Survival of borderline tumors of the ovary and its prognostic factors at Dr. Cipto Mangunkusumo hospital from 1990 to 1999

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Abstrak

Penelitian survival secara historical cohort pada enam puluh dua penderita tumor ovarium borderline. Terdapat 9 penderita stadium FIGO IA, 9 stadium IC, 3 stadium IIIA, 2 stadium IIIB, 4 stadium IIIC, 1 stadium IV dan 34 stadium inadekuat. Dua puluh satu penderita dilakukan pembedahan radikal, 10 penderita hanya dilakukan histerektomi total dan salfingo-ooforektomi bilateral, 6 penderita dilakukan pembedahan konservatif, 24 penderita hanya dilakukan unilateral salfingo-ooforektomi atau kistektomi dan 1 penderita hanya biopsi saja. Enam belas penderita mendapat kemoterapi adjuvan kombinasi dengan platinum base, yaitu 8 penderita stadium inadekuat, 7 stadium III dan 1 stadium IV. Lama pengamatan lanjut antara 0,002 sampai 10,48 tahun dengan median 3,5 tahun. Lima puluh sembilan penderita tetap hidup. Tiga penderita meninggal karena penyakitnya. Residif terjadi pada 4 penderita. Ketahanan hidup penderita 2 tahun 96% dan 10 tahun 94%. Pada test "log rank" didapatkan residu dan tipe histologi merupakan faktor prognostik yang bermakna mempengaruhi survival. ***(Med J Indones 2002; 11: 222-9)***

Abstract

Sixty-two patients with borderline tumors of ovary were historical cohort analyzed for survival characteristics. There were 9 patients with FIGO stage IA, 9 with stage IC, 3 with stage IIIA, 2 with stage IIIB, 4 with stage IIIC, 1 with stage IV and 34 with inadequate stage tumors. Twenty one patients had surgical staging with radical surgery, 10 patient had at least a total abdominal hysterectomy and bilateral salpingo-oophorectomy, 6 patient had surgical staging with conservative surgery, 24 patient had at least a unilateral salphingo-oophorectomy or ovarian cystectomy and 1 patient had biopsy. Sixteen patients received cisplatin-based combination chemotherapy, that were 8 with inadequate stage tumors, 7 with stage III tumors and 1 with stage IV tumor. Follow-up range from 0.02 to 10.48 years, with a median of 3.5 years. Fifty nine patient were alive. Three patients died, all of disease. Recurrence were found in 4 patients. The overall 2-years survival rate was 96% and 10-years survival rate was 94%. In log rank test, residual disease and histology type were significant predictor of survival. ***(Med J Indones 2002; 11:222-9)***

Keywords*: borderline tumors of ovary, survival*

In 1929, Taylor reported a series of patients with ovarian epithelial tumors that appeared malignant but behave in a relatively benign manner. His concept was not immediately accepted. In 1961, the International Federation of Gynecology and Obstetrics (FIGO) suggested a histologic classification dividing epithelia ovarian tumors into benign neoplasms, carcinomas of low malignant potential, and tumors with distinctly malignant characteristic.

This classification system became effective in 1971. In 1973, the World Health Organization internationally accepted classification of ovarian neoplasms.[1,2,3] According to these criteria, tumors with epithelial proliferation, nuclear abnormalites and mitotic activity of intermediate degree,[1,4] and no obvious invasion of the stroma are placed in a group between clearly benign neoplasms and malignant tumors and are designated tumors of low malignant potential. These tumors, also known as borderline tumor of the ovary (BTO).

BTO accounts for 9.2-16.3% of all non-benign epithelial ovarian tumor, resulting in an overall annual incidence rate of 24.7 per million female in the USA.[2] BTO are primarily diagnosed in young females and a higher percentage are discovered as stage I disease. BTO generally have an excellent prognosis.[3,4]

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Treatment modalities for these tumors have paralleled those for invasive carcinoma. This includes surgery with adjuvant radiation therapy and/or cytotoxic chemotherapy. In young patients, preservation of the reproductive potential might be important. Recently, some reports recommended a more conservative approach, "ovarian-saving surgery," for patients with early-stage disease.[1,5-8]

The purpose of this study was to determine survival rate and prognostic factors that influence of survival with borderline tumors of the ovary.

MATERIALS AND METHODS

From January 1990 through December 1999, 62 patient with borderline tumor of the ovary were diagnosed and treated at Dr. Cipto Mangunkusumo Hospital University of Indonesia, Jakarta and represented 2.5% of all cases of ovarian tumors (2534 cases).

Twenty-eight were treated in conformity with the protocols for invasive carcinoma during the study period. The standard radical surgical staging procedure was total abdominal hysterectomy, bilateral salpingo-oophorectomy and infracolic omentectomy and was performed in 21 patients. Six patients were treated by conservative surgical staging. Ten patients were treated by total abdominal hysterectomy plus bilateral salphingo-oophorectomy alone. Seven patients were treated by cystectomy and seventeen were treated by unilateral adnexectomy.

