Of all gynecologic malignancies, ovarian cancer continues to have the highest mortality and is the most difficult to diagnose. In the United States female population, ovarian cancer ranks fifth in absolute mortality among cancer related deaths (13,000/yr). In most reported cases, ovarian cancer, when first diagnosed is in stages III or IV in about 60 to 70% of patients which further complicates treatment of the disease (Barber, 3).

Early detection in ovarian cancer is hampered by the lack of appropriate tumor markers and clinically, most patients fail to develop significant symptoms until they reach advanced stage disease. The characteristics of ovarian cancer have been studied in primary tumors and in established ovarian tumor cell lines which provide a reproducible source of tumor material. Among the major clinical problems of ovarian cancer, malignant progression, rapid emergence of drug resistance, and associated cross-resistance remain unresolved. Ovarian cancer has a high frequency of metastasis yet generally remains localized within the peritoneal cavity. Tumor development has been associated with aberrant, dysfunctional expression and/or mutation of various genes. This can include oncogene overexpression, amplification or mutation, aberrant tumor suppressor expression or mutation. Also, subversion of host antitumor immune responses may play a role in the pathogenesis of cancer (Sharp, 77).

Ovarian clear cell adenocarcinoma was first described by Peham in 1899 as "hypernephroma of the ovary" because of its resemblance to renal cell carcinoma. By 1939, Schiller noted a histologic similarity to mesonephric tubules and classified these tumors as "mesonephromas." In 1944, Saphir and Lackner described two cases of "hypernephroid carcinoma of the ovary" and proposed "clear cell" adenocarcinoma as an alternative term. Clear cell tumors of the ovary are now generally considered to be of mullerian and in the genital tract of mullerian origin.
A number of examples of clear cell adenocarcinoma have been reported to arise from the epithelium of an endometriotic cyst (Yoonessi, 289). Occasionally, a renal
cell carcinoma metastasizes to the ovary and may be confused with a primary clear cell adenocarcinoma.

Ovarian clear cell adenocarcinoma (OCCA) has been recognized as a distinct histologic entity in the World Health Organization (WHO) classification of ovarian tumors since 1973 and is the most lethal ovarian neoplasm with an overall five year
survival of only 34% (Kennedy, 342). Clear cell adenocarcinoma, like most ovarian cancers, originates from the ovarian epithelium which is a single layer of cells found on
the surface of the ovary. Patients with ovarian clear cell adenocarcinoma are typically
above the age of 30 with a median of 54 which is similar to that of ovarian epithelial
cancer in general. OCCA represents approximately 6% of ovarian cancers and bilateral
ovarian involvement occurs in less that 50% of patients even in advanced cases.

The association of OCCA and endometriosis is well documented (De La Cuesta, 243). This was confirmed by Kennedy et al who encountered histologic or intraoperative
evidence of endometriosis in 45% of their study patients. Transformation from endometriosis to clear cell adenocarcinoma has been previously demonstrated in sporadic cases but was not observed by Kennedy et al. Hypercalcemia occurs in a

significant percentage of patients with OCCA. Patients with advanced disease are more typically affected than patients with nonmetastatic disease. Patients with OCCA are also more likely to have Stage I disease than are patients with ovarian epithelial cancer in general (Kennedy, 348).

Histologic grade has been useful as an initial prognostic determinant in some studies of epithelial cancers of the ovary. The grading of ovarian clear cell adenocarcinoma has been problematic and is complicated by the multiplicity of histologic patterns found in the same tumor. Similar problems have been found in attempted grading of clear cell adenocarcinoma of the endometrium (Disaia, 176). Despite these problems, tumor grading has been attempted but has failed to demonstrate prognostic significance. However, collected data suggest that low mitotic activity and a predominance of clear cells may be favorable histologic features (Piver, 136).

