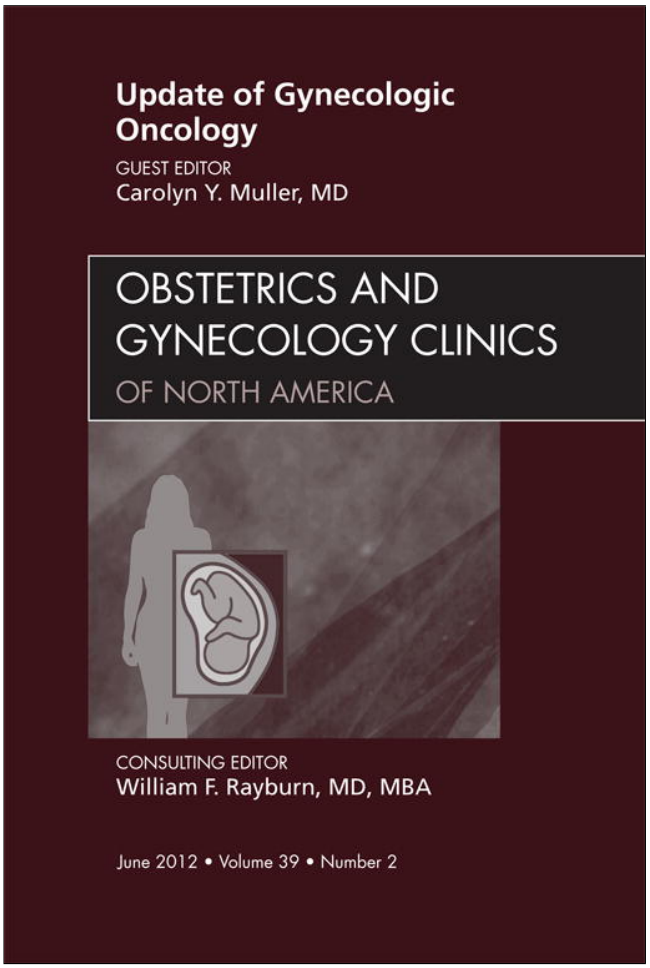

Epithelial Ovarian Cancer

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KEYWORDS

• Ovarian cancer • Chemotherapy • Staging • Surgery • Pathology

KEY POINTS

- Ovarian cancer is the second most common cancer of the female genital tract, yet is the deadliest of all.
- Most ovarian cancers are diagnosed in later stages, this is caused by both the absence of screening method and atypical presenting symptoms.
- Treatment includes optimal surgical debunking, followed by chemotherapy.
- The 5 years survival varied between 20–39%.

Epithelial ovarian cancer is the deadliest gynecologic malignancy, constituting the fourth most common cause of death in women and the fifth most common among United States women, after cancers of the lung, breast, colon, and uterus.[1] More than 21,550 cases of ovarian cancer are diagnosed annually in the United States, with approximately 14,500 dying from this disease.[1] A woman's overall lifetime risk for epithelial ovarian cancer is 1.7 % unless increased because of familial risk.

PATHOLOGY AND STAGING

Nearly 80% of epithelial cancers are of serous histologic type. Less frequently encountered histologic types include mucinous (10%), endometrioid (10%), and either clear cell, Brenner, or undifferentiated carcinomas (fewer than 1%).

Regardless of the histology, the behaviors of ovarian cancer cells are categorized into three distinct clinical types; borderline tumors, low-grade tumors, and invasive cancer.

Borderline tumors, which account for 15% of epithelial ovarian tumors, occur more frequently in premenopausal women and overall have a favorable prognosis.[2–4]

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Borderline tumors, however, can have metastatic implants categorized as invasive and noninvasive implants. Invasive implants are more likely to proliferate in the peritoneal cavity, leading to intestinal obstruction and death.[3,4]

Low-grade ovarian epithelial cancers are usually either serous or mucinous cancers that are generally unresponsive to chemotherapy. Low-grade mucinous tumors may have corresponding pseudomyxoma peritonei, or "jelly belly," which is characterized by copious production of gelatinous mucin, which alone can cause functional bowel obstruction. Low-grade serous carcinomas frequently arise from a borderline precursor and are molecularly distinct from high-grade serous tumors. These tumors contain B-raf and K-ras mutations as compared with p53 mutations seen in high-grade serous cancers.[5,6] Compared with high-grade serous carcinomas (grades 2 and 3), low-grade serous carcinomas have a significantly longer progression-free survival (PFS; 45 vs 19.8 months).[7]

