Clinical Characteristics and Survival in Non-EpithelialOvarian Cancer

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Abstract

Ovarian cancer is often asymptomatic, grows rapidly and most diagnosed at advanced stage. Till now there is no method for early detection. Its incidence and mortality rate are increasing. Actually, non-epithelial type of ovarian cancer most found in young women and has better prognosis with adequate therapy. The main therapy for non-epithelial ovarian cancer is surgery, both radical and conservative (fertility sparing). Postoperative chemotherapy depends on the type and stage, although platinum-based chemotherapy regimens are used in almost all cases because of their chemosensitivity. The first-line regimens used are bleomycin, etoposide and cisplatin. Some clinical characteristics could affect prognosis including recurrence and survival rate. They include patient's age, cancer stage, tumor size, tumor marker, post-operative tumor residue, histopathological type of cancer, and chemotherapy. Better knowledge of those prognostic factor will lead to better management of patients with non-epithelial ovarian cancer and increase survival rate.

Keywords: Non-epithelial ovarian carcinoma, survival, clinical characteristics

1. Introduction

Ovarian cancer has a lower prevalence than breast cancer and cervical cancer but it is three times more likely to be life-threatening (1). Ovarian cancer is called *the silent killer* because it is often asymptomatic, grows rapidly, and most diagnosed at advanced stage. There is no method for early detection of ovarian cancer. In 2020 there were 313,959 cases of ovarian cancer worldwide with a death rate of 207,252 cases (2). In Indonesia, ovarian cancer ranks third for cancer in women in 2020 with 14,896 new cases and 9,581 deaths (3).

Non-epithelial ovarian cancer accounts for 10% of all ovarian cancers (4). The most common type of histopathology is germ cell tumor with an incidence rate of four per million women each

year. It is more common in young women and has a better prognosis with cure rate of up to 100% at early stage (5). The main therapy for non-epithelial ovarian cancer is surgery, both radical and conservative (fertility sparing). Postoperative chemotherapy depends on the type and stage, although platinum-based chemotherapy regimens are used in almost all cases because of their chemosensitivity. The first-line regimens are bleomycin, etoposide and cisplatin (BEP) (6).

Survival rate of patients with non-epithelial ovarian cancer affected by some prognostic factors. They consist of clinical, pathology and biological factors. We don't have screening tools of ovarian cancer, but we can increase survival rate of the patients by modifying the prognostic factors. It is important to know the characteristics affecting the survival and prognosis. Some researches done can be references in managing patients with non-epithelial ovarian cancer.

2. Ovarian Cancer

Ovarian cancer is a gynecological malignancy in the ovaries of women. Most of these cancer patients come at an advanced stage, which causes these cancer patients to have limited choice of treatment and generally have a poor survival rate and prognosis (7). Ovarian cancer accounted for approximately 295,414 new cases and 184,799 deaths worldwide in 2018 (8). In 2020 there were 313,959 cases of ovarian cancer worldwide with a death rate of 207,252 cases (2). Clinical symptoms are not typical so that 70% of patients are diagnosed at an advanced stage. Perimenopausal age patients come with complaints of irregular menstruation, when the tumor mass has enlarged to press on the bladder or rectum, complaints of urinary frequency, dysuria or constipation will appear. Acute symptoms associated with torsion or adnexal rupture may develop (4).

Generally, there are some risk factors that may increase the probability of having ovarian cancer. When compared with black and Hispanic women, the risk of white race increases by 30% to 40% (7). Women with early menarche (age < 12 years) and late menopause (age > 50 years) have a higher risk of ovarian cancer due to the large number of ovulatory cycles (9). The risk of ovarian cancer decreases with increasing parity (10). Based on the analysis of the Nurses Health Study (NHS) data, it was found that the risk of ovarian cancer increased by about 2% each year with increasing age in women aged <50 years and 11% in women aged> 50 years. According to the American Cancer Society, about 10% of people with ovarian cancer have a family history of the disease. Genetic predisposition is found in 10-15% of ovarian cancer cases (11). Research conducted by the European Prospective Investigation into Cancer and Nutrition in 2006 stated that women with a BMI above 30 had a relative risk of developing ovarian cancer of 1.59 times compared to women with a normal BMI (12).

