Recent advances in the detection of ovarian cancer: A review

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Epithelial ovarian cancer is one of the more aggressive malignancies among American women today, and its incidence is increasing. The major obstacle in combatting ovarian cancer is the remarkable lack of symptoms in early-stage disease. Symptoms usually occur in advanced stages when tumor dissemination within the peritoneal cavity induces ascites with resultant increasing abdominal girth.

Physicians have been unable to reach women who have early-stage ovarian cancer, a time when a high cure rate could be expected. However, during the past few years, significant developments in the areas of serum tumor markers, transvaginal ultrasonography with color flow Doppler analysis, immunodiagnostic techniques, and immunotherapy have been reported. These new modalities show promise for use in the early diagnosis and treatment of ovarian cancer. The authors review some of the new data and discuss patient outcomes when these new modalities are used.

(Key words: Cancer detection, monoclonal antibodies, ovarian cancer, radioimmunoscintigraphy)

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Early and accurate diagnosis, appropriate treatment, and close follow-up appear to be the most successful current approaches to cancer. These approaches are particularly appropriate for epithelial ovarian cancer, which is the sixth most common cancer and the fourth leading cause of death in American women.[1] Nearly 21,000 new cases of ovarian cancer were diagnosed in the United States in 1992, and 13,000 patients died of that disease.[1] Ovarian cancer claims more lives than cervical and endometrial cancers combined.

Symptoms first appear in about 67% of women when the disease is in an advanced stage.[2] This phenomenon most likely occurs because the ovaries are mobile structures deep in the pelvis. In this location, considerable tumor growth can occur before symptoms arise. Hundreds of small superficial metastases may be present on the entire peritoneal surface before a diagnosis is made.

Survival rates

The 5-year survival rate of patients with advanced disease (stages II, III, and IV) is 25% to 30%.[1] This rate has not changed in the past 20 years, despite recent advances in detection and therapeutic methods.[3] In fact, in the United States, a 25-year trend in age-adjusted cancer deaths per 100,000 women shows approximately an 8.9% increase for ovarian carcinoma. Only lung cancer has surpassed this increase.[1] Ovarian cancer develops in 1 woman in 70, with an expected-overall cure rate of 30% for all stages.[1]

One reason for the discouraging survival rate associated with ovarian cancer is the clinical and radiologic difficulty of detecting early-stage or recurrent disease (or both). As this cancer grows

Table 1
Risk Factors Associated With the Development of Epithelial Ovarian Cancer

- Number of ovulation years (> 40 ovulation years)
- First pregnancy after age 30
- Nulliparous
- Late onset of menopause
- First-degree family member with ovarian cancer
- Concomitant cancers (breast, colon, endometrial, cervical, adenocarcinoma)
- Exposure to asbestos and talc
- Diet high in meat and animal fat
- Obesity

and progresses to an advanced stage, patients often present with nonspecific signs and symptoms. A significant reduction in the death rate of this disease can be achieved only by early and accurate diagnosis, combined with more effective treatment. After initial surgical staging and resection, the 5-year survival rate for ovarian cancer when detected early is greater than 80% for women treated with radiation, 68% for those given chemotherapy, and 91% for those receiving combined radiation and chemotherapy.[3]

The clinician's goal should be the identification of high-risk patients and a thorough understanding of the effective use of sensitive methods for detection and treatment of primary and recurrent ovarian cancer. We will discuss some of the basic biologic and medical aspects of ovarian cancer and describe present developments in the early detection of primary and recurrent disease. A short discussion of future treatment modalities follows herein.

Histology

Of benign and malignant ovarian tumors, 65% originate from the surface epithelium, 25% from the germ cells, 5% from the rete cord (granulosa cells and Sertoli's cells) and mesenchyme, and the remaining 5% from malignancies outside the ovary. Overall, 80% of ovarian tumors are benign and 20% malignant. Among the malignant ovarian tumors, more than 90% are epithelial in origin, and the rest are germ cell and rete cord tumors. The most common histologic subtype of epithelial ovarian cancer is serous, accounting for 42% of such subtypes. Other subtypes include mucinous cystadenocarcinomas (12%), and endometrioid carcinomas (15%). Undifferentiated carcinomas, clear cell carcinomas, and Brenner tumors make up the remainder.[4]

The diverse cell types reflect the preservation of müllerian duct differentiation by the ovarian surface epithelium. During embryonic development, the ovarian surface is covered by a similar coelomic epithelium, which gives rise to the müllerian ducts by invagination. The müllerian duct develops into the fallopian tubes, endometrium, cervix, and upper aspect of the vagina.

The remaining types of ovarian tumors (nonepithelial) arise from the germ and stromal cells of the ovary. Germ cell tumors account for about 8% of all ovarian tumors. They usually occur in women younger than 20 years of age and represent approximately two thirds of malignant ovarian tumors in that age group.

In contrast, epithelial tumors are rarely seen before menarche and have a peak incidence in the 40- to 70-year-old age group, with a median age of 53 years.

The incidence of epithelial ovarian cancer is highest in the Western Industrialized nations, particularly in Northern Europe and North America.[4] In the United States, it is found primarily among white women of Northern European descent. Japan has one of the lowest prevalence rates, although first- and second-generation Japanese women born in the United States have an incidence approaching those in caucasian women born in the United States.[5] The disease is relatively uncommon in developing countries, perhaps because it is not often diagnosed.

Risk factors

Most often, the primary care physician is the first healthcare professional to see a patient with the initial signs and symptoms of epithelial ovarian cancer. For this reason, a high index of suspicion should exist when women in high-risk categories have persistent, vague abdominal complaints.

The causes of epithelial ovarian cancer are multifactorial. Epidemiologic studies have identified factors that may increase the risk of ovarian carcinoma *(Table 1)*. These factors are genetic, environmental, hormonal, and viral. The number of ovulation years (more than 40) in a woman's lifetime is one of the major risk factors for developing epithelial ovarian cancer.[6] Other risk factors include a history of late menopause; nulliparous women older than 44 years; first pregnancy after age 30; first-degree family member with ovarian cancer; presence of other cancers (breast, colon, endometrial, or cervical adenocarcinoma); exposure to asbestos and talc; diet high in red meat and fat; and obesity.