CAUSES

Risk factors for ovarian cancer have been widely studied. Ovarian cancer incidence varies with geographic location. Low parity, infertility, early menarche, and late menopause are associated with elevated ovarian cancer risk.[8,9] One possible mechanism for raising the risk level is repeated cycles of disruption and repair of the ovarian surface epithelium leading to a high rate of p53 overexpression.[10,11] Other risk factors are obesity in adolescence, fertility-enhancing medications,[12] and hormone replacement therapy.[13] Genetic predisposition is seen in approximately 10% to 15% of patients with ovarian cancer, the majority of those women possessing a BRCA1 or BRCA2 gene mutation.[14] For those with BRCA mutation, the use of oral contraceptives or prophylactic removal of the ovaries and fallopian tubes is essential to minimize the cancer risk.

SCREENING

To date there is no effective method of screening for ovarian cancer. In premenopausal women, transvaginal ultrasonography and CA125 have a high rate of false-positives Routine annual pelvic examinations have provided poor results. Recent data from the Prostate, Lung, Colorectal and Ovarian Cancer Screening randomized controlled trial in postmenopausal women confirmed that routine screening in the general population did not reduce ovarian cancer mortality. In fact, in 3285 women with false-positive tests, 1080 underwent surgical management of whom 163 (15%) experienced at least one major complication.[15]

CA125 increases the early diagnosis of epithelial ovarian cancer.[16–24] Sensitivity of CA125 is 50% for stage I disease and 60% for stage II.[24] Specificity improves when CA125 is used in conjunction with transvaginal ultrasonography.[16]

Family history of ovarian cancer increases a woman's risk of the disease over the general population. Of the two BRCA gene mutations, BRCA1 predisposes a woman to a lifetime risk between 28% and 44%, and BRCA2 carries a 27% lifetime risk. When combined there is an 82% lifetime risk of breast cancer.[14,25–27]

Lynch II syndrome and hereditary nonpolyposis colorectal cancer syndrome (HNPCC syndrome) are autosomal dominant genetic causes of ovarian cancer.[28] HNPCC syndrome involves familial colon cancer (known as Lynch I syndrome) and increased rates of ovarian, endometrial, and breast cancers.[28]

Management of Women at High Risk for Ovarian Cancer

The American Society of Clinical Oncologists strongly recommends that women at high risk for ovarian cancer undergo careful evaluation by geneticists. BRCA1 and

BRCA2 testing is clearly beneficial; however, it must be conducted in conjunction with genetic counseling.[29] For those who test positive for a BRCA mutation, the National Institutes of Health Consensus Conference on Ovarian Cancer recommends screening with transvaginal ultrasonography or CA125 levels starting at the age of 35 or 10 years earlier than the youngest age that a family member was diagnosed with ovarian or breast cancer. Beyond screening, prophylactic bilateral salpingo-oophorectomy reduces ovarian cancer risk by 92% and breast cancer risk between 50% and 80%.[30]

CLINICAL PRESENTATION

With early diagnosis of ovarian cancer, cure is possible. Prompt detection and treatment are essential to decreasing disease morbidity and mortality. Unfortunately, the signs and symptoms of ovarian cancer are vague and initially subtle, which often can delay diagnosis.

Symptoms

Most symptoms of ovarian cancer are nonspecific; however, nearly all women will have at least one symptom that is pelvic, abdominal, or menstrual in nature.[31–33] One recent study[34] developed an ovarian cancer symptom index that illustrates many of the common symptoms of ovarian cancer including pelvic or abdominal pain, urinary frequency or urgency, increased abdominal size or bloating, and difficulty eating or feeling full. The overall sensitivity for early disease with this index was 56.7% and 79.5% for advanced stage cancer. Other symptoms can include fatigue, weight changes, indigestion, nausea, anorexia, constipation, back pain, and pain with intercourse.[34] These symptoms are typically insidious in onset and occur daily. It is uncommon for ovarian cancer to present with acute symptoms such as torsion.