Table 1. Staging of ovarian cancer according FIGO 2014

FIGO	Description	TNM
I	Tumor confined to ovaries or fallopian tube(s)	T1
IA	Tumor limited to one ovary (capsule intact) or fallopian tube, no tumor on ovarian of fallopian tube surface. No malignant cells in the ascites or peritoneal washings.	T1a
IB	Tumor limited to both ovaries (capsule intact) or fallopian tubes. No tumor on ovarian or fallopian tube surface. No malignant cells in the ascites or peritoneal washings	T1b
IC	Tumor limited to one or both ovaries or fallopian tubes	T1c
IC1	Surgical spill intraoperatively	T1C1
IC2	Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface	T1C2
IC3	Malignant cells present in the ascites or peritoneal washings	T1C3
II	Tumor involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or peritoneal cancer	T2
IIA	Extension and/or implants on the uterus and/or fallopian tubes/and/or ovaries	T2a
IIB	Extension to other pelvic intraperitoneal tissues	T2b
III	Tumor involves one or both ovaries, or fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes	T3
IIIA	Metastasis to the retroperitoneal lymph nodes with or without microscopic peritoneal involvement beyond the pelvis	T1,T2,T3aN1
IIIA1	Positive retroperitoneal lymph nodes only (cytologically or histologically proven)	N1
IIIA1i	Metastasis $\leq$ 10 mm in greatest dimension	N1a
IIIA1ii	Metastasis > 10 mm in greatest dimension	N1b
IIIA2	Microscopic extra pelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes	T3a
IIIB	Macroscopic peritoneal metastases beyond the pelvic brim $\leq$2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes	T3b
IIIC	Macroscopic peritoneal metastases beyond the pelvic brim > 2 cm in greatest dimension, with or without metastases to the retroperitoneal nodes	T3c
IV	Distant metastasis excluding peritoneal metastases	M1
IVA	Pleural effusion with positive cytology	M1a
IVB	Metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of abdominal cavity)	M1b

3. Non-epithelial ovarian cancer

WHO classifies the histopathological types of ovarian tumors based on the tissue of origin. Ovarian tumors are divided into epithelial and non-epithelial. Non-epithelial tumors are divided into germ cell and sex-cord stromal tumors. The following is a classification based on the type of histopathology:

Table 2. Histological classification of germ cell tumor

Germ Cell Tumor
Dysgerminoma
Teratoma
A. Immature
B. Mature
1. solid
2. cystic
a. dermoid (mature cystic teratoma)
b. dermoid with malignant transformation
C. Monodermal and highly specialized
1. struma ovarii
2. carcinoid
3. struma ovarii dan carcinoid
4. others
Yolk Sac Tumor /Endodermal Sinus Tumor
Embryonal carcinoma
Polyembryoma
Choriocarcinoma
Mixed

Table 3. Classification of sex-cord stromal tumor according WHO 2014

Sex Cord-Stromal Tumor
Pure Stromal Tumors
Fibroma
Cellular Fibroma
Thecoma
Luteinized thecoma associated with sclerosing peritonitis
Fibrosarcoma
Sclerosing stromal tumor
Signet-ring stromal tumor
Microcystic stromal tumor
Leydig cell tumor
Steroid cell tumor
Steroid cell tumor malignant
Pure Sex Cord Tumor
Adult granulosa cell tumor
Juvenile granulosa cell tumor
Sertoli cell tumor
Sex cord tumor with annular tubules
Mixed Sex Cord Stromal Tumors
Sertoli-Leydig cell tumor
Well differentiated
Moderately differentiated
With heterologous elements
Poorly differentiated
With heterologous elements
Retiform
With heterologous elements
Sex cord stromal tumor, NOS

3.1 Germ cell tumor

This type of cancer occurs in various age groups, with the highest incidence in the age range of 15-19 years (4). There is a major clinical difference between germ cell tumors and epithelial ovarian cancer, namely that germ cell tumors are much larger and grow rapidly. The main presenting symptoms were abdominal pain (in 87% of patients) and a mass in the abdomen (in 85% of patients).

Approximately 10% of patients present with acute abdominal pain due to tumor torsion, bleeding, or tumor rupture (which is more common in yolk sac tumors or mixed tumors) (13).