Risk factors for OCCA and ovarian cancer in general are much less clear than for other genital tumors with general agreement on two risk factors: nulliparity and family history. There is a higher frequency of carcinoma in unmarried women and in married women with low parity. Gonadal dysgenesis in children is associated with a higher risk of developing ovarian cancer while oral contraceptives are associated with a decreased risk. Genetic and candidate host genes may be altered in susceptible families. Among those currently under investigation is BRCA1 which has been associated with an increased susceptibility to breast cancer. Approximately 30% of ovarian adenocarcinomas express high levels of HER-2/neu oncogene which correlates with a poor prognosis (Altcheck, 375-376). Mutations in host tumor suppresser gene p53 are found in 50% of ovarian carcinomas. There also appears to be a racial predilection, as the vast majority of cases are seen in Caucasians (Yoonessi, 295).

Considerable variation exists in the gross appearance of ovarian clear cell adenocarcinomas and they are generally indistinguishable from other epithelial ovarian carcinomas. They could be cystic, solid, soft, or rubbery, and may also contain hemorrhagic and mucinous areas (O'Donnell, 250). Microscopically, clear cell carcinomas are characterized by the presence of variable proportions of clear and hobnail cells. The former contain abundant clear cytoplasm with often centrally located nuclei, while the latter show clear or pink cytoplasm and bizarre basal nuclei with atypical cytoplasmic intraluminal projections. The cellular arrangement may be tubulo acinar, papillary, or solid, with the great majority displaying a mixture of these patterns. The

hobnail and clear cells predominate with tubular and solid forms, respectively (Barber, 214).

Clear cell adenocarcinoma tissue fixed with alcohol shows a high cytoplasmic glycogen content which can be shown by means of special staining techniques. Abundant extracellular and rare intracellular neutral mucin mixed with sulfate and carboxyl group is usually present. The clear cells are recognized histochemically and ultrastructurally (short and blunt microvilli, intercellular tight junctions and desmosomes, free ribosomes, and lamellar endoplasmic reticulum). The ultrastructure of hobnail and clear cells resemble those of the similar cells seen in clear cell carcinomas of the remainder of the female genital tract (O'Brien, 254). A variation in patterns of histology is seen among these tumors and frequently within the same one.

Whether both tubular components with hobnail cells and the solid part with clear cells are required to establish a diagnosis or the presence of just one of the patterns is sufficient has not been clearly established. Fortunately, most tumors exhibit a mixture of these components. Benign and borderline counterparts of clear cell ovarian adenocarcinomas are theoretical possibilities. Yoonessi et al reported that nodal metastases could be found even when the disease appears to be grossly limited to the pelvis (Yoonessi, 296). Examination of retroperitoneal nodes is essential to allow for more factual staging and carefully planned adjuvant therapy.

Surgery remains the backbone of treatment and generally consists of removal of the uterus, tubes and ovaries, possible partial omentectomy, and nodal biopsies. The effectiveness and value of adjuvant radiotherapy and chemotherapy has not been clearly demonstrated. Therefore, in patients with unilateral encapsulated lesions and histologically proven uninvolvement of the contralateral ovary, omentum, and biopsied nodes, a case can be made for (a)no adjuvant therapy after complete surgical removal and (b) removal of only the diseased ovary in an occasional patient who may be young and desirous of preserving her reproductive capacity (Altchek, 97). In the more adv- anced stages, removal of the uterus, ovaries, omentum, and as much tumor as possible followed by pelvic radiotherapy (if residual disease is limited to the pelvis) or chemotherapy must be considered. The chemotherapeutic regimens generally involve adriamycin, alkylating agents, and cisPlatinum containing combinations (Barber, 442).

OCCA is of epithelial origin and often contains mixtures of other epithelial tumors such as serous, mucinous, and endometrioid. Clear cell adenocarcinoma is characterized

by large epithelial cells with abundant cytoplasm. Because these tumors sometimes occur in association with endometriosis or endometrioid carcinoma of the ovary and resemble clear cell carcinoma of the endometrium, they are now thought to be of mullerian duct origin and variants of endometrioid adenocarcinoma. Clear cell tumors of the ovary can be predominantly solid or cystic. In the solid neoplasm, the clear cells are arranged in sheets or tubules. In the cystic form, the neoplastic cells line the spaces. Five-year survival is approximately 50% when these tumors are confined to the ovaries, but these tumors tend to be aggressive and spread beyond the ovary which tends to make 5-year survival highly unlikely (Altchek, 416).