Signs

Several signs are typical of ovarian cancer. A mass found on examination that is solid, fixed, or irregular could be malignant. Masses can sometimes be palpated on abdominal examination due to omental caking or peritoneal disease. Another hallmark of ovarian cancer is the presence of ascites, which can occur with pleural effusions and dyspnea. The combination of more than one of these findings raises the possibility for pelvic neoplasm and bears further workup. As with any malignancy, there is increased risk of thromboembolic disease, which may present as deep venous thrombosis, pulmonary embolus, or cerebrovascular accident.

Diagnosis

Combining history, physical examination, laboratory findings, and radiologic findings supports the diagnosis of ovarian cancer. Definitive diagnosis is made via tissue or cytologic diagnosis. A thorough abdominal and pelvic examination, especially a rectovaginal examination, is key to suspecting a diagnosis of ovarian cancer. A delayed diagnosis often results because patients complain about abdominal symptoms, so pelvic examinations are not performed.

A bimanual and rectovaginal examination that reveals an adnexal mass that is fixed, solid, and irregular may indicate cancer; however, tubo-ovarian abscesses and endometriomas can present similarly. A rectovaginal exam can help detect rectal masses and can be enhanced by performing a guaiac test for occult blood. The ovaries are also often better evaluated on rectovaginal examination, because they can lie posterior to the uterus.

The abdominal examination may reveal peritoneal masses, omental caking in the mid to left upper abdomen, or grossly enlarged adnexal masses on palpation. Evaluating for a fluid wave can aid in identifying ascites. Groin and supraclavicular lymph nodes should also be evaluated.

Serum markers and radiology

Routine screening of low-risk women by serum markers and imaging have not been shown to be cost-effective because of a high false-positive rate. However, ultrasound and serum level of CA125 are essential to the evaluation of symptomatic patients.

Transvaginal ultrasound provides better resolution than an abdominal one for evaluation of adnexal masses.[35–38] Complex adnexal features favor malignancy and include irregular borders; solid components (especially those with color Doppler flow); multiple, thick septations (>2–3 mm); and masses that are complex and bilateral or large (>8–10 cm in diameter).[39–41] Simple cysts are more commonly benign. Morphologic features that may indicate malignant neoplasia include large, mostly solid, relatively fixed, or irregularly shaped.

Any significant intraperitoneal ascites, especially in postmenopausal women, is typically abnormal. Additionally, enlarged lymph nodes, peritoneal masses, or carcinomatosis noted on ultrasound suggests malignancy. In patients with a definite pelvic mass, abdominopelvic computed tomography (CT) or magnetic resonance imaging (MRI) provides little addition to characterizing the mass.[42,43] (CT or CT/positron emission tomography [PET] scan, however, is helpful to evaluate distant disease, adenopathy, intraparenchymal metastases, or extraperitoneal disease, all of which may alter the possibility of optimal cytoreductive surgery, favoring a neoadjuvant chemotherapy approach.)

Serology

CA 125 greater than the institutional normal when an adnexal mass is present should be interpreted with caution. When evaluating an adnexal mass, this value must be taken in context to avoid false-positive results, because it is widely distributed in adult tissues. CA125 can be elevated for numerous reasons:

- Physiologically in menstruation, ovulation, and pregnancy
- Other gynecologic causes, including pelvic inflammatory disease, endometriosis, and fibroids
- Any disease causing inflammation of the pleura, pericardium, or peritoneum
- Malignancies, including breast, endometrial, pancreatic, colon, and lung cancers
- Other diseases including hepatitis, cirrhosis, ascites, and tuberculosis.

More than 80% of patients with epithelial ovarian cancer have elevated CA125 levels. When thoughtfully applied, this test can detect 50% of patients with stage I disease and over 90% of those with disease in stages II to IV.[36] CA125 specificity can be further improved when combined with transvaginal ultrasound or when these levels are followed over time.[23] Jacobs and colleagues[16] developed a Risk of Malignancy Index, which combines menopausal status, transvaginal ultrasound findings, and CA125 level to determine high or low risk of malignancy[44] (**Table 1**).

