

BORDERLINE OVARIAN CANCER: A CASE STUDY OF FIFTEEN
PATIENTS TREATED AT MOUNTAIN STATES TUMOR INSTITUTE
IN BOISE, IDAHO

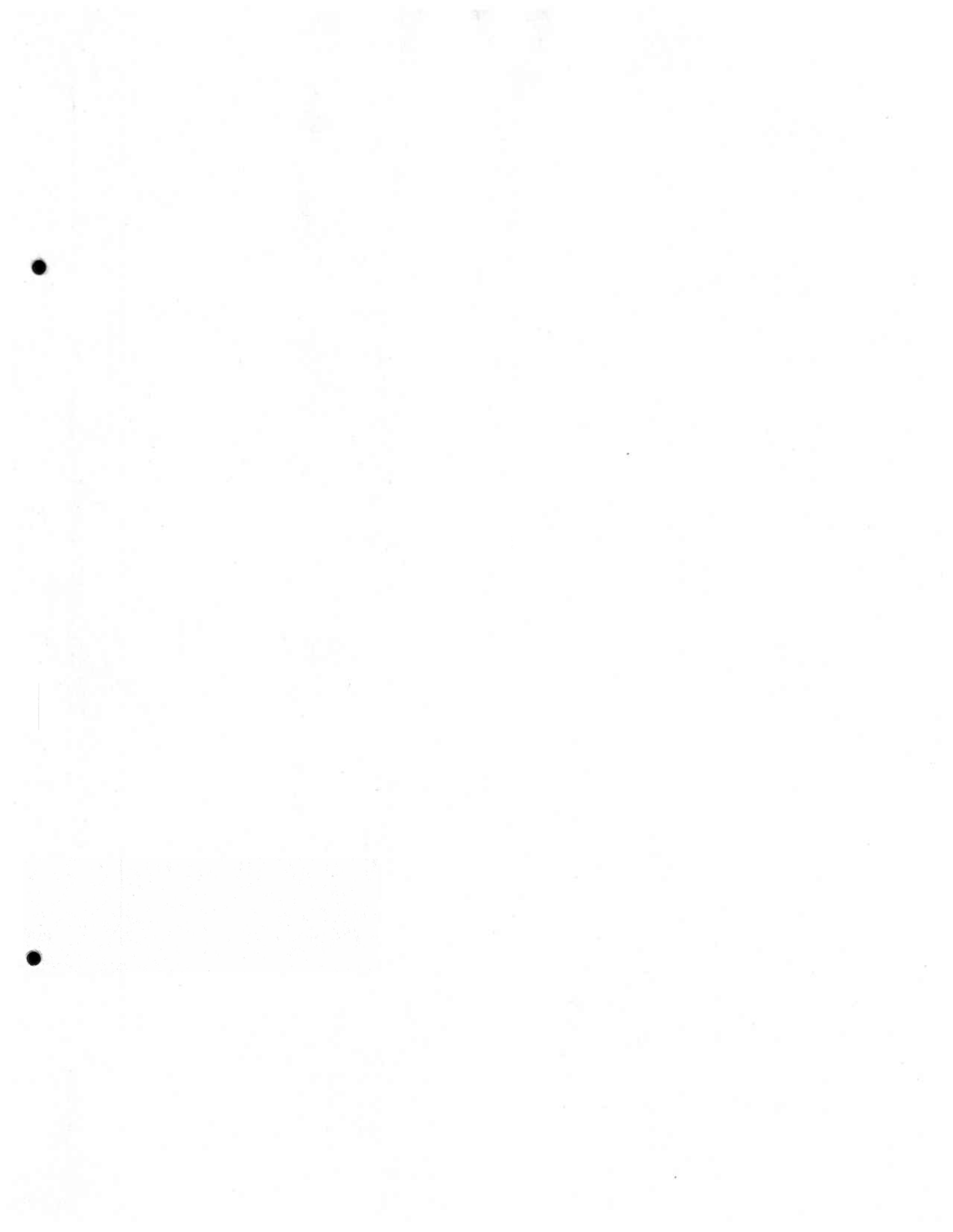
Submitted in Partial Fulfillment of the Requirements
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at Carroll College, Helena, Montana