On the contrary, early menopause, multiparity, first pregnancy before age 25, and the use of oral contraceptives are considered "protective" factors.[7,8]

Familial predisposition

Evidence now suggests that a familial predisposition to ovarian cancer may be an important risk factor, and more prevalent than previously realized. In 1981, the first national registry was established at Roswell Park (Buffalo, NY) to collect data related to familial ovarian cancer. The stated mission of this registry is to document the number of ovarian cancer cases occurring in the United States and to study its modes of inheritance.

A dramatic increase in the number of cases reported to this registry occurred immediately after the 1989 death of the popular comedienne Gilda Radner. The media attention generated after her death increased public awareness of a possible genetic link associated with ovarian cancer. The Roswell Park Group was renamed the Gilda Radner Familial Ovarian Cancer Registry and now has become an important national resource for the study of the genetic and familial patterns in ovarian cancer.

Researchers now think that ovarian cancer is inherited in an autosomal dominant pattern with variable penetrance.[3,4] This pattern represents between 5% and 10% of cases. Women who have two or more first-degree relatives (mother, sister, or daughter) with ovarian cancer are 50% more likely to have this disease develop than women without a family history, who have a 1.4% chance.[5] However, some medical researchers question the actual incidence of genetic defect associated with ovarian cancer in the general population because of the selective nature of this registry's data. Current data suggest an increased lifetime risk of 5% for ovarian cancer in the daughters of afflicted mothers with no other family members having such involvement.

Although the familial relationship has been well described and is often referred to as Lynch syndrome II,[1] the mechanisms and etiologic agents for these relationships are not well understood.

Other genetic factors

Other genetic disorders, such as Peutz-Jeghers syndrome, basal cell nevus syndrome, and gonadal dysgenesis are also associated with an increased incidence of ovarian cancer, but these tumors are usually benign and stromal in nature. The common occurrence of ovarian tumors at the same time or shortly before the development of breast, colon, or endometrial cancer suggests that these malignancies may have a common cause.[5]

Diet

A diet rich in meat and animal fat may also be associated with an increased incidence of ovarian cancer.[9] Positive correlations have also been reported with diets high in meat and dairy products.[10] Conversely, negative correlations have been reported with diets rich in vitamin A, fiber, vegetables, and fruits.[9-11]

Obesity may be a risk factor.[11] Exposure to asbestos and talc has been implicated as causing ovarian cancer in women as well.[12]

For purposes of further discussion in this article, we define a high-risk patient as a woman of advanced age (older than 40 years), nulliparous, with a previous history of cancer or a family history of breast, ovarian, or endometrial cancer, or nonspecific abdominal pain.

Staging

Ovarian cancer, like most gynecologic cancers, is almost always staged surgically. Staging is determined by clinical, operative, and pathologic findings from exploration of the entire abdominal cavity. Cytologic sampling of the abdominal cavity, omentectomy, sampling of retroperitoneal nodes, and liver biopsy—if liver involvement is detected—are also used to determine the staging. The International Federation of Gynecology and Obstetrics (FIGO) classification is the staging system most commonly used. These classifications are based on findings at laparotomy. The FIGO classifications are listed in *Table 2*.

The prognostic value of the FIGO staging system has been published elsewhere.[13] Briefly, the 5-year survival rates for stage I is 72% to 90%; stage II, 45% to 60%; stage III, 10% to 15%; and stage IV, less than 5%. In approximately 75% of newly diagnosed cases, ovarian cancer will have spread beyond the ovary (stage III) and, in 60% of cases, it will have spread to the pelvic and abdominal organs (stage IV).

Epithelial ovarian carcinomas are graded in the following manner: well-differentiated, moderately differentiated, and poorly differentiated.[3] In well-differentiated carcinomas, the papillary structures are distinctly formed, with prominent fibrous stalks. The papillary structure is less regular in moderately differentiated tumors. In poorly differentiated tumors, the papillary pattern is largely obliterated, with the tumor composed of solid cell sheets.

Broder[14] developed a histologic grading sys-

Table 2
Staging of Epithelial Ovarian Carcinoma (FIGO* Cancer Committee Criteria)

Stage I: Tumor limited to ovaries
- Limited to one ovary with intact capsule
- Limited to both ovaries with intact capsule
- Tumor detected through capsule or positive peritoneal washings

Stage II: Tumor involves one or both ovaries with pelvic extension
- Extension to uterus or fallopian tubes (or both)
- Extension to other pelvic tissues
- Ascites detected with malignant cells or positive peritoneal washings

Stage III: Tumor involves one or both ovaries with peritoneal metastases or spread to regional lymph nodes (or both)
- Microscopic seeding of abdominal peritoneal cavity
- Tumor involves one or both ovaries with peritoneal metastases < 2 cm in diameter
- Tumor implants > 2 cm in diameter or positive regional lymph nodes (or both)

Stage IV: Growth involves one or both ovaries with distant metastases

*International Federation of Gynecology and Obstetrics.

tem based on cell differentiation and the rate of cell growth. The percentage of undifferentiated cells present in a microscopic field determines the grade: grade I, 0% to 25%; grade II, 25% to 50%; grade III, 50% to 75%; and grade IV, 75% to 100%. Grade I is the least malignant and thus has the best prognosis. Both Broder's and the FIGO staging systems can be found in the literature.

Pathogenesis

An understanding of the natural history of ovarian cancer can give the clinician special insight into the prognosis of this disease. Epithelial tumors disseminate primarily by surface shedding, lymphatic spread, and, occasionally, hematogenous spread. Intraperitoneal dissemination is thought to occur when malignant cells are shed from the surface of the primary tumor. These exfoliated tumor cells attach to peritoneal surfaces to form micrometastases which, in turn, will also shed cells.

Free-floating cells in the peritoneal cavity travel through—and are captured by—the lymphatic channels located in the diaphragm. Clearance or movement of these cells occurs more extensively on the right side overlying the liver. Lymphatic channels at this site drain into submesothelial lymphatic capillaries of the diaphragm. These capillaries communicate with the pleural surface and subsequently with the anterior mediastinal lymph nodes. This pathway accounts for 80% of the peritoneal clearance.