Table 4. Tumor marker of ovarian germ cell tumor (13)

Tipe Histologi	AFP	β-hCG	LDH
Dysgerminoma	-	±	+
Yolk sac tumor	+	-	+
Immature teratoma	±	-	±
Mixed germ cell tumor	±	±	±
Choriocarcinoma	-	+	±
Embryonal carcinoma	±	±	±
Polyembryoma	+	+	-

3.1.1 Dysgerminoma

Dysgerminomas are found in 30-40% of cases with germ cell tumors of the ovaries. As many as 75% of dysgerminomas occur in the age range of 10-30 years, 5% in those under 10 years, and are very rare in those over 50 years of age. The dominant route of spread of this type of cancer is the gonadal, renal and paraaortic lymph nodes. This cancer is highly radiosensitive with radiotherapy doses of 2500-3500 cGy (4). Approximately 85-90% of dysgerminomas in stage I are confined to one ovary, 10-15% of cases are bilateral.

Dysgerminoma is a solid tumor with an average diameter of 15 cm, when divided into lobes, soft and grayish white or light brown in color with areas of necrosis and hemorrhage. The microscopic appearance consists of a spherical population of cells resembling primordial germ cells that form nests and there is an infiltration of T-lymphocytes. The cells have clear to eosinophilic cytoplasm with large round nuclei (14).

Treatment for dysgerminoma is minimally surgical unilateral oophorectomy. Conservative procedures are very likely to be performed in this type of cancer despite metastases due to the sensitivity of the tumor to chemotherapy (14). More frequent monitoring should be carried out in conservative procedures, namely clinical examination and tumor markers every 2 months and CT scan every 3 months for the first 2 years. In patients whose contralateral ovary is preserved, cancer may develop in 5% to 15% of cases within the next 2 years (4). Chemotherapy that is often used is the BEP regimen (bleomycin, etoposide, and cisplatin), VBP (vinblastine, bleomycin, and cisplatin), and VAC (vincristine, actinomycin, and cytoxan).

The disease-free survival rate can reach 90% in cases that have not been treated previously and 70% in repeated cases on the use of chemotherapy regimens. Stage IA with conservative surgery provides 5-year disease free survival of more than 95% (15).

3.1.2 Immature teratoma

Immature teratomas account for less than 1% of all ovarian cancers. It is found in 10-20% of all ovarian malignancies found in women under the age of 20 years and causes 30% of deaths from ovarian cancer in this age group. The macroscopic appearance of immature teratomas is larger than that of mature teratomas. An encapsulated mass with a predominantly solid, soft component with small internal cysts. Lesions can grow rapidly, so signs and symptoms often appear subacute.

Management of immature teratomas in young patients with lesions confined to a single ovary, unilateral oophorectomy or salpingo-oophorectomy and surgical staging should be performed. In elderly patients who do not require fertility function, TAH-BSO is performed. Contralateral lesions are rare so in the contralateral ovary, routine resection or biopsy is not necessary. The most common site of spread is the peritoneum. Metastases are often hematogenous to parenchyma organs, such as the lungs, liver, or brain (4). Adjuvant chemotherapy regimen BEP was given in all cases except immature teratoma stage IA grade 1.

Five-year survival rates for grades 1, 2 and 3 were 82%, 62%, and 30%, respectively. Patients whose tumors were incompletely resected before starting therapy had a significantly lower 5-year survival rate of 50% than patients whose tumor masses were completely resected of 94% (16). Overall, the 5-year survival rate of patients in all stages of immature teratoma is 70% to 80%, whereas for patients with stage I it is 90-95% (17).

3.1.3 Endodermal sinus tumor or yolk sac tumor

Endodermal sinus tumor found in patients in the age range of 16-18 years. The most common symptom is abdominal or pelvic pain in about 75% of cases, 10% are asymptomatic (13). The macroscopic appearance of the yolk sac tumor was a large encapsulated mass with a diameter of about 15 cm with a smooth surface and gray-brown color. Unilateral lesions are present in almost 100% of cases, so a contralateral ovarian biopsy is not required (13).