Some debate continues as to whether clear cell or mesonephroid carcinoma is a separate clinicopathological entity with its own distinctive biologic behavior and natural history or a histologic variant of endometrioid carcinoma. In an effort to characterize clear cell adenocarcinoma, Jenison et al compared these tumors to the most common of the epithelial malignancies, the serous adenocarcinoma (SA). Histologically determined endometriosis was strikingly more common among patients with OCCA than with SA. Other observations by Jenison et al suggest that the biologic behavior of clear cell adenocarcinoma differs from that of SA. They found Stage I tumors in 50% of the observed patient population as well as a lower incidence of bilaterality in OCCA (Jenison, 67-69). Additionally, it appears that OCCA is characteristically larger than SA, possibly explaining the greater frequency of symptoms and signs at presentation.

Risk Factors

There is controversy regarding talc use causing ovarian cancer. Until recently, most talc powders were contaminated with asbestos. Conceptually, talcum powder on the perineum could reach the ovaries by absorption through the cervix or vagina. Since talcum powders are no longer contaminated with asbestos, the risk is probably no longer important (Barber, 200). The high fat content of whole milk, butter, and meat products has been implicated with an increased risk for ovarian cancer in general.

The Centers for Disease Control compared 546 women with ovarian cancer to 4,228 controls and reported that for women 20 to 54 years of age, the use of oral contraceptives reduced the risk of ovarian cancer by 40% and the risk of ovarian cancer decreased as the duration of oral contraceptive use increased. Even the use of oral contraceptives for three months decreased the risk. The protective effect of oral contraceptives is to reduce the relative risk to 0.6 or to decrease the incidence of disease by 40%. There is a decreased risk as high as 40% for women who have had four or more children as compared to nulliparous women. There is an increase in the incidence

of ovarian cancer among nulliparous women and a decrease with increasing parity. The "incessant ovulation theory" proposes that continuous ovulation causes repeated trauma to the ovary leading to the development of ovarian cancer. Incidentally, having two or more abortions compared to never having had an abortion decreases one's risk of developing ovarian cancer by 30% (Coppleson, 25-28).

Etiology

It is commonly accepted that cancer results from a series of genetic alterations that disrupt normal cellular growth and differentiation. It has been proposed that genetic changes causing cancer occur in two categories of normal cellular genes, proto-oncogenes and tumor suppressor genes. Genetic changes in proto-oncogenes facilitate the transformation of a normal cell to a malignant cell by production of an altered or overexpressed gene product. Such genetic changes include mutation, translocation, or amplification of proto-oncogenes Tumor suppressor genes are proposed to prevent cancer. Inactivation or loss of these genes contributes to development of cancer by the lack of a functional gene product. This may require mutations in both alleles of a tumor suppressor gene. These genes function as regulatory inhibitors of cell proliferation, such as a DNA transcription factor, or a cell adhesion molecule. Loss of these functions could result in abnormal cell division or gene expression, or increased ability of cells in tissues to detach. Cancer such as OCCA most likely results from the dynamic interaction of several genetically altered proto-oncogenes and tumor suppressor genes (Piver, 64-67).

Until recently, there was little evidence that the origin of ovarian was genetic. Before 1970, familial ovarian cancer had been reported in only five families. A familial cancer registry was established at Roswell Park Cancer Institute in 1981 to document the number of cases occurring in the United States and to study the mode of inheritance. If a genetic autosomal dominant transmission of the disease can be established, counseling for prophylactic oophorectomy at an appropriate age may lead to a decrease in the death rate from ovarian cancer in such families.