Partial or complete obstruction of the diaphragm's lymphatics by tumor cells allows for implantation on the omentum and various other sites on the serosal surface of the peritoneum. Ascites can form from local reaction at these loci. Epithelial cancer also spreads by direct extension and may involve the peritoneal surfaces of adjacent structures such as the bladder, rectosigmoid colon, or pelvic peritoneum.[15] Current radiologic imaging procedures are particularly insensitive to these types of metastatic spread.

Diagnostic methods

Physical examination

The most important prognostic factor for ovarian cancer patients is the clinical stage at which the disease is first discovered.[15] To detect ovarian cancer early when the cure rate is high, the physician should conduct regular and thorough abdominal-pelvic examinations on women at high risk. Early symptoms of ovarian carcinoma depend on the size, weight, and location of the tumor and the presence of bleeding, ascites, torsion, infection, or rupture. Whenever a mass in the ovarian area or an irregular abdominal mass with "shotty" consistency or bilateral pelvic abnormalities are discovered, the physician should investigate.

Other physical signs of ovarian cancer may include nodular hepatomegaly, ascites, palpation of an omental "cake," and fixation and adhesions in the ovarian region. Sall and Stone[16] reported that 37% of patients had abdominal discomfort or pain and 15% experienced vaginal bleeding at the time of diagnosis.

Another large multicenter study[17] confirmed these findings; in addition, this same study found that gastrointestinal symptoms were present in 10% and urinary tract symptoms in 1.5% of patients. A partial list of early- and late-stage signs and symptoms for ovarian cancer is presented in *Table 3*.

Examination should include a careful history and physical examination, including breast and pelvic examination, and a Papanicolaou smear. All pelvic and abdominal masses should be thor-

Table 3
Clinical Characteristics of Patients With Epithelial Ovarian Cancer

Early-stage signs and symptoms
- Vague abdominal pain and discomfort
- Abdominal bloating and swelling
- Other digestive disturbances (dyspepsia, flatulence)

Late-stage signs and symptoms
- Abdominal and pelvic pain
- Abdominal and pelvic masses
- Ascites and distention

Table 4
Recommended Procedures for Evaluating High-risk Patients

- Complete history and physical examination (including pelvic and breast examination)
- Frequent Papanicolaou smears
- Complete blood cell count, chemistry profile, and tumor marker analysis (CA-125)
- Chest roentgenogram
- Intravenous pyelogram
- Transvaginal pelvic ultrasonography
- Computed tomography or magnetic resonance imaging (or both)
- Upper and lower gastrointestinal tract barium studies *
- Upper gastrointestinal tract panendoscopy *

* Order if patient has related signs or symptoms.

oughly investigated. Except for several tumor markers, no chemical, hematologic, or enzymatic abnormalities are found in the early stages of ovarian carcinoma. In advanced disease, however, anemia, hypoalbuminemia, and an elevated lactate dehydrogenase level may be present.[18]

Workup

Table 4 outlines a suggested workup for patients with signs and symptoms suggesting ovarian cancer as well as high-risk patients. Routine screening in high-risk patients with no physical findings that suggest active disease should include the measurement of CA-125 serum antigen levels and transvaginal ultrasonography (TVUS) with color Doppler flow analysis.

The laboratory workup for the high-risk patient (without pelvic or abdominal masses) should include a complete blood cell count, biochemical profile, and measurement of CA-125 serum antigen levels or other ovarian tumor marker measurements. The radiologic workup should include a chest x-ray and TVUS with color Doppler flow analysis.

Optional studies may include intravenous pyelogram, barium enema, computed tomography (CT), or magnetic resonance imaging (MRI) (or both MRI and CT) of the abdomen and pelvis. If the patient has gastrointestinal complaints, an upper gastrointestinal roentgenographic series may be helpful along with small-bowel follow-through or colonoscopy (or both). If the patient has urinary tract symptoms, cystoscopy may be informative. Even with this extensive workup, early-stage ovarian cancer cannot be detected with certainty.

Computed tomography, MRI, and transabdominal ultrasonography (when used alone or in the absence of a pelvic mass) may not always be reliable in revealing the presence of early-stage ovarian cancer.[19] When a pelvic mass is present and palpated, CT, ultrasound, or MRI (or all of these modalities) may be helpful in defining the extent of disease. These diagnostic procedures can detect well-defined ovarian masses, which is of the utmost importance in the preoperative evaluation of an ovarian neoplasm. Findings from these diagnostic procedures enable the surgeon to identify carcinoma of the ovary before the operation so that adequate surgical procedures can be planned.

Figure 1 and *Figure 2* show CT images of the pelvis and upper abdomen in a 49-year-old woman with advanced-stage ovarian cancer. The information obtained from these images significantly influenced the surgical and medical management of the patient.

Transabdominal ultrasonography remains the most common imaging modality for screening patients with adnexal masses.[20, 21] However, it lacks specificity in distinguishing between benign and malignant ovarian lesions.[20] Yet, abdominal ultrasonography is more sensitive than pelvic examination in detecting ovarian abnormalities.

Campbell and colleagues[22] evaluated more than 5000 self-referred asymptomatic women who had undergone transabdominal ultrasonography to screen for early-stage ovarian cancer. Six percent had abnormal sonograms, with five early-stage ovarian carcinomas detected from this group. Only one of these cancers could be detected by bimanual examination. Most of the other sonographic abnormalities found in this study were due to tumor-like conditions, such as simple cysts. This same study demonstrates that early-stage ovari-