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ABSTRACT

Over a fourteen-year period, 1970-1984, 213 patients with malignant ovarian tumors were seen at Mountain States Tumor Institute in Boise, Idaho. Of these, fifteen (7%) were pathologically diagnosed with ovarian tumors of borderline malignancy. Seven of the cases were Stage I, two were Stage II, six were Stage III, and no Stage IV patients were diagnosed. Ten patients were diagnosed as serous cystadenocarcinomas of borderline malignancy and five were diagnosed as borderline mucinous tumors. A varied regimen of both chemotherapy and radiation treatment was administered to the patients. Twelve patients received adjuvant therapy following surgery, six received chemotherapy. Of these, two were Stage I and four were Stage III. Six patients were administered radiation therapy (of these two were Stage I, two were Stage II, and two were Stage III). Three patients received no treatment, all were Stage I. The mean age for all borderline patients was 40.1 years. Seven had bilateral tumors, while eight were unilateral. Four patients had second look laparotomies following chemotherapy. Only one had recurrent disease; the other three showed no evidence of cancer. The mean follow-up was 73 months and the five-year survival rate was 100%.

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INTRODUCTION

Each year, approximately 18,000 women in the United States are diagnosed with ovarian cancer. Of these cases, less than ten percent are diagnosed ovarian tumors of borderline malignancy. These neoplasms are distinguished from other tumor types by their neoplastic epithelial cells, detached cellular clusters from sites of origin, increased mitotic activity, nuclear abnormalities and, most importantly, lack of stromal invasion (Devita et al., 1982).

Because such a small number of women are diagnosed with borderline ovarian tumors (BOT) each year, there is relatively little information dealing with this subject. The purpose of this paper is to present a concise report on fifteen cases of BOT which were diagnosed and treated at Mountain States Tumor Institute, Boise, Idaho. The results which were obtained dealing with follow-up and survival will be compared to other authors in an attempt to learn more about this perplexing disease.

LITERATURE REVIEW

Properties of Borderline Ovarian Tumors

Borderline ovarian tumors (BOT) occur in less than 10% (Nikrui, 1981) of all malignant ovarian tumors (MOT). The World Health Organization defines BOT as tumors that have some but not all of the morphological features of malignancy (Nikrui, 1981). To qualify as a BOT, the tumor must meet the following criteria:

1. Multiple extensively branching papillae with fibrous cores.
2. Stratification of the papillae, three layers or less.
3. Exfoliation of cellular clusters.
4. Slightly or moderately atypical nuclei which are enlarged, irregular and hyperchromatic.
5. Nucleoli, if present, are usually small.
6. Low mitotic activity.
7. No evidence of invasion of stroma (Nikrui, 1981).

Lack of stromal invasion by the tumor is the major characteristic used to diagnose BOT (Anderson, et al., 1983; Baak, et al., 1981; Creasman, et al., 1982; Devita, et al., 1982). Stenback in his study gives a good description of a BOT.

Invasion of the epithelium were common with separate epithelial cysts sometimes scattered throughout the ovary. The epithelium covering the papillae was frequently stratified into several layers with a tendency of piling up causing exfoliation of cellular clusters from the papillae. The surface structures were not as well developed in borderline ovarian tumors as in benign tumors. Most of the epithelial cells were nonciliated low columnar or cuboidal cells with an irregular surface. The surface cells, slightly irregular in shape and size, were covered by microvilli. The ciliated cells were not as numerous as in the benign. Frequently, focal denuded areas with histological atypias were seen (Stenback, 1981).

Pathogenesis

Pathogenically, BOT develop in the following manner. The ovary arises from three primordia: the primary germ cells, which migrate into the genital ridge; the mesenchyme of the ventromedial aspects of the mesonephroi adjacent to the root of the mesentary; and the coelomic epithelium overlying this mesenchyme. The last two components form the genital ridge. The origin of epithelial carcinomas appears to be from the serosal mesothelial layer of the gonads or the paramesonephric coelomic epithelium. The serosal layer is differentiated from the coelomic epithelium which overlies the mesenchyme of the genital ridge. It is the paramesonephric coelomic epithelium that develops into the mullerian duct which later differentiates into the fallopian tubules, the squamous epithelium of the vagina, and the epithelium of the endometrium and endocervix. The paramesonephric epithelium has a multipotential capability of developing into endometrioid, serous, or

mucinous epithelium which line ovarian tumors. Therefore, the common epithelial tumors in the ovary may give rise to malignancies having the characteristics of these three epithelial types. In other words, as the germ cells, which differentiate into the ovaries, migrate down to the genital ridge they must pass through the paramesonephric coelomic epithelium (PCE) picking up PCE cells which may later form ovarian tumors (Devita, et al., 1982; Gray et al., 1972).