Surgical staging of ovarian cancer is a methodologic process that includes removing or sampling all the tissues that might harbor the tumor. Accordingly the surgery should include:

1. Peritoneal washing with normal saline for cytology analysis.
2. Hysterectomy with bilateral salpingo-oophorectomy.

Table 1
Ovarian cancer surgical staging and debulking

Stage I		Cancer limited to the ovaries.
	IA	Cancer is present in one ovary.
	IB	Cancer is present in both ovaries.
	IC	Cancer is present in one or both ovaries and one or more of the following is true: cancer is found on the outside surface of one or both ovaries, the outer covering of the tumor has ruptured, or cancer cells are found in the fluid or tissue linings of the abdomen.
Stage II		Cancer is present in one or both ovaries, and has spread to other parts of the pelvic region.
	IIA	Cancer has spread to the uterus and/or fallopian tubes.
	IIB	Cancer has spread to other organs in the pelvic region such as the bladder, rectum, or sigmoid colon.
	IIC	Cancer has spread to the uterus, fallopian tubes, bladder, sigmoid colon, or rectum. Additionally, cancer may be present in tissue and fluid samples of the lining of the abdominal cavity.
Stage III		Cancer is found in one or both ovaries and has spread to the abdomen.
	IIIA	Cancer is found in one or both ovaries and has microscopically spread to other parts of the abdominal peritoneum.
	IIIB	Cancer has spread to the peritoneum in an amount less than 2 centimeters.
	IIIC	Cancer has spread to the peritoneum more than 2 centimeters and/or has spread to the lymph nodes.
Stage IV		Stage IV ovarian cancer is the most advanced stage of the disease. In this stage, cancer is found in one or both ovaries and has spread to parts of the body beyond the abdomen, or in the liver parenchyma.

Ovarian cancer is staged according to International Federation of Gynecology and Obstetrics (FIGO) staging.

3. Bilateral pelvic and para-aortic lymphadenectomy.
4. Omentectomy.
5. Peritoneal biopsies from the pelvis, paracolic gutters, and diaphragm. This step should be done if the tumor is limited to one of two ovaries or to the pelvis.

A careful initial surgical staging is very important. A national study[45] has shown that up to 28% of patients initially thought to have stage I disease were "upstaged" when reexplored for proper staging, as well as 43% of those thought to have stage II disease.

Surgical debulking of ovarian cancer, on the other hand, means a surgical approach that includes the removal of all ovarian cancer, regardless where the cancer has spread. This approach may include bowel resection, splenectomy, and removal of the peritoneum, or even segmental liver resection.

What is considered an optimal debulking has also evolved with time. In 1969 a study showed that debulking an ovarian tumor to no palpable status showed a dramatic effect on survival. It was not until 1975 that Griffiths,[46] in a secondary analysis of a study for adjuvant chemotherapy, showed a median overall survival

increase of 27 months when the debulking surgery was done to a no-residual status. Further studies in the 1980s and 1990s set the mark to 2 cm for an optimal debulking. Combined studies from the Gynecologic Oncology Group (GOG)[40,41] showed that debulking to a microscopic status produced a dramatic effect on both the median progression-free and overall survival. It has since been decided that debulking to a microscopic status is optimal for ovarian cancer.

ADJUVANT TREATMENT

Mainline treatment after optimal ovarian cancer surgery is chemotherapy. Other modalities of treatment for early ovarian cancer, including radiotherapy, have been used to supplement chemotherapy; however, this treatment is not the standard of care in the United States.

Early Ovarian Cancer

Early ovarian cancer is defined as stages I and II. The stages are further classified by pathology to early low-risk ovarian cancer (stage IA, grade 1 or 2) and early high-risk ovarian cancer (stage IA, grade 3 or stage IB–II with any grade).

Patients with early low-risk ovarian cancer (stage IA, grade 1 or 2) need no further treatment after surgery. A study published by Young and colleagues[47] has shown that compared with no treatment there is no survival benefit when patients are treated with melphalan after surgery. Similarly, Trope and colleagues[48] have shown that treating with carboplatin offers no survival benefit compared with observation.