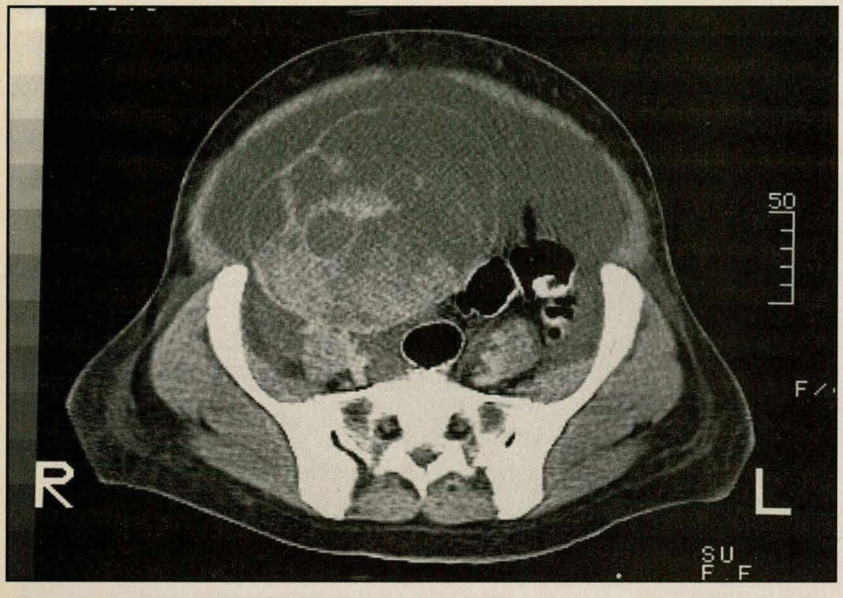

Figure 1. *Contrast-enhanced CT image of pelvis of a 49-year-old woman with abdominal fullness and pelvic mass. The CT image demonstrates ascites and a large pelvic mass with cystic and solid components. At surgery, the patient was found to have advanced ovarian cancer.*

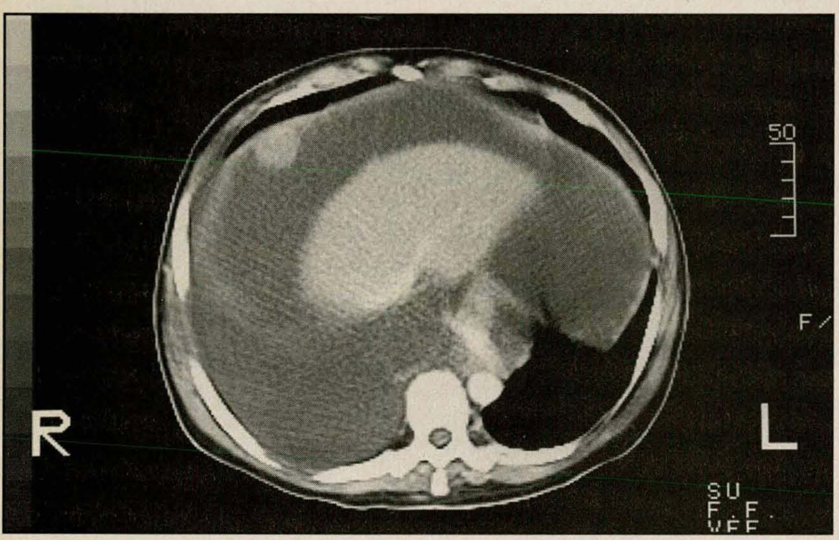

Figure 2. Contrast-enhanced CT image of the upper part of abdomen in this same patient shows 2 × 2-cm metastatic nodule attached to peritoneal surface of right side of diaphragm. Note large pleural effusion on right.

an cancer can be detected using transabdominal ultrasonography, despite a high false-positive rate.[22]

Several other studies[23,24] have also demonstrated that MRI has a high degree of diagnostic specificity for certain types of ovarian masses, such as dermoid cysts and endometriomas. The potential value of MRI for characterizing ovarian epithelial tumors has not been defined completely, but investigations are in progress.[21]

Transvaginal ultrasonography

With its high resolution and proximity to the pelvic organs, TVUS can increase sensitivity and specificity in the diagnosis of pelvic neoplasms.[25] The combination of color Doppler flow with the transvaginal probe strengthens ultrasonography's role in the detection of early-stage ovarian cancer. Studies[26] have shown that TVUS with color Doppler flow analysis is a sensitive means to detect ovarian neoplasms even in women whose ovaries are not readily palpable.

Researchers have found that color Doppler TVUS with spectral waveform analysis can recognize blood flowing throughout the field of view in real time. This combined method can also identify the *direction* of blood flow. Because arterial and venous flow usually occur in opposite directions, this technique assigns a color to each flow. The experienced sonographer can make arterial flow appear on the image as red and venous flow appear as blue.

When increased diastolic flow is seen in a lesion in the ovary, it is most likely due to the neovessels found in tumors. These vessels lack the muscular elements found in normal ovarian vessels. In addition, an increased incidence can be found in the arteriovenous shunting in ovarian malignant tissues. This shunting can be detected by Doppler flow analysis. *Figure 3* illustrates this type of image and flow analysis.

Bourne and associates[27] examined 50 women with TVUS color Doppler flow; 20 of these women had undergone a previous sonogram, the results of which showed an abnormal growth. Primary ovarian cancer was found in 8 of these 20 patients, and 5 patients had stage III or IV ovarian cancer. Three patients had stage IA disease; 7 of the 8 patients with malignancies had a decreased pulsatility index. Kurjak and coauthors[28] evaluated 14,317 asymptomatic women for ovarian carcinoma. They found neovascularization in 6 of 7 patients with stage I ovarian carcinomas. The authors of both of these studies concluded that color Doppler flow enhances the value of TVUS in screening for ovarian cancer.

The use of TVUS without color Doppler flow analysis can yield a number of nonspecific findings similar to those of transabdominal ultrasonography. As such, these techniques cannot distinguish between benign and malignant ovarian lesions and would require further evaluation for all patients with abnormal scan results. The need for further evaluation holds especially true among premenopausal patients. Needed are longitudinal screening studies that combine serum tumor marker assays with color Doppler TVUS in high-risk patients.