Therapy for yolk sac tumors is surgery, whether conservative or not, followed by chemotherapy (14). Prior to the routine use of chemotherapy, the 2-year survival rate in patients was only 25%. After the use of chemotherapy, the survival rate increases to 60-70%, indicating that this tumor is chemo-sensitive. Reproductive function can be conserved with conservative surgery and adjuvant chemotherapy. Four cycles of BEP chemotherapy every 3 weeks is the first line chemotherapy (4). Five-years overall survival of yolk sac tumor was 66,6%. The prognostic factors of this type of cancer were stage, ascites, and tumor residue (18).

3.1.4 Embryonal carcinoma

This cancer is very rare and is distinguished from choriocarcinoma because of the absence of syncytiotrophoblastic and cytotrophoblastic cells. Embryonal carcinoma causes some patients to experience precocious pseudopuberty and irregular bleeding. As in yolk sac tumors, lesions secrete AFP and -hCG, these markers useful for monitoring response to subsequent therapy. Surgical therapy is the same as for yolk sac tumors, namely unilateral oophorectomy or salpingo-oophorectomy followed by combination chemotherapy with BEP (4).

3.1.5 Choriocarcinoma

Pure non-gestational choriocarcinoma of the ovary is histologically similar to gestational choriocarcinoma that metastasizes to the ovary. The majority of people with this cancer are under 20 years old. Precocious puberty occurs in 50% of patients with this cancer before menarche. The patient's prognosis is relatively poor, with most of the patients having metastases to the organ parenchyma at the time of initial diagnosis (14).

3.1.6 Mixed germ cell tumor

Most of these lesions contain poorly differentiated elements, so they must be treated with combination chemotherapy. Tumor markers when initially positive may become negative during chemotherapy, but this may reflect regression occurring only in certain components of the mixed lesion. The most important prognostic features are the size of the primary tumor and the relative amount of the most malignant component. In stage IA lesions smaller than 10 cm, the survival rate is 100% (4).

3.2 Sex cord-stromal tumor

This type of tumor is found in about 5% of all ovarian tumors. Approximately 90% of hormonally active ovarian tumors fall into this category and are associated with physiologic and pathological signs of estrogen or androgen excess (or both), which can lead to precociousness, hirsutism, vaginal bleeding, endometrial hyperplasia, and an increased risk of breast cancer (19).

Sex-Cord Stromal Tumors (SCST) tend to grow slowly so they last longer. The median time of recurrence is five to ten years, with some relapses up to twenty years after diagnosis. The 10-year survival rate is 90% for stage I cancer and 0% - 22% for stage III. Prognostic factors that affect survival rate based on multivariate analysis are age younger than 50 years, tumor size smaller than 10 cm, diagnosed at an early stage, and no residual tumor (19).

3.2.1 Granulosa cell tumor

The tumor is a few millimeters in diameter to 20 cm or more. Tumors are rarely bilateral and have a smooth, lobulated or insulated surface, and are yellow or yellowish-gray in color. Risk factors associated with the occurrence of this type of tumor are non-white race and obesity as a hyper-estrogenic state that favors the occurrence of granulosa-stromal cell tumors, while parity and the use of oral contraceptives have a protective effect (19).

Approximately 15% of patients with granulosa cell tumors present with an acute abdomen associated with hemoperitoneum. In women who have not been menopausal, irregular menstruation or secondary amenorrhea may occur. Granulosa cell tumors consist of 2 types of subtypes, namely adult and juvenile (19).

Adult granulosa cell tumors account for nearly 95% of all granulosa cell tumors. It occurs more frequently in postmenopausal patients and is the most common estrogen-producing tumor. The most common symptom in postmenopausal women is vaginal bleeding as a result of endometrial stimulation. A study by Ayhan et al in 2009 found that this type of cancer occurs in patients with an average age of 47 years with the most symptoms being postmenopausal bleeding at 27.5% and irregular menstruation 26.2%. Endometrial biopsy results showed 40% were simple hyperplasia without atypia. Endometrial cancer is found in patients with stage III who are more than 60 years old. Adult granulosa cell tumors are usually low-grade malignancy, grow slowly and are often stage I in more than 90% of cases. The most important prognostic factor is the stage at surgery. Recurrence can occur within 5 to 30 years after diagnosis (14). Juvenile granulosa cell tumors are mostly found in the first three decades of life. Most tumors are hormonally active, producing estradiol, progesterone, and androgens. Symptoms that patients complain of are precocious puberty with breast development and pubic and axillary hair, some also complain of irregular uterine bleeding. This type of tumor is aggressive and can recur within 3 years after diagnosis. A case series by the Mayo Clinic states that as many as 92% of patients with this type of tumor survive 5-10 years (82% of cases are diagnosed at stage I). The recurrence rate was 18.6% and 23% of recurrences occurred within more than 13 years of therapy (19).