Patients with early high-risk ovarian cancer (stage IA, grade 3, or stage IB–II with any grade) need three cycles of chemotherapy after surgery. A study published by Trimbos and colleagues[49] showed that treating patients with chemotherapy improves overall survival to 82% compared with 72% for patients who did not get any chemotherapy. A GOG study 157[50] showed that six cycles of carboplatin and paclitaxel did not add survival when compared with three cycles. A recent GOG study 175[51] also showed that maintenance chemotherapy after the three cycles is not necessary.

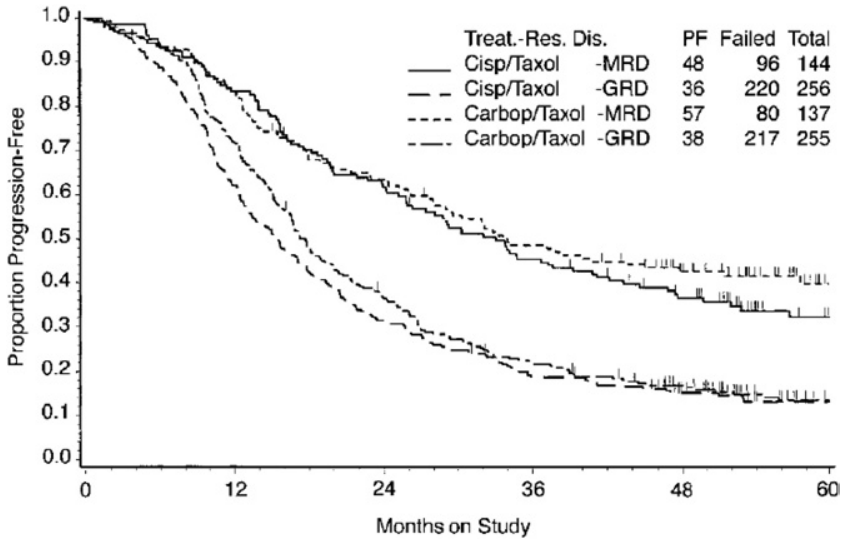

Fig. 1. Superior PFS of the combination carboplatin/paclitaxel. (*From* Katsumata N, Yasuda M, Takahashi F, et al. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. Lancet 2009, 374(9698), 1331–1338; with permission.)

Advanced Ovarian Cancer

Many trials have been published that showed combination chemotherapy after ovarian cancer surgery is needed to achieve a better survival compared with single agent chemotherapy.[52] A series of studies[53–58] has compared combinations of chemotherapy; the latest[58] has concluded that six cycles of combination chemotherapy with carboplatin and paclitaxel are superior (**Fig. 1**), and that is now the standard of care in the United States. The main side effects of this combination include hair loss, bone marrow suppression, and neuropathy. The modalities of administering this combination of chemotherapy are evolving.

Two modalities are the most commonly used now in the United States. The first is intravenous chemotherapy and the second is a combination of intravenous and intraperitoneal chemotherapy.

The "conventional" intravenous chemotherapy modality involves giving the carboplatin in a dose of 5 AUC and the paclitaxel in a dose of 175 mg/m2 every 3 weeks.[58] A recently published modified version of the latter, called "dose-dense" chemotherapy,[59] combines carboplatin (5 AUC) given every 3 weeks with weekly paclitaxel (80 mg/m2). Results of this study showed the dose-dense chemotherapy outcome was progression-free survival of 28 months versus 17 months ($P = 0.0015$) for the conventional course (**Fig. 2**). The dose-dense chemotherapy, however, caused more anemia as a side effect compared with the conventional approach.

Intraperitoneal chemotherapy is the second modality of treatment. The results of many trials[60–63] have been published, but most recently, the GOG-172 trial[62] showed