The registry at Roswell Park reported 201 cases of ovarian cancer in 94 families in 1984. From 1981 through 1991, 820 families and 2946 cases had been observed. Familial ovarian cancer is not a rare occurrence and may account for 2 to 5% of all cases of ovarian cancer. Three conditions that are associated with familial ovarian cancer are (1) site specific, the most common form, which is restricted to ovarian cancer, and

(2)
breast/ovarian cancer with clustering of ovarian and breast cases in extended pedigrees
(Altchek, 229-230). One characteristic of inherited ovarian cancer is that it occurs at a
significantly younger age than the non-inherited form.

Cytogenetic investigations of sporadic (non-inherited) ovarian tumors have revealed
frequent alterations of chromosomes 1,3,6, and 11. Many proto-oncogenes have been mapped to these chromosomes, and deletions of segments of chromosomes (particularly 3p and 6q) in some tumors is consistent with a role for loss of tumor suppressor genes.
Recently, a genetic linkage study of familial breast/ovary cancer suggested linkage of
disease susceptibility with the RH blood group locus on chromosome 1p.

Allele loss involving chromosomes 3p and 6q as well as chromosomes 11p, 13q, and
17 have been frequently observed in ovarian cancers. Besides allele loss, point mutations
have been identified in the tumor suppressor gene p53 located on chromosome17p13.
Deletions of chromosome 17q have been reported in sporadic ovarian tumors suggesting
a general involvement of this region in ovarian tumor biology. Allelic loss of MYB and
ESR genes map on chromosome 6q near the provisional locus for FUCA2, the locus for a-L-fucosidase in serum. Low activity of a-L-fucosidase in serum is more prevalent in
ovarian cancer patients. This suggests that deficiency of a-L-fucosidase activity in serum
may be a hereditary condition associated with increased risk for developing ovarian cancer. This together with cytogenetic data of losses of 6q and the allelic losses at 6q
point to the potential importance of chromosome 6q in hereditary ovarian cancer (Altchek, 208-212).

Activation of normal proto-oncogenes by either mutation, translocation, or gene
amplification to produce altered or overexpressed products is believed to play an important role in the development of ovarian tumors. Activation of several proto-oncogenes (particularly K-RAS, H-RAS, c-MYC, and HER-2/neu) occurs in ovarian tumors. However, the significance remains to be determined. It is controversial as to
whether overexpression of the HER-2/neu gene in ovarian cancer is associated with poor
prognosis. In addition to studying proto-oncogenes in tumors, it may be beneficial to
investigate proto-oncogenes in germ-line DNA from members of families with histories
of ovarian cancer (Barber, 323-324). It is questionable whether inheritance or rare
alleles of the H-RAS proto-oncogene may be linked to susceptibility to ovarian cancers.

Diagnosis and Treatment

The early diagnosis of ovarian cancer is a matter of chance and not a triumph of
scientific approach. In most cases, the finding of a pelvic mass is the only

available method of diagnosis, with the exception of functioning tumors which may manifest endocrine even with minimal ovarian enlargement. Symptomatology includes vague abdominal discomfort, dyspepsia, increased flatulence, sense of bloating, particularly after ingesting food, mild digestive disturbances, and pelvic unrest which may be present for several months before diagnosis (Sharp, 161-163).

There are a great number of imaging techniques that are available. Ultrasounds, particularly vaginal ultrasound, has increased the rate of pick-up of early lesions, particularly when the color Doppler method is used. Unfortunately, vaginal sonography and CA 125 have had an increasing number of false positive examinations. Pelvic findings are often minimal and not helpful in making a diagnosis. However, combined with a high index of suspicion, this may alert the physician to the diagnosis.