Metastasis

Once BOT are formed, metastasis occurs at a slower rate than in true malignant tumors (Devita, et al., 1982). Borderline tumor cell metastasis may follow two pathways: surface implantation or lymphatic dissemination. The most common mechanism of spread is intraperitoneal dissemination or surface implantation. When a suspension of red blood cells, India ink, colloidal silver, or radiographic contrast media is injected into the peritoneal cavity of experimental animals, it is removed primarily by the lymph system lining the diaphragmatic peritoneum. The rolling motion of the intestines and the fluctuating intra-abdominal pressure appear to be responsible for the cephalad movement of the suspension along the peritoneum toward the diaphragm. On the diaphragm, the suspension will intercommunicate with lymphatic capillaries, which will eventually drain into the subclavian vein. Therefore,

cancerous cells within the peritoneal cavity will metastasize throughout the cavity and eventually, the entire body, via the diaphragmatic lymphatic system even when gross intra-abdominal disease is not present (Devita, et al., 1982).

The other mode of metastasis is through the ovarian lymphatics. The ovary contains an extensive lymphatic network in the corpus luteum and theca externa. The vessels run throughout the pelvic region and eventually drain into the subclavian vein. Thus, cancer cells can metastasize from the ovaries to the rest of the body by the lymphatic drainage system.

Within the pelvic cavity, ovarian cancer most frequently spreads to the uterus. The peritoneum, omentum, and bowel surfaces are the most frequent areas of metastases by ovarian cancer outside the pelvic cavity. Those distant organs which may be involved with ovarian metastasis include: liver, lung, pleura, kidneys, bone, adrenal, bladder, and spleen (Devita, et al., 1982).

Histology

Several differing forms of borderline ovarian tumors have been discovered throughout the years. Serous and mucinous neoplasms seem to be the most prevalent of all the borderline ovarian tumor types.

Borderline epithelial serous tumors comprise 8 to 15% of all ovarian tumors according to Anderson, et al.

(1983). Bilaterality occurs in 27.9% of all serous borderline tumors (Nikrui, 1981). Bilaterality is due to two primary tumors in the respective ovaries rather than metastasis from the primary ovary to the uneffected one (Anderson, et al., 1983).

Gross features of serous tumors find them to be large, spherical, and ovoid cysts which may vary from 30-40 centimeters in diameter. Smaller cysts contain only one cystic cavity but as the tumors enlarge, they become multilocular and lose their symmetric external appearance. Small, solid nodules or irregularities are found just beneath the serosa or sometimes may protrude through it. Once opened, the cysts contain clear serous fluid (Robbins, 1962). Figure 1 is an example of a cross-sectioned borderline serous tumor (Robbins, 1962).

Histologically, serous tumors are lined by tall columnar ciliated epithelial cells (Robbins, 1962). These cells, in turn, form rather fine branching papillae. The epithelial covering of the papillae is usually stratified into several layers with a tendency to pile, causing exfoliation of cellular clusters from the papillae (Stenback, 1981). The cellular clusters will break off and float freely within the cyst while fusion of the tips of adjacent buds may result in a honeycombed pattern (Anderson, 1983). Epithelial cells on the surface of the cysts are nonciliated, low columnar, or cuboidal cells, and usually covered by microvilli.