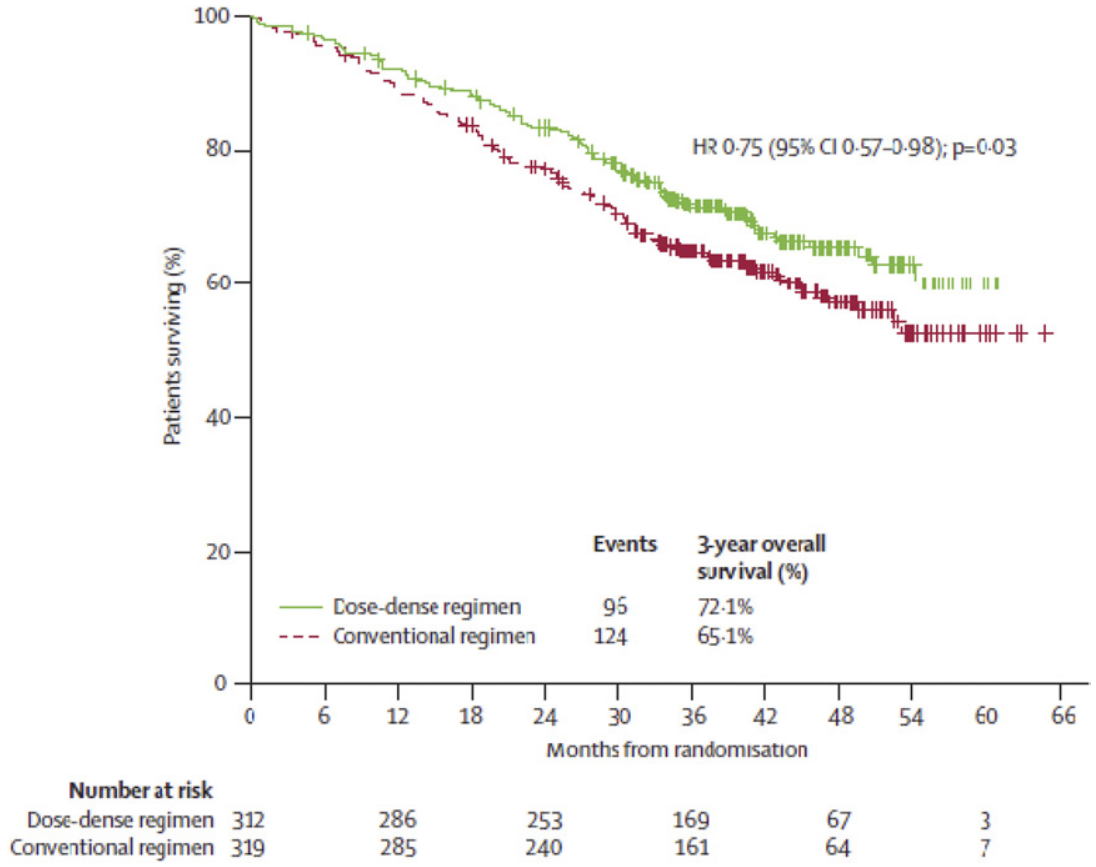

Fig. 2. Superior PFS of the dose-dense chemotherapy. CI, confidence interval; HR, hazard ratio. (*From* Katsumata N, Yasuda M, Takahashi F, et al. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. Lancet 2009, 374(9698), 1331–1338; with permission.)