These pelvic signs include:

- Mass in the ovarian area
- Relative immobility due to fixation of adhesions
- Irregularity of the tumor
- Shotty consistency with increased firmness
- Tumors in the cul-de-sac described as a handful of knuckles
- Relative insensitivity of the mass
- Increasing size under observation
- Bilaterality (70% for ovarian carcinoma versus 5% for benign cases) (Barber, 136)

Tumor markers have been particularly useful in monitoring treatment, however, the markers have and will probably always have a disadvantage in identifying an early tumor. To date, only two, human gonadotropin (HCG) and alpha fetoprotein, are known to be sensitive and specific. The problem with tumor markers as a means of making a diagnosis is that a tumor marker is developed from a certain volume of tumor. By that time it is no longer an early but rather a biologically late tumor (Altchek, 292).

Many reports have described murine monoclonal antibodies (MAbs) as potential tools for diagnosing malignant ovarian tumors. Yamada et al attempted to develop a MAb that can differentiate cells with early malignant change from adjacent benign tumor cells in cases of borderline malignancy. They developed MAb 12C3 by immunizing mice with a cell line derived from a human ovarian tumor. The antibody reacted with human ovarian carcinomas rather than with germ cell tumors. MAb 12C3 stained 67.7% of ovarian epithelial malignancies, but exhibited an extremely low reactivity with other malignancies. MAb 12C3 detected a novel antigen whose distribution in normal tissue is restricted. According to Yamada et al, MAb 12C3 will serve as a powerful new tool for the histologic detection of early malignant changes in borderline epithelial neoplasms. MAb 12C3 may also be useful as a targeting agent for cancer chemotherapy (Yamada, 293-294).

Currently there are several serum markers that are available to help make a diagnosis. These include CA 125, CEA, DNB/70K, LASA-P, and serum inhibin. Recently the urinary gonadotropin peptide (UCP) and the collagen-stimulating factor have been added. Although the tumor markers have a low specificity and sensitivity, they are often used in screening for ovarian cancer. A new tumor marker CA125-2 has greater specificity than CA125. In general, tumor markers have a very limited role in screening for ovarian cancer.

The common epithelial cancer of the ovary is unique in killing the patient while being, in the vast majority of the cases, enclosed in the anatomical area where it initially developed: the peritoneal cavity. Even with early localized cancer, lymph node metastases are not rare in the pelvic or aortic areas. In most of the cases, death is due to intraperitoneal proliferation, ascites, protein loss and cachexia. The concept of debulking or cytoreductive surgery is currently the dominant concept in treatment.

The first goal in debulking surgery is inhibition of debulking surgery is inhibition of the vicious cycle of malnutrition, nausea, vomiting, and dyspepsia commonly found in patients with mid to advanced stage disease. Cytoreductive surgery enhances the efficiency of chemotherapy as the survival curve of the patients whose largest residual mass size was, after surgery, below the 1.5 cm limit is the same as the curve of the patients whose largest metastatic lesions were below the 1.5 cm limit at the outset (Altchek, 422-424).

The aggressiveness of the debulking surgery is a key question surgeons must face when treating ovarian cancers. The debulking of very large metastatic masses makes no sense from the oncologic perspective. As for extrapelvic masses the debulking, even if more acceptable, remains full of danger and exposes the patient to a heavy handicap. For these reasons the extra-genital resections have to be limited to lymphadenectomy, omentectomy, pelvic abdominal peritoneal resections and rectosigmoid junction resection. That means that stages IIB and IIC and stages IIIA and IIB are the only true indications for extrapelvic cytoreductive surgery. Colectomy, ileectomy, splenectomy, segmental hepatectomy are only exceptionally indicated if they allow one to perform a real optimal resection. The standard cytoreductive surgery is the total hysterectomy with bilateral salpingoophorectomy. This surgery may be done with aortic and pelvic lymph node sampling, omentectomy, and, if necessary, resection of the rectosigmoidal junction (Barber. 182-183).

The concept of administering drugs directly into the peritoneal cavity as therapy of ovarian cancer was attempted more than three decades ago. However, it has only been within the last ten years that a firm basis for this method of drug delivery has become established. The essential goal is to expose the tumor to higher concentrations of drug for longer periods of time than is possible with systemic drug delivery. Several agents have been examined for their efficacy, safety and pharmacokinetic advantage when administered via the peritoneal route.