The most important prognostic factor is the stage of the cancer. Tumor residues and DNA-ploidy were important predictors of progression-free survival. Patients with tumor residues whose ploidy DNA was negative had a 10-year progression-free survival rate of 96% (14). Serum inhibin has an important role as a marker to monitor the outcome of therapy and to detect tumor recurrence. Inhibin B has better sensitivity than inhibin A (89% vs. 67%) with 100% specificity for diagnosing recurrence of granulosa cell tumors (19).

3.2.2 Thecoma

Thecoma are less common than granulosa cell tumors, but have a similar tumor appearance. Dense fibromatous lesions that show varying degrees of yellow or orange coloration. Granulosa cell tumors are found bilaterally in 2-5% of patients, whereas thecoma is almost always confined to one ovary. Hormonal active thecoma, 15-37% associated with endometrial hyperplasia and 25% of cases associated with endometrial cancer so that endometrial biopsy is mandatory (19).

3.2.3 Fibroma

Fibroma is the most common type of SCST and is found in postmenopausal women. Fibroma can be associated with ascites and hydrothorax as a result of increased capillary permeability due to the production of vascular endothelial growth factor (VEGF). Meigs syndrome (ovarian fibroma, ascites, and hydrothorax) is rare and usually resolves after surgical excision of the ovarian fibroma (19).

3.2.4 Sertoli-leydig cell tumor

This type of tumor is found in less than 0.5% of all ovarian tumors. Nearly 97% of these tumors are unilateral. Occurs in the age group of 20-30 years. These tumors produce androgens and cause virilization in 70-85% of patients (14). Classically, there is progressive masculinization characterized by hirsutism, a deeper voice, and an enlarged clitoris. Other cases may show secondary amenorrhea, breast atrophy, and marked increase in libido. The 5-year survival rate in patients with Sertoli-Leydig cell tumors is 92% with an overall five-year survival rate ranging from 70-90% (19).

These tumors occur mainly in young women and are found to be bilateral in less than 5% of cases. Removal of the tumor alone may be performed if fertility function is still required and if there is no evidence of extension beyond the ovary involved. Tumors with poorly differentiated, advanced stages, or recurrent lesions should be treated with adjuvant chemotherapy. The recommended chemotherapy is BEP (19).

3.2.5 Sex-cord with annular tubules

Sex-cord tumor with annular tubules (SCTAT) is a unique ovarian tumor that presents histologically as a granulosa cell tumor and a Sertoli-Leydig tumor. These tumors are usually unilateral and present with symptoms of vaginal bleeding or postmenopausal bleeding, which is evidence of the endocrine activity of the tumor. Approximately 30% of SCTAT tumors are associated with Peutz-Jeghers Syndrome (PJS). Tumors associated with PJS are benign but are

associated with cervical malignant adenomas in 15% of cases. In contrast, SCTAT which is not associated with PJS, has a malignancy rate of 20% (19).

3.2.6 Gynandroblastoma

Tumors with a low degree of malignancy. It is an androgenic tumor that may be associated with paraneoplastic manifestations such as hypercalcemia, erythrocytosis, or ascites. In 20% of cases, the tumor spread to adjacent organs at the time of surgery (19).

3.2.7 Steroid cell tumor

Steroid cell tumors are tumors that cannot be categorized as stromal luteoma or Leydig cell tumors. Steroid cell tumors (lipid cell tumors) are a group of heterologous tumors that share a parenchymal similarity that consists of polygonal cells containing lipids. Most of these tumors are benign, but about 20% of lesions greater than 8 cm in diameter are associated with metastatic lesions. Metastases usually occur in the peritoneal cavity but distant metastases can occur. The main treatment is surgery for the primary lesion. There are no data regarding the effectiveness of radiation and chemotherapy for therapy in these tumors (14).