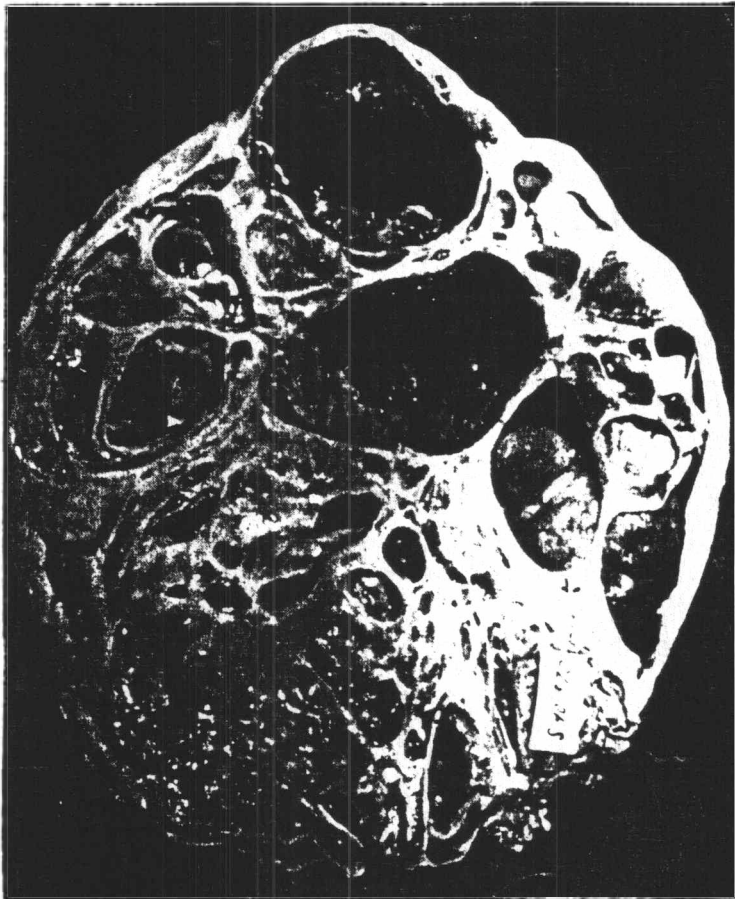


Figure 1. Serous borderline tumor shown in cross section.

Mitochondria, ribosomes, rough endoplasmic reticulum and Golgi apparatus can be seen throughout the cytoplasm. Nuclei are slightly enlarged with hyperchromatic nucleoli which may vary in size and shape (Stenback, 1981).

Mucinous tumors of borderline malignancy comprise 20% of all ovarian tumors. Bilaterality is not as prominent; only 5-10% of mucinous tumors are bilateral (Anderson, et al., 1983).

Grossly, mucinous tumors are similar to serous tumors. They are large and multilocular with a lining which is generally smooth (Hart, et al., 1973). Within the cysts, sticky, slightly gelatinous fluid rich in glycoproteins can be found (Robbins, 1962). This characteristic differentiates mucinous tumors from their serous counterparts. Figure 2 is an example of a mucinous borderline tumor. Notice the shiny gelatinous fluid filling the tumor lumen.

Histologically, mucinous tumors are identified by the apical mucinous vacuolations of the tall, columnar, lining epithelial cells, usually stratified into two or three layers, and the absence of cilia (Robbins, 1962). Exfoliation of clusters of epithelial cells together with mucinous debris is common (Hart, et al., 1973). The epithelium of the cysts show a complex glandular pattern and is often characterized by short papillary infoldings which gives the epithelium a serrated appearance (Anderson, et al., 1983). The position of nuclei and the amount of intracytoplasmic mucin within the epithelium are differ-