Cisplatin has undergone the most extensive evaluation for regional delivery. Cisplatin reaches the systemic compartment in significant concentrations when it is administered intraperitoneally. The dose limiting toxicity of intraperitoneally administered cisplatin is nephrotoxicity, neurotoxicity and emesis. The depth of penetration of cisplatin into the peritoneal lining and tumor following regional delivery is only 1 to 2 mm from the surface which limits its efficacy. Thus, the only patients with ovarian cancer who would likely benefit would be those with very small residual tumor volumes. Overall, approximately 30 to 40% of patients with small volume residual ovarian cancer have been shown to demonstrate an objective clinical response to cisplatin-based locally administered therapy with 20 to 30% of patients achieving a surgically documented complete response. As a general rule, patients whose tumors have demonstrated an inherent resistance to cisplatin following systemic therapy are not considered for treatment with platinum-based intraperitoneal therapy (Altchek, 444-446).

In patients with small volume residual disease at the time of second look laparotomy, who have demonstrated inherent resistance to platinum-based regimens, alternative intraperitoneal treatment programs can be considered. Other agents include mitoxantrone, and recombinant alpha-interpheron. Intraperitoneal mitoxanthone has been shown to have definite activity in small volume residual platinum-refractory ovarian cancer. Unfortunately, the dose limiting toxicity of the agent is abdominal pain and adhesion formation, possibly leading to bowel obstruction. Recent data suggests the local toxicity of mitoxanthone can be decreased considerably by delivering the agent in microdoses.

Ovarian tumors may have either intrinsic or acquired drug resistance. Many mechanisms of drug resistance have been described. Expression of the MDR1 gene that encodes the drug efflux protein known as p-glycoprotein, has been shown to confer the characteristic multi-drug resistance to clones of some cancers. The most widely considered definition of platinum response is response to first-line platinum treatment and disease free interval. Primary platinum resistance may be defined as any progression on treatment. Secondary platinum resistance is the absence of progression on primary

platinum-based therapy but progression at the time of platinum retreatment for relapse
(Sharp, 205-207).

Second-line chemotherapy for recurrent ovarian cancer is dependent on preferences of
both the patient and physician. Retreatment with platinum therapy appears to offer significant opportunity for clinical response and palliation but relatively little hope for
long-term cure. Paclitaxel (trade name: Taxol), a prototype of the taxanes, is cytotoxic
to ovarian cancer. Approximately 20% of platinum failures respond to standard doses of
paclitaxel. Studies are in progress of dose intensification and intraperitoneal administration (Barber, 227-228). This class of drugs is now thought to represent an
active addition to the platinum analogs, either as primary therapy, in combination with
platinum, or as salvage therapy after failure of platinum.

In advanced stages, there is suggestive evidence of partial responsiveness of OCCA to
radiation as well as cchemotherapy, adriamycin, cytoxan, and cisPlatinum-containing combinations (Yoonessi, 295). Radiation techniques include intraperitoneal radioactive
gold or chromium phosphate and external beam therapy to the abdomen and pelvis. The
role of radiation therapy in treatment of ovarian canver has diminished in prominence as
the spread pattern of ovarian cancer and the normal tissue bed involved in the treatment
of this neoplasm make effective radiation therapy difficult. When the residual disease
after laparotomy is bulky, radiation therapy is particularly ineffective. If postoperative
radiation is prescribed for a patient, it is important that theentire abdomen and pelvis are
optimally treated to elicit a response from the tumor (Sharp, 278-280).

In the last few decades, the aggressive attempt to optimize the treatment of
ovarian clear cell adenocarcinoma and ovarian cancer in general has seen remarkable improvements in the response rates of patients with advanced stage cancer without dramatically improving long-term survival. The promises of new drugs with activity when platinum agents fail is encouraging and fosters hope that, in the decades to come,
the endeavors of surgical and pharmacoogical research will make ovarian cancer an easily treatable disease.

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