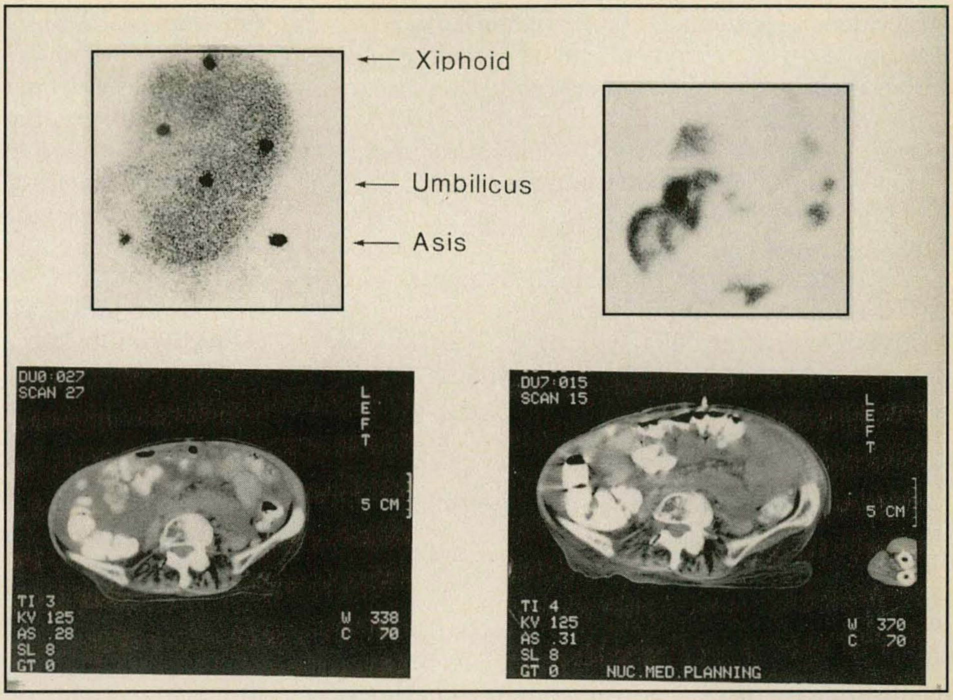

Figure 3. *Transvaginal color Doppler sonographic image includes spectral waveform of postmenopausal woman with malginant ovarian mass, detected with monoclonal antibody ^{111}In-SCN-Bz-DTPA-B72.3 (top left). Right upper corner shows cystic mass with associated neovascularity. Spectral waveform at bottom demonstrates abnormally high diastolic flow pattern, which is a key feature of malignant neovascularity.*

New immunodiagnosis detection systems

Besides the aforementioned modalities, radioimmunoscintigraphic localization of ovarian tumors may also help in diagnosing persistent or early-stage ovarian cancer.

Table 5
Some Common Tumor Markers for Epithelial Ovarian Cancer *

■ CA 125	■ CA 19.9
■ NB/70K	■ Tumor-associated glycoprotein (TAG-72)
■ CEA	■ Placental alkaline phosphatase (PLAP)
■ Human milkfat globules (HMFG)	■ CA 15.3

* See *Seminars in Oncology* 1991;18:177-185 for a more complete list of tumor markers.

Tumor markers

Circulating serum tumor antigens, measured by various "sandwich" tests using radiolabeled murine monoclonal antibody (MoAb) and enzyme immunoassay techniques, can be very helpful in the patient workup. A partial list of these antigens for ovarian cancer can be found in *Table 5*. Numerous monoclonal antibodies have been developed for possible clinical application which have considerable binding affinity for ovarian and other cancer cells, as well as their shed products (antigens). Although tumor markers are useful for the detection of advanced ovarian cancer, their sensitivity and specificity is markedly reduced for early-stage disease. A MoAb that binds exclusively to ovarian cancer cells or their antigens has yet to be produced.

The most extensively studied ovarian-associated antigen is CA 125. A high molecular weight glycoprotein, CA 125 has become a useful serum tumor marker in approximately 80% of patients with epithelial ovarian cancer. Elevated levels are detected in approximately 50% of patients with early-stage disease.[29] Unfortunately, elevated serum CA 125 levels are detected in a number of other pathologic and physiologic conditions,[30] including malignancies arising from the gastrointestinal tract, lung, breast, and hematologic system. The presence of endometriosis, pelvic inflammatory disease, uterine fibroids, and the luteal phase of the menstrual cycle have been reported to cause elevations in serum CA 125 levels. Nevertheless, serum CA 125 levels greater than 65 U/mL have been found in 0.6% of healthy women older than 40 years.[31]

Despite the low specificity of elevated serum CA

125 values in patients without ovarian cancer, this serum assay measurement can be especially useful in therapeutic follow-up, as rising titers correlate well with active disease in 93% of ovarian cancer patients.[32] Besides CA 125, other highly sensitive and specific screening assays (NB/70K, CA 19.9, and Mucin TAG-72) are currently being investigated.[33]

Elevated carcinoembroyonic antigen (CEA) levels are found in approximately 58% of patients with late-stage epithelial cancers, but CEA is not specific and is of limited use in ovarian cancer patients.

Several companies are designing ovarian tumor-marker assays that would use several different MoAbs (MoAb "cocktails") to increase the assays' sensitivity and specificity.

Radioimmunoscintigraphy

The use of radiolabeled MoAbs directed against tumor cells or antigens (or both) for detecting and confirming early-stage or recurrent ovarian cancer (or both) has great promise.[33-54] Monoclonal antibodies can be conjugated with radioisotopes for diagnostic as well as therapeutic purposes. The procedure of external imaging for disclosure of foci of tumor using radiolabeled antibodies is termed *radioimmunoscintigraphy* (RIS). The major indications for the use of RIS in patients with ovarian carcinoma appear to be in the disclosure of intra-abdominal and, in particular, peritoneal spread.[34]

Omental and lymph node metastases, which are particularly difficult to discern by other methods (CT and transabdominal ultrasonography, for example) may be revealed by RIS. As such, RIS may be particularly useful in detecting early-stage ovarian cancer. Many European institutions are presently using RIS in their radiologic workup of patients with ovarian cancer.[41,42,47,53]

Current and investigational applications of radioimmunoscintigraphy

In the United States, multiple reports of ovarian carcinoma detected with RIS have been published in the literature in the past several years.[33-54] These studies have relied on a variety of antibodies, none of which are absolutely specific for ovarian carcinoma. Four of the best-known MoAbs are OC-125, anti-CEA, MoAb B72.3, and the antihuman milk fat globule antibodies (HMFG-1 and HMFG-2). Regardless of the antibody chosen, it is clear that a definite need exists for imaging techniques more sensitive for detecting ovarian cancer than CT. In some series,[44] CT detected ovarian cancer foci in only 40% of the cases.