One patient was performed biopsy. Only six patients had residual tumor after primary surgery. Postoperative treatment consisted of chemotherapy. Forty-six patients received no postoperative treatment and sixteen patients received adjuvant chemotherapy. Chemotherapy was administered cyclophosphamide, cisplatinum and/or without adriamycin.

The cases were staged at laparotomy retrospectively by review of the medical records, in accordance with the recommendation of the FIGO. The following clinical and histopathologic parameters were analyzed in relation to survival: age, parity, stage, postoperative residual tumor, histology type, adjuvant chemotherapy and surgical type. The follow-up information was collected from medical record and the cancer registry of oncologic gynecology. The follow-up was complete, and may 2001 was entered as the end point of the study.

Statistical methods

Disease-free survival and corrected survival were defined as the time form treatment in our institution to relapse and death of disease, respectively. The Kaplan-Meier method and the log-rank test were used to estimate and compare survival curves. Corrected (cancer-related) survival rates were based on death resulting from borderline malignancy only. The Cox proportional hazards regression model was used to identify the independent prognostic factors.

RESULTS

The follow-up varied from 0.02 to 10.48 years, with a median of 3.5 years. The corrected five-and ten years survival rates for all patients in this study group are 94%. (Figure 1).

The median patient age was 35.5 years (range, 13-70 years). The age of patients were divided into two groups; younger than or equal 40 (64.52%) and older than 40 years old (35,48%). A statistically significant difference was not found between two groups (p=0,16) regarding death of disease. After 1.7 years of follow up, differences in survival were found (X^2 = 1,98) (Figure 2). Detailed characteristic of independent variable are shown in Table 1.

Table 1. Independent variable characteristics of patients

	Total	Percent	Died of disease	Percent
Age (year)				
≤ 40	40	64.52	1	1.6
> 40	22	35.48	2	3.2
Parity				
0	22	35.48	1	1,6
1	8	12.90	0	
2	10	16.13	0	
> 2	22	35.48	2	3.2
Surgical type				
Surgical staging	28	45.16	0	
No surgical type	34	54.84	3	4.8
Stage				
FIGO stage	28	45.16	0	
No stage	34	54.84	3	4.8
Adjuvant chemotherapy				
No	46	74.2	0	
Yes	16	25.8	3	4.8
Residual tumor				
No	56	90.3		
Yes	6	9.7	3	4.8
Histology type				
Mucinous	40	64.52	0	
Serous	16	25.81	1	1.6
Sero-mucinous	3	4.84	0	
Other	3	4.84	2	4.8

Figure 1. Survival of all patients with borderline tumor of the ovary

Log rank test : $X^2 = 1.98$; $p = 0.16$

Figure 2. Survival of patients with a borderline tumor of the ovary related to age

The median parity was 2 (range, 0 - 10); nulliparity and nulligravidity was found 35.48% and 12.9%. A statistically significant difference in survival was not found between four groups of patients (p = 0.58). (Figure 3).

The dominant histopathologic types were mucinous (40 cases; 64.52%) and serous (16 cases; 25.81%). Only 3 tumors (4.84%) were other types: 2 endometrioid and 1 clear cell. There was a significant difference in survival among patients with different histologic types (p=0.00) (Figure 4).

Log rank test; $X^2 = 1.9$; $p = 0.58$

Figure 3. Survival of patients with a borderline tumor of the ovary related to parity

Log rank test; $X^2 = 26.53$; $p = 0.00$

Figure 4. Survival of patients with a borderline tumor of the ovary related to histology type

Log rank test; $X^2 = 2.54$; $p = 0.47$

Figure 5. Survival of patients with a borderline tumor of the ovary related to primary surgical treatment

Log rank test; $X^2 = 2.42$; $p = 0.12$

Figure 6. Survival of patients with a borderline tumor of the ovary related to surgical/non surgical staging

Table 2. Stage in relation to adjuvant chemotherapy

Stage	No	Percent	Adjuvant chemotherapy	Percent
IA	9	14.52	0	
IB	0		0	
IC	9	14.52	0	
IIA,B,C	0		0	
IIIA	3	4.84	2	3.23
IIIB	2	3.23	1	1.66
IIIC	4	6.45	4	6.45
IV	1	1.66	1	1.66
Inadequate	34	54.84	8	12.90
	62	100	16	25.8

The FIGO staging in the 28 patients and inadequate staging in the 34 patients are listed in table 2. There was not a significant difference in survival among patients with these groups (X^2 = 2.63; p = 0.45) (Figure 7). However, the patients were divided into two groups : adequate and inadequate staging, statistically significant different in survival were not found too. But patients with inadequate staging had a tendency worse than adequate staging (X^2 = 2.63; p = 0.1) (Figure 8).

