germ cell tumours achieving cure rates of well over 90%.<sup>7,8</sup> In our series, there were 9 nulliparous women; 6 of whom underwent fertility-conserving unilateral salpingo-oophorectomy. Of the other 3, 1 had bilateral oophorectomy because of 46 XY chromosome while the remaining 2 had TAHBSO because of gross involvement of both ovaries and uterus. Almost all our patients had postoperative adjuvant chemotherapy mainly using the BEP regime. All patients with stage 1 disease had disease free survival ranging from ½ year to 5 years. Optimal debulking was an important prognostic factor among the 5 cases with stage IIB and IIIC tumours. All 3 cases with optimal debulking were alive with no disease. Of the 2 cases with bulky residual tumours, one died of disease and the other was alive with progressive disease. Although the role of debulking surgery in malignant ovarian germ cell tumour is debatable with some advocating chemotherapy alone as the primary treatment of choice in view of the high chemosensitivity of the tumours, others would advocate optimal debulking within limits of safety followed by chemotherapy in the majority of cases.<sup>8</sup> Several studies have shown that patients with completely resected disease and those with minimal residual disease did much better than those with bulky residual disease at primary surgery.<sup>4,15</sup> This is certainly our experience.

In conclusion, our findings, together with reports from China, suggest that Orientals may have a higher proportion of non-dysgerminomatous malignant ovarian germ cell tumours when compared to reports in the Western literature. Fertility conserving surgery is found to be safe for malignant ovarian germ cell tumours in young patients with early as well as advanced tumours. In advanced diseases, adequate cytoreduction seems to be an important prognostic factor in the successful treatment of this group of tumours. Alpha-fetoprotein is a useful

tumour marker for endodermal sinus tumour and its regression has prognostic significance. However, the role of tumour markers in immature teratoma is more limited.

## REFERENCES

1. Kurman R J, Norris H J. Endodermal sinus tumor of the ovary: a clinical and pathological analysis of 71 cases. *Cancer* 1976; 38:2404-19.
2. Smith J P, Rutledge F N. Advance in chemotherapy for gynecologic cancer. *Cancer* 1975; 36:669-74.
3. Newlands E S, Begent R H, Rustin G J, Bagshawe K D. Potential for cure in metastatic ovarian teratomas and dysgerminomas. *Br J Obstet Gynaecol* 1982; 89:555-60.
4. Slayton R E, Park R C, Silverberg S G, Shingleton H, Creasman W T, Blessing J A. Vincristine, dactinomycin, and cyclophosphamide in the treatment of malignant germ cell tumors of the ovary. A Gynecologic Oncology Group Study (a final report). *Cancer* 1985; 56:243-8.
5. Gershenson D M, Kavanagh J J, Copelend L J, Junco G D, Cangir A, Saul P B, et al. Treatment of malignant non-dysgerminomatous germ cell tumors of the ovary with vinblastine, bleomycin and cisplatin. *Cancer* 1986; 57:1731-7.
6. Gershenson S D, Morris M, Cangir A, Kavanagh J J, Stringer C A, Edwards C L, et al. Treatment of malignant germ cell tumors of the ovary with bleomycin, etoposide and cisplatin (BEP). *J Clin Oncol* 1990; 8:715-20.
7. Wu P C, Huang R L, Lang J H, Huang H F, Lian L J, Tang M Y. Treatment of malignant ovarian germ cell tumors with preservation of fertility: a report of 28 cases. *Gynecol Oncol* 1991; 40:2-6.
8. Gershenson D M. Management of early ovarian cancer: germ cell and sex cord-stromal tumors. *Gynecol Oncol* 1994; 55:S62-S72.
9. Piura B, Dgani R, Zalel Y, Nemet D, Yanai-Inbar I, Cohen Y, et al. Malignant germ cell tumors of the ovary: a study of 20 cases. *J Surg Oncol* 1995; 59:155-61.
10. Weiss N S, Homonchuk T, Young J L. Incidence of the histologic type of ovarian cancer. *Gynecol Oncol* 1977; 5:161-7.
11. Nakashima N, Nagasaka T, Fukata S. Study of ovarian tumor treated at Nagoya University Hospital 1965-1988. *Gynecol Oncol* 1990; 37:103-7.
12. Singh P, Ilancheran A, Singh P, Tan B Y, Tock P C, Ratnam S S. Ovarian cancer in Oriental women from Singapore. *Int Surg* 1990; 75:115-22.
13. Gershenson D M, Wharton J T. Malignant germ cell tumor of the ovaries. In: Alberts D S, Surwit E A, editors. *Ovarian Cancer*. Boston: Martinus Nijhoff, 1985:227-69.
14. Kawai M, Kano T, Kikkawa F, Morikawa Y, Oguchi H, Nakashima N, et al. Seven tumour markers in benign and malignant germ cell tumors of the ovary. *Gynecol Oncol* 1992; 45:248-53.
15. Kawai M, Kano T, Furuhashi Y, Mizuno K, Nakashima N, Hattori S E, et al. Prognostic factors in yolk sac tumors of the ovary. A clinicopathologic analysis of 29 cases. *Cancer* 1991; 67:184-92.