A variety of radioisotopes has been tagged to MoAbs for imaging purposes, including indium (^{111}In) and isotopes of iodine (^{123}I and ^{131}I). These radioisotopes have been used for labeling of MoAbs, such as SM-3, B.72.3, and OC-125, without destroying their immunologic activity. Several groups[24,34,36,37,39] are working with MoAbs that can be labeled with technetium-99m (Tc-99m). This labeling allows for serial gamma camera imaging of tumors over a relatively short period (hours) after the intravenous or intraperitoneal administration of radiolabeled MoAbs.

Monoclonal antibodies directed against CEA were the first to be used for the imaging of epithelial ovarian tumors.[36,37] Since these initial studies, a variety of other MoAbs (HMFG-2,[38,39] OC-125, B72.3,[40-43] 791T/36,[44] OV-TL3 and SM-3[45,46]) have been successfully used to image ovarian tumors. Many investigators[43,46,52,54] have reported that they were able to image early-stage ovarian cancer sites previously not detected with standard radiologic procedures. The RIS with antibodies to HMFG-2 has resulted in sensitivities ranging from 90% to 100%.[39] Tumor lesions as small as 0.8 cm have been identified with RIS.[47,48]

Placental alkaline phosphatase (PLAP) is expressed on the surface of many epithelial ovarian tumors.[49] With PLAP antibodies tagged with ^{123}I, it is possible to localize ovarian tumor sites in 77% to 90% of patients with either primary or recurrent cancer.[49,50] For radiolabeled MoAb OC-125, the reported detection rate ranges between 72% and 90%.[51]

A recent report[52] examined the sensitivity of ^{111}In-labeled MoAb B72.3 in detecting ovarian cancer in 103 patients. In this study, CT demonstrated a 44% sensitivity rate while the radiolabeled MoAb B72.3 had a sensitivity of 66%. Furthermore, patient management was affected positively in 27% of women when RIS results were used to determine a treatment regimen. Immunologic reactions to radiolabeled MoAb B72.3 in the form of human antimurine antibodies (HAMA) developed in only 32% of the patients; HAMA levels were measured using serum assay techniques. However, no clinically significant side effects were observed as a result of these HAMA formations.[52]

In another phase III clinical study,[43] a sensitivity of 75% was reported with the use of ^{111}In-B72.3, with no false-positive findings and the detection of one surgically confirmed, clinically undetected lesion. *Figure 4* shows an anterior abdominal view of a 72-year-old woman thought to have recurrent ovarian carcinoma. She had received ^{111}In-B72.3 48 hours before this CT scan was taken. The two planar views are separated in time by 6 weeks and by route of administration (intravenous, then intraperitoneal). Corresponding abdominal CTs of the same region are also displayed below the planar images. Very informative, these RIS images influenced patient management, whereas the CT images were nonspecific and therefore not helpful. These RIS findings were confirmed at autopsy.

In an important prospective multicenter French trial[53] of ^{111}In-OC-125, RIS alone had a sensitivity rate of 69% and excluded recurrent ovarian cancer in 47 patients. When combined with CT, RIS had an even higher sensitivity for detecting recurrent tumor sites in early-stage disease ($>$ 80%).

A study[45] involving the use of ^{111}In-OV-TL3 F(ab')$_2$ fragment, detected ovarian tumors in 16 of 17 patients (94%). Of the 45 tumor sites found at surgery, 67% were localized by RIS, whereas CT and ultrasound detected tumors 53% and 23% of the time, respectively.

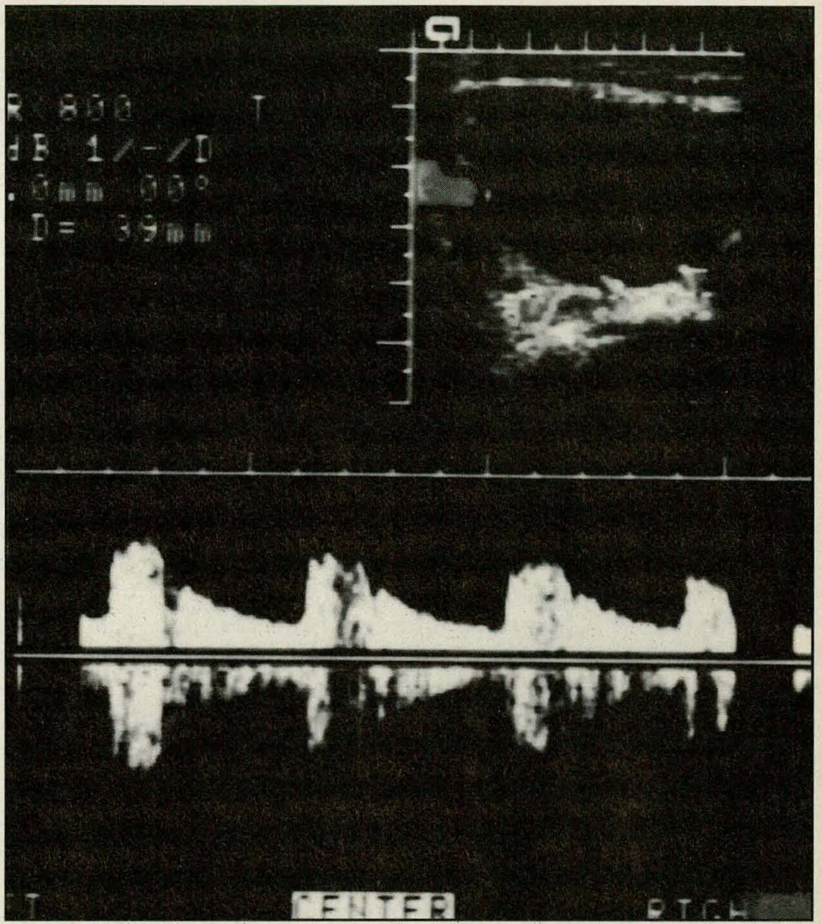

Figure 4. Two anterior planar views of a 72-year-old woman's abdomen with corresponding transaxial CT imaging obtained with the use of ^{111}In-SCN-Bz-B72.3. shows recurrent ovarian cancer. The initial image (top right) was obtained 48 hours after intravenous injection with ^{111}In-SCN-Bz-B72.3. Intense uptake can be seen around the serosal layers of the large and small bowel.