Management of non-epithelial ovarian cancer in RSUD dr. Soetomo Surabaya was carried out according to the applicable guidelines. Staging is classified in non-epithelial ovarian cancer according to FIGO 2014 as in epithelial ovarian cancer. Adequate surgical staging or debulking is standard at all stages. In cases that still require fertility function, the uterus and contralateral ovary can still be conserved.

Based on the guidelines for the management of gynecologic cancer at RSUD Dr. Soetomo, the principle of management of non-epithelial ovarian cancer is adequate surgery. Surgery can be performed in the form of surgical staging or debulking of the tumor mass. Patients who still need fertility function can undergo conservative surgical staging. Complete surgical staging includes TAH-BSO or USO, peritoneal washing, peritoneal biopsy, omental biopsy and biopsy of enlarged lymph nodes. Germ cell tumors of the type of dysgerminoma stage IA and immature teratoma stage IA grade I do not need to be continued with adjuvant chemotherapy. Sex cord-stromal tumors were treated with surgery, surgical staging/debulking and continued with adjuvant chemotherapy in advanced cases with residual tumor. The first-line chemotherapy given was BEP (Bleomycin, Etoposide, and Cisplatin).

4. Prognostic Factors

Several factors that influence the prognosis and survival of ovarian cancer are broadly divided into clinical, pathological, and biological factors. Clinical factors include age, menarche, menopause and parity. Pathological factors include stage, tumor grading, cytologic findings, ascites and tumor residues. Biological factors include the expression of different genes in response to chemotherapy that can affect the prognosis (20).

a. Patient's age

Age became an independent prognostic factor after controlling for confounding factors such as general condition and medical comorbidities. Young women tend to get epithelial ovarian cancer which is slightly invasive and well differentiated, less comorbid when compared to old age, resulting in good survival (21). In adult granulosa cell tumor ovarian cancer, the recurrence rate and poor prognosis are more common in those over 50 years of age with a risk of up to 3.3 times. Two recent multivariate analysis studies reported that advanced age is an independent prognostic factor influencing disease prognosis (22, 23)

A multicenter retrospective study in Italy showed that one of the predictors of germ cell tumor recurrence of ovarian cancer is age. Patients aged more than 45 years had a relative risk of 6.124 with p=0.003 95% CI (1.88-19.947). According to a retrospective multicenter cohort study in London, 75% of patients with malignant ovarian germ cell tumor (MOGCT) who died were aged >40 years. At the age of >40 years, patients with this type of ovarian cancer will present with advanced stages and may metastasize who must receive adjuvant chemotherapy, while chemotherapy resistance begins to increase so that their PFS and OS will also be worse than in young adults. At the age of > 40 years, the immune condition begins to decline, there are differences in tumor biology and cancer pathogenesis mechanisms and many medical comorbidities, so therapy will be less aggressive. Most studies also show that the prognosis of patients with sex-cord stromal tumors has a much better prognosis at the age of less than 40 years (22, 24-26).

b. Stage

The FIGO system has been studied for more than two decades and is significant as an independent prognostic factor (26). Factors that influence the prognosis of patients with recurrent and persistent germ cell tumors are the stage of disease at diagnosis, optimal surgery and standard chemotherapy (27). The earlier the stage is diagnosed, the better the prognosis for the disease.

Patients with germ cell tumors as much as 70.7% were found in stage I and 75.6% of cases underwent surgery to conserve fertility giving a 5-year survival rate of 95.6% in stage I and 73.2%

in advanced stages. Cancer stages that are more than stage I have a relative risk of 5.576 with p=0.004 95% CI (1.715-18.1) (28).

Disease free survival rate in patients with germ cell tumors who underwent surgery with fertility conservation was 79.9%, which was still higher than the group without fertility conservation, which was 57.8% (p = 0.016). Most germ cell tumors are chemosensitive so that lymph node dissection does not have a significant correlation with prognosis, so lymph node dissection is not necessary if there is no lymph node enlargement during surgery (29).