In this study, 4 patients had recurrent, detailed characteristic of recurrent are shown in Table 3.

Log rank test X^2 = 2.63; p = 0.45

Figure 7. Survival of patients with a borderline tumor of ovary related to stage

Log rank test X^2 = 2.63; p = 0.1

Figure 8. Survival of patients with a borderline tumor of ovary related to adequate or inadequate staging

Log rank test $X^2 = 33.08$; $p = 0.00$

Figure 9. Survival of patients with a borderline tumor of ovary related to residual tumor

Table 3. Recurrent disease

Stage	Histology	Primary therapy	Adjuvant	Residual	Disease-free(mo)	Site
IIIB	mucinous	radical	CAP	+	14	Pelvis
IIIC	Serous	radical	CAP	+	24	Pelvis
IIIB	Mucinous	radical	no	-	19	Pelvis
IV	Sero-muci	radical	CAP	+	23	Pelvis

Three patients died from their disease. All of patients had an inadequate staging. At the time of initial cytoreductive surgery were left with greater than 2 cm residual tumor. All of patients was treated with cyclophosphamide and cysplatin. One patient died 1 month after 3 courses therapy with partial response, one patients died 14 months after 4 courses therapy with no response and one patients died 12 month after 6 course therapy with no response.

In univariate analysis, presence of residual tumor and histology type were important variables affecting corrected survival, shown in Table 4.

After univariate analysis, the independent prognostic factor were not identified by Cox regression multivariate analysis and evaluated for corrected survival, because there had variable no filled.

Table 4. Univariate analysis

No	Independent variable	X^2	R
1	Residual tumor	33.08	0.00
2	Histology type	26.53	0.00
3	Stage adequate/inadequate	2.63	0.10
4	Surgical staging/non	2.42	0.12
5	Age	1.98	0.16
6	Parity	1.90	0.59

DISCUSSION

Burger et al retrospectively reviewed cases of BTO, five-year survival rate 92% and ten-year survival rate 82%.[5] Barnhill et al also noted that five-year survival rate 95% and ten-year survival rate 87%.[9] In that

study, the two-year survival rate 96% and five and ten year survival rate 94%.

Aure et al retrospective reviewed 161 cases of BTO. The mean age of the patient was 46 years, youngest patient was 7 years and oldest patient was 53 years. Klimam et al also had that the mean age of the patients was 47 years, youngest patient was 82 years.[10] In that study, the mean age of patients was 38 years, youngest patient was 13 years and oldest patient was 70 years.

Forty cases (64.5%) of the patients were younger than/equal 40 years. This means that preservation of reproductive potential is of interest to many patients with stage I and inadequate stage without residual tumor, of course, stresses the importance of conservative surgery that saves ovarian function.

Some studies reviewed 132 cases conservative surgery of BTO, 6 patients (4.5%) had relapses and 1 patient was died.[10] All of patients stage I with conservative surgery had 10 year survival rate 100% in this study.

The overall prognosis is excellent (4.84% of all patients died of disease with inadequate stage and residual tumor more than 2 cm). Of the four cases (6.45%) who had relapses, all of patients with stage III and IV with pelvic relapse were treated with radical surgery, received combination chemotherapy (cisplatin / cyclophosphamide / adriamycin) with good a response. Therefore, despite the debate about chemotherapy treatment in borderline tumor, our policy is to administer postoperative adjuvant cisplatin to patients with advanced stage.

Burger et al retrospective reviewed cases of BTO, the dominant histopathology type were mucinous (40%) and serous (55%), statistically significant difference in survival were not found between patient mucinous and serous. Ten years survival rate for mucinous and serous 90% and five years survival rate for others type of histology 70%.[5] In that study, the dominant histopathology type also were mucinous (64.5%) and serous (25.8%), there was a significant different in survival among mucinous, serous and others type. Ten years survival rate for mucinous 100% and serous 93% and others type 67%.[5]

In 56 patient without residual disease, the performance of less extensive surgical procedure did not affect the survival rate. The difference in survival between patient with residual and without residual was significant ($p = 0.00$).

By the log rank test, residual tumor, histopathology type, stage, surgical procedure and patients age, respectively, were independent prognostic parameters for survival in this study. Kaern J, et al, FIGO stage, histology type, and patient age were the variables of independent prognosic significance in regard to disease-free survival.[1]

CONCLUSION

Conservative therapy is indicated in patients with stage I disease who desire to remain fertile. Standard treatment should be primary total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, random peritoneal biopsies and a pelvic and para-aortic lymphadenectomy. Second surgical effort is not indicated for inadequate staging, if there is no evidence of residual tumor.

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