One multicenter clinical trial[53] showed the highest sensitivity for early-stage ovarian cancer of any diagnostic imaging procedure available to date. Specifically, MoAb B72.3 was labeled with ^{111}In by a site-specific process, forming an immunocomplex known as ^{111}In-GYK-DTPA B72.3. (The US Food and Drug Administration [FDA] approved this agent in December 1992.)

Immunoscintigraphy with ^{111}In-GYK-DTPA-B72.3 was successful in identifying occult lesions in 28% of the 108 patients studied. This identification altered the treatment plans and outcomes in these patients. The RIS was also more successful than CT in detecting carcinomatosis. The results of this multicenter trial suggest that whole-body RIS may be a valuable presurgical diagnostic procedure in patients with suspected primary or persistent (recurrent) ovarian carcinoma.

Drawbacks of radiolabeled monoclonal antibodies

The clinical trials conducted to date have enabled investigators to recognize several key problems and obstacles that prevent radiolabeled MoAbs from being the idealized "magic bullet." The percent of injected dose (radiolabeled MoAb) per gram of tumor is extremely low (range 0.01% to 0.1%). This low dose may be related to poor tumor access and the avidity of the available MoAbs presently being tested. Although sufficient for detection, this percent of localization affords ineffective treatment.

Because of this low uptake, the sensitivity of most RIS studies reported to date are influenced both by the size of the tumor ($<$ 1.5 cm) and by the degree of tumor antigen expression. Pretreatment of tumor sites with external beam radiation appears to improve the immunocomplex access to tumor tissues. In addition, studies are now under way that are designed to modulate (increase) the degree of antigen expression on tumor cells using various biologic response modifiers. Preliminary findings are impressive.[55] If the quantity of target antigen on the cell surface can be increased at the time that the radiolabeled immunocomplex is administered, then the detection and treatment of cancer cells can be improved. High-dose (up to 30 mCi) ^{99m}Tc-labeled MoAbs and high-resolution collimators on gamma cameras are also being used to improve spacial resolution.

The reliance on murine MoAbs poses one of the greatest problems of this technology, namely, the human immune system recognizes the murine MoAb as a foreign substance. The response of the patient to the murine antibody in the form of HAMAs poses a problem that is being successfully addressed with the development of "humanized" murine MoAbs (chimeric antibodies) and human MoAbs using molecular genetic techniques. Improvements in conjugation chemistry have also decreased the immunogenicity of murine immunocomplexes and decreased the percent of nonspecific liver uptake.[56] Nonspecific binding of the MoAb to "innocent" tissues will be solved with the production of more specific MoAbs, many of which are now being tested in the United States and Europe.

Impact of radioimmunoscintigraphy on patient management

Radioimmunoscintigraphy has been reported to have its greatest impact on patient management when occult tumor lesions are identified, specifically miliary or microscopic tumor deposits and lymph node metastases. Often, these RIS-identified lesions confirm the findings of other nonimaging diagnostic tests, increasing the physician's confidence that a particular surgical procedure should be undertaken. Other times, these identified lesions can assist in the correct assignment of a benign or malignant pathogenesis to an undiagnosed pelvic mass. Other studies[52,53] have shown that patient benefit is likely when antibody imaging provides new or confirmatory data to supplement the other evaluations that make up the presurgical workup.

The ability of RIS to detect carcinomatosis, often consisting of small peritoneal or serosal implants, represents a significant advantage in this type of imaging. Diffuse miliary disease is quite common in advanced ovarian carcinoma, and other diagnostic tests are limited in their ability to detect these tumor deposits. The ability of RIS to detect carcinomatosis can enhance the management of patients thought to have primary ovarian carcinoma. It can also be used before a second-look laparotomy is performed on patients who have undergone chemotherapy.

In patients evaluated for residual disease after the completion of first-line chemotherapy, the detection of diffuse, subclinical disease could have an effect on patient management. A more limited operative procedure (laparoscopy, for example) may be suggested or second-look procedures and the administration of additional chemotherapy courses (or other avenues of therapy) may be delayed.[55]

False-positive RIS scans were reported to have had a negative impact on the management of 2 of 108 patients who were found to be free of malignant disease at surgery. False-positive RIS images in 11 of these patients were rated as having no effect on their clinical management.[55]

To date, relatively little toxicity has developed in patients participating in the trials using murine MoAbs. Minor allergic reactions such as pruritus or urticaria have been reported, but these reactions are uncommon, occurring in less than 4% of patients receiving this treatment. Besides being well-tolerated, these tests are relatively easy to administer. Most of the radioimmunoconjugates are produced in a kit form so that individual nuclear medicine departments are able to use them.

Future treatment trends

New combination chemotherapy regimens appear to offer promise in the treatment of ovarian cancer. Clinical trials involving high-dose carboplatin and carboplatin/cisplatin are in progress. Decreased myelosuppression with the use of bone marrow-stimulating factors has made an important contribution to these studies.

Drug resistance

Acquired drug resistance is one of the main problems with chemotherapy. Salvage therapy has often been ineffective because of a broad cross-resistance that develops after initial chemotherapy regimens have been completed. However, newer salvage treatments, some of which are listed in *Table 6*, are being used successfully in patients with advanced-stage epithelial ovarian cancer. The same mechanism that operates in acquired resistance may account for intrinsic drug resistance, because approximately one third of patients fail to respond to initial chemotherapy. An increased understanding of the mechanisms involved has led to new clinical strategies aimed at inhibiting biochemical pathways that may be responsible for drug resistance. Drug resistance may also be eliminated with the successful development of non–cross-resistant chemotherapeutic drugs, such as paclitaxel for injection concentrate (Taxol) and sterile ifosfamide (Ifex). Although already approved by the FDA, these relatively new drugs are continuing to be tested in various ways.

Radioimmunotherapy

Recent progress in our understanding of the immunobiology of ovarian cancer has opened a new spectrum of therapeutic approaches. Nonspecific bacterial or synthetic immunoadjuvants (or both) have been studied that can facilitate the host's immune response to specific tumor antigens or augment nonspecific immunity. Intraperitoneal immunotoxins, recombinant purified cytokines (interferons), and lymphokines (interleukins) are now being evaluated in clinical trials.