Patients with early stage (stage I and II) ovarian cancer type SCST had disease free survival (DFS) at 5 years by 77% and at 10 years by 43%. This figure is much better than in the advanced stage only 44% and 29% (30). Overall survival in germ cell tumor stage I was 95.6% and in stage II-IV 73.2% with p=0.001 (31). Research in 2009 also stated that the stage of cancer in adult granulosa cell tumors will determine the recurrence and prognosis of patients. In stage I the recurrence is 5% and at an advanced stage it is around 33% (p=0.019) (32).

c. Tumor residue

Optimal surgery is the removal of the tumor mass without leaving a residue. Surgery with optimal tumor removal will improve the response to chemotherapy (27). Incomplete surgical staging resulted in poorer progression free survival and overall survival (33). Tumor residue after surgery is also a significant prognostic factor that determines survival time (26, 34). Recurrence is more common in patients with residual tumor. The 5-year overall survival in patients with malignant ovarian germ cell tumors with and without postoperative tumor residues was 65.7% and 91.5% (31).

d. Tumor size

In several multivariate analyzes it was stated that the larger the tumor size was associated with a much worse prognosis (35, 36). The study by Thrall states that tumor size is one of the predictors of survival. Survival time was better in patients with tumor size less than 10 cm and no recurrence was found in patients with tumor size less than 7 cm (37). A multivariat analysis research found that patients with sex-cord stromal tumor that younger than 50 years old, tumor size less than 10 cm, diagnosed at early stage and no tumor residue had better survival rate (19).

e. Tumor marker

Elevated preoperative tumor marker levels will increase the risk of cancer recurrence and progression and is a prognostic factor for poor progression free survival (PFS). Progressive and recurrent cancer occurred in 26.2% of patients with elevated tumor marker levels and was not found

in patients with normal tumor markers (p=0.001) (33). Increased levels of tumor markers in malignant ovarian germ cell tumors will affect the prognosis to be worse with RR 4.05 p = 0.043 95% CI (1.04-15.68) (31). High levels of -hCG and AFP on MOGCT are associated with a poor prognosis (38).

f. Histopathological type

Histological type of ovarian cancer will affect the progression free survival and overall survival. Malignant ovarian germ cell tumor has the best prognosis because it is highly chemosensitive and is supported by an effective BEP chemotherapy regimen that allows for fertility conservation (39).

The prognosis of patients with yolk sac tumor ovarian cancer will be worse with an RR of 6.31 p=0.001 95% CI (2.064-19.3) (31). The same study in 2017 showed that 5-year overall survival in patients with yolk sac tumors or mixed germ cell tumors was lower at 83.7% compared to other histologic types in germ cell tumors, which was 98.6% ($p<0.05$). (28). The type of ovarian cancer with the largest recurrence rate was embryonal carcinoma and the highest cause of death was the yolk sac (p=0.04) (40)

In another study, it was stated that the ovarian sex-cord stromal tumor had a lower survival rate and caused 42.3% of deaths with HR 0.53 compared to survival in the type of ovarian germ cell tumor with a mortality rate of 23.8% and HR 0.41. (41). Type of tumor histology is an independent prognostic factor that affects the survival of patients with malignant ovarian germ cell tumor. The 5-year survival rate for all histologic types is above 85%, with dysgerminoma as the best-prognostic type and embryonal carcinoma with the worst prognosis (42).

g. Chemotherapy

Surgery with optimal tumor removal will improve the response to chemotherapy. The standard chemotherapy is chemotherapy with a BEP regimen (bleomycin, etoposide, cisplatin) which is started within 1 week after surgery. Chemotherapy was given on time 21 days apart and given >3 cycles (27). Inadequate chemotherapy will lead to treatment failure. The combination of surgical therapy and chemotherapy will provide a longer survival time in patients with malignant ovarian germ cell tumor (42). The use of BEP chemotherapy has also been shown to be associated with a decrease in serum tumor marker levels (AFP and HCG) which affect overall survival. Patients with malignant ovarian germ cell tumors who underwent surgery and chemotherapy had an overall survival of 86% (95% CI 74%-93%) (38).

5. Conclusion

Based on literatures, prognostic factors of non-epithelial ovarian cancer include patient's age, cancer stage, tumor size, tumor marker, post-operative tumor residue, histopathological type of cancer, and chemotherapy. Better knowledge of those prognostic factor will lead to better management of patients with non-epithelial ovarian cancer and increase survival rate.

Conflicts of Interest

No declare

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