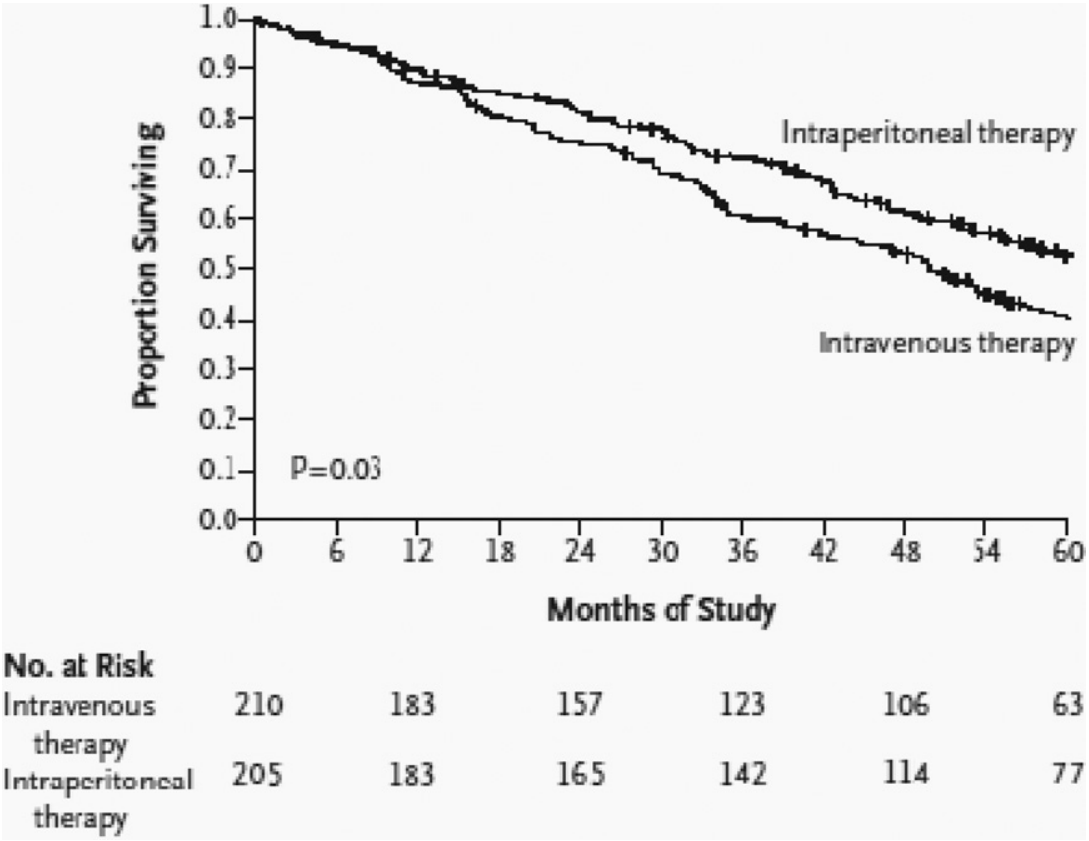

Fig. 3. The superiority of intraperitoneal chemotherapy. (*From* Katsumata N, Yasuda M, Takahashi F, et al. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. Lancet 2009, 374(9698), 1331–1338; with permission.)

the superiority of giving intraperitoneal/intravenous chemotherapy compared with intravenous conventional chemotherapy. The former modality offered an overall survival of 65 months versus 49 months ($P = 0.03$) for the conventional approach (**Fig. 3**). However, the intraperitoneal/intravenous chemotherapy regimen has more toxicity and side effects, and therefore a high rate of chemotherapy incompletion with lower quality of life. Those factors should be weighed against the increased survival benefit. There is an ongoing GOG randomized clinical trial comparing outcomes of the three modalities.

Bone marrow suppression is the most frequent side effect that causes both significant morbidity and mortality. Carboplatin or paclitaxel doses can be lowered to ameliorate those side effects, or the therapy can be delayed for a week or two to allow proper recovery of the bone marrow. Neuropathy is a more permanent side effect; if it is detected early in the treatment, the paclitaxel can be changed to docetaxel[56] or liposomal doxorubicin[63] without compromising the survival outcome to reduce the incidence of neuropathy.

A randomized European study[64] has shown that neoadjuvant chemotherapy can lower the operative morbidities compared with the conventional adjuvant chemotherapy (upfront surgery followed by the same chemotherapy). This study also has shown the modalities have a similar survival outcome, but unfortunately the survival outcome is much lower than what has been shown in United States randomized trials. Neoadjuvant therapy can be an option to improve surgical outcomes for patients with a high level of preoperative morbidity, understanding that it might lower patients' overall survival.

NEW MOLECULAR TARGETED THERAPY

A new molecular targeted treatment for ovarian cancer includes many medications, the most important of which is a vascular endothelial growth factor inhibitor, also called bevacizumab. Two studies have been published looking at the effect of bevacizumab as an additive treatment to traditional chemotherapy for ovarian cancer. The first study, GOG 218,[65] used bevacizumab with chemotherapy in the adjuvant setting and as maintenance afterward. This study showed a net gain of 4 months of progression-free survival with use of bevacizumab during and up to 10 months after carboplatin and paclitaxel chemotherapy, with no effect on overall survival in early survival analysis. The other international study is ICON-7,[66] which similarly showed a gain of 2 months of progression-free survival without affecting overall survival.