Monoclonal antibody immunotherapy can involve the administration of unconjugated, or native, intact antibodies as agents for direct killing and as active immunogens (vaccines). These antibodies may also be carriers of drugs, toxins, or isotopes. Toxin and drug immunoconjugates need to be taken up by each cell and then transferred into the cytosol to be effective. In contrast, radiolabeled MoAbs can kill cells from a short distance of the target, without the need for the MoAb conjugate to be internalized. The MoAbs' merely attaching themselves to the tumor-cell surface can kill the tumor cell, as well as several layers of surrounding tumor cells.

Most intact MoAbs can bind to tumor cells for long periods, thus making them desirable as both treatment and imaging agents. These antitumor MoAbs can be labeled with radioisotopes that have a high linear energy transfer (LET) in tissues. Examples of high LET isotopes that are lethal to tumor cells are iodine 131, rhenium 186, and yttrium 90. All of these emit beta particles. Other radioisotopes that can be used therapeutically as antibody conjugates are samarium 152, copper 67, ruthenium 103, lead 100, rhodium 101m, gadolinium 159, holmium 165, and astatine 211.[35,57-59] Data are scarce from the past 10 years on the systemic and intraperitoneal radioimmunotherapy of ovarian cancer. Stewart and colleagues[58] studied MoAb HMFG-1, an antibody directed against a mucin molecule expressed by most ovarian carcinomas. This MoAb was conjugated with yttrium (^{90}Y) and used in a two-phase trial examining the feasibility of intraperitoneal administration for the treatment of localized recurrent ovarian carcinomas.

Myelosuppression was not observed until doses greater than 25 mCi were administered. Despite the intracavitary approach used, systemic toxicity was observed. This toxicity was due to absorption of the radioisotope into the blood, with subsequent deposition in bone and bone marrow. In an attempt to prevent binding of this free ^{90}Y to bone, later patients received intravenous infusions of ethylenediaminetetraacetic acid, a metal chelator. One of the 14 patients with measurable tumor had a partial response.

Table 6
Newer Salvage Treatments for Patients With Advanced Epithelial Ovarian Cancer

- Intraperitoneal chemotherapy
- External beam radiation therapy
- Intraperitoneal administration of P-32 radiocolloid
- Intraperitoneal administration of biologic response modifiers

The most extensive experience published in this area to date is that of Stewart and colleagues[59,60] and, separately, by Epenetos and coauthors.[61] Of 24 patients treated with ^{131}I-antitumor MoAb, 8 patients with large (> 2 cm) bulk tumors did not respond to treatment. Sixteen patients with smaller tumor volumes (< 2 cm) had partial or complete responses. Using a recently developed chelation procedure, these same researchers reported that ^{90}Y-labeled MoAbs resulted in a 30% remission rate.[60,61]

Some partial remissions have also been observed after intraperitoneal radiation therapy, but too few patients have been treated to make any reasonable conclusions at present. Although the results of initial studies are encouraging, more data are needed to determine if this type of adjuvant therapy will have a significant effect on patient outcome.

Comment

Clearly, early diagnosis of ovarian cancer is essential to improve patients' survival rates. Clinicians should identify those patients who are at an increased risk and continue close follow-up. At present, no standard screening or radiologic procedures exist. Therefore, high-risk patients should be seen often and undergo routine pelvic examinations as well as periodic TVUS with color Doppler flow analysis and measurements of serum tumor markers. High-risk patients should consider enrollment in familial cancer registries as well as cancer centers with well-run surveillance programs. Genetic counseling, as well as prophylactic oophorectomy, should be presented as treatment options to the high-risk patient.

Monoclonal antibody technology is presently being used in the workup of patients with ovarian cancer in some medical centers. Diagnostic scanning of ovarian cancer patients with isotope-tagged antibodies will become more routine in the coming decade. Patients should be informed about the many radioimmunoscintigraphic imaging and therapy protocols that are now being offered in major clinical centers. Use of the antiovarian RIS agent (OncoScint OV, Cytogen Corporation, Princeton, NJ) should be considered in any hospital with a well-run nuclear medicine department.

The major indications for using RIS in diagnosing and treating ovarian carcinoma appear to be the disclosure of intra-abdominal and, in particular, peritoneal spread. Omental and lymph node metastases, which are particularly difficult to discern during early-stage disease by other methods, may be revealed with RIS. As with any new procedure, the essential question is whether RIS provides accurate and specific diagnostic information that will positively influence patient management and outcome.

Prospective studies indicate that the functional imaging characteristics of RIS are a good complement to the more conventional, anatomically oriented radiologic modalities (CT and MRI). As more tumor-specific markers become available and our patient selection criteria improve, imaging and possible adjuvant radioimmunotherapy may become important tools in the detection and treatment of this disease.

Progress in the development of new and more effective chemotherapeutic agents during the past 10 years has been slow. Yet, overall response rates, complete remission rates, and disease-free intervals have continued to increase. Also, the treatment of patients with early-stage disease has become more specific. Many patients can now be spared the toxicities of chemotherapy while having a greater-than-90% probability of being cured.

Disappointingly, however, the prolongation of overall survival rate has not improved. The vast majority of patients with advanced ovarian cancer are still dying of their disease.

The combination of cisplatin and cyclophosphamide is currently regarded as the regimen of choice for first-line treatment of advanced-stage ovarian cancer. Yet, a significant number of these patients relapse. Several treatment alternatives are currently under investigation and include the cisplatin analogue carboplatin and the the antineoplastic agent paclitaxel for injection concentrate. High-dose platinum regimens and intraperitoneal instillation of chemotherapy agents are other potentially useful experimental approaches to the management of ovarian cancer. Therapeutic trials of antiovarian carcinoma antibodies with high LET radionuclides attached are ongoing at several major medical centers. It is likely that radiolabeled antibody treatment will have its greatest impact on low-bulk, accessible disease.

Cautious optimism surrounds the prospect that in the next decade significant diagnostic and treatment breakthroughs will result from our increased understanding of the biology and immunology of ovarian cancer. New insights into the pathogenesis of ovarian carcinoma and the mechanisms associated with multi-drug resistance are also a cause for optimism.

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