Although the effect of bevacizumab is only on progression-free survival, it is still being studied in current GOG studies. Further studies are needed to delineate the true effect of bevacizumab on long-term survival. Adding bevacizumab to conventional chemotherapy in both trials, however, added more side effects. The most important ones are bowel perforation and additional bone marrow suppression.

POSTTREATMENT SURVEILLANCE

After completion of the adjuvant chemotherapy, a systematic follow-up is needed. **Table 2**[67] outlines the necessary follow-up. Clinical examination is done accordingly, with a CT scan of the abdomen and pelvis to be performed only if a clinical suspicion is raised.

Serum levels of CA125 increase early in cancer recurrence. Although results of a recent randomized blinded trial United Kingdom study of early versus delayed chemotherapy indicate that diagnosing and treating recurrent disease earlier based on the knowledge of high CA125 serum levels does not increase the patient's overall survival, rather patients who initiated chemotherapy when CA125 levels reached twice the upper limit of normal had more chemotherapy and a worse quality of life compared with women who initiated treatment at the time of symptoms.[68,68] In the United States, CA125 serum level is still routinely used in patient follow-up because it might trigger a CT scan that detects cancer recurrence that can be surgically removed, which was not considered in the Rustin study.[69] In the event of an isolated high level of serum CA125 with the absence of radiologic evidence of cancer recurrence, reinitiating chemotherapy should be decided on an individual patient basis.

RECURRENCE

The overall recurrence rate of ovarian cancer is 62%; however, recurrence varies from 10% for stage I to 85% for stage IV with suboptimal debulking. The mean time of recurrence also varies from 12 months for a suboptimal debulked Stage III ovarian cancer to 24 months when optimal debulking is achieved. More important, the timing of recurrence largely determines how the patient is to be treated, and hence recurrence is classified as follows:

1. Platinum-refractory recurrence: the tumor continues to progress during the adjuvant chemotherapy.
2. Platinum-resistant recurrence: the tumor recurs less than 6 months after completing chemotherapy.
3. Platinum-sensitive recurrence: the tumor recurs more than 6 months after completing chemotherapy.

Table 2
Surveillance for ovarian cancer after completion of therapy

	Months			Years	
Variable	**0–12**	**12–24**	**24–36**	**3–5**	**>5**
Review of symptoms and physical examination	Every 3 mo	Every 3 mo	Every 4–6 mo	Every 6 mo	Yearly
Papanicolaou test/cytologic evidence	Not indicated	Not indicated	Not indicated	Not indicated	Not indicated
Cancer antigen 125	Optional	Optional	Optional	Optional	Optional
Radiographic imaging (chest radiograph, PET/CT/MRI)	Insufficient data to support routine use	Insufficient data to support routine use	Insufficient data to support routine use	Insufficient data to support routine use	Insufficient data to support routine use
Recurrence suspected	CT/or PET scan	CT and/or PET scan	CT and/or PET scan	CT and/or PET scan	CT and/or PET scan
	Cancer antigen 125	Cancer antigen 125	Cancer antigen 125	Cancer antigen 125	Cancer antigen 125

Both platinum-refractory and platinum-resistant recurrence are to be treated with second line chemotherapy, because further surgical resection is of no benefit. Chemotherapy options include paclitaxel, topotecan, liposomal doxorubicin (PLD), or gemcitabine. The patient should know that the best case response to chemotherapy is 12% after PLD, and that the longest median survival is 10 months as reported after topotecan.[70,71]

For platinum-sensitive recurrence, surgical intervention can be considered if the recurrence is limited to a few accessible lesions and if at least 12 months have lapsed since the completion of the chemotherapy. The longer the progression-free survival and the fewer the lesions, the more successful the surgical debulking will be. The GOG is performing the first randomized trial in an attempt to answer the question of the true impact of secondary cytoreduction at the time of first recurrence in platinum-sensitive patients. With or without surgery, second line chemotherapy is also considered the mainstay of treatment for platinum-sensitive recurrence. Because the recurrence is considered platinum-sensitive, carboplatin-based chemotherapy can be initiated. Carboplatin and paclitaxel can be considered,[72] or carboplatin and PLD, because the CALYPSO study has shown that combination offers a superior overall survival when compared with carboplatin and paclitaxel.

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