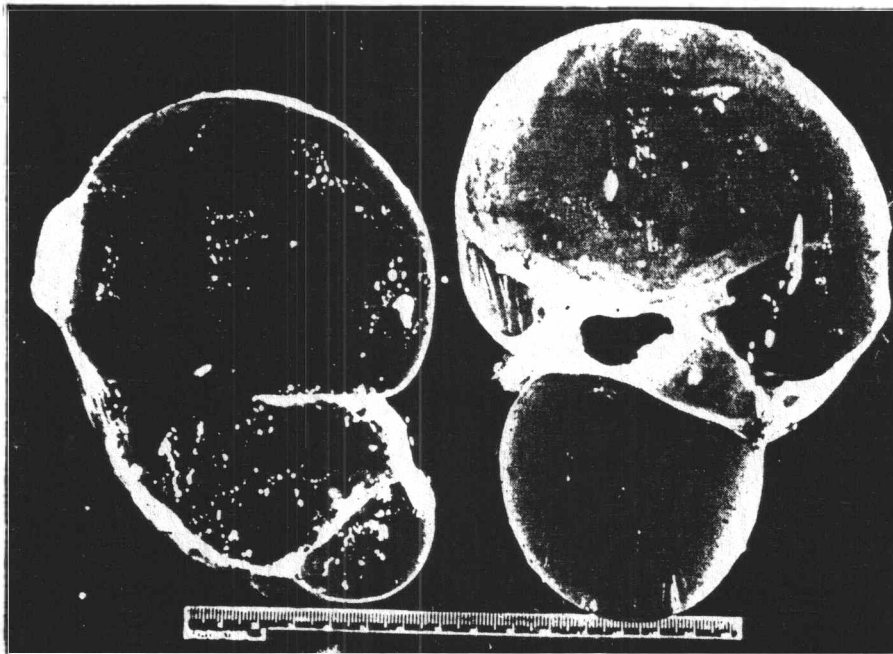


Figure 2. Mucinous borderline tumor shown in cross section.

ent from the serous epithelial cells. Nuclei are atypical, slightly larger, have an enlarged nucleoli, and are hyperchromatic (Hart, et al., 1973).

Tumors of borderline malignancy differ from cystadenomas (benign tumors) histologically by the fact that borderline tumors show epithelial stratification and cellular atypia. Papillar processes are common in borderline tumors but are rarely found in benign tumors. Epithelial buds, detachment of atypical cellular clusters and increased mitotic activity further differentiate borderline ovarian tumors from cystadenomas.

Cystadenocarcinomas (malignant tumors) tend to be more poorly differentiated than BOT. These poorly differentiated tumors are composed of sheets of neoplastic cells with only occasional glandlike structures. Cell interdigitations along lateral borders are fewer and flatter among malignant tumors (Stenback, 1981). Epithelial buds, detachment of atypical cell clusters and increased mitotic activity are more pronounced in malignant tumors than in BOT.

Tumor Staging

A universal system of staging ovarian tumors was proposed by the International Federation of Gynecology and Obstetrics (FIGO) in 1961. After much discussion, the proposal was accepted. FIGO subdivided ovarian tumors into three groups: benign cystadenomas, cystadenoma with proliferative activity of epithelial cells and nuclear

abnormality but no infiltration and destructive growth (borderline malignancy), and cystadenocarcinomas (Nikrui, 1981). Borderline and malignant tumors were then further divided into four, more specific groups according to the degree of metastasis. Table 1 lists the FIGO stages (Am. Jt. Comm. on Cancer, 1983).

Staging is a method used to designate the state of the cancer at various points in time and to indicate the degree of spread throughout the body by the cancer. It is intended to provide a way by which information can be readily communicated to others, to assist in decisions regarding treatment, and to be a factor in determining prognosis. Ultimately, it provides a mechanism for comparing like or unlike groups of cases, particularly with regard to the results of different therapeutic procedures (Am. Joint Council on Cancer, 1983).

As a primary tumor increases in size throughout its time span, at some point (probably early) local invasion occurs, followed by spread to the regional lymph nodes draining the area of the tumor. Usually later in the life span of the tumor, distant spread or metastasis becomes evident. These three significant events in the life history of a cancer, tumor growth, spread to primary lymph nodes, and metastasis are used to indicate the degree of extension of the cancer (Am. J.C. on Cancer, 1983).

Surgery or exploratory laparotomy are essential when staging the patient. The purpose of surgical exploration

STAGING CLASSIFICATION

Stage I. Growth is limited to the ovaries.

- Stage IA Growth limited to one ovary; no ascites
 - IAi No tumor on the external surface; capsule intact
 - IAii Tumor present on the external surface, or capsule(s) ruptured, or both
- Stage IB Growth limited to both ovaries; no ascites
 - IBi No tumor on the external surface; capsule intact
 - IBii Tumor present on the external surface, capsule(s) ruptured, or both
- Stage IC Tumor either stage IA or IB, but with ascites* present or with positive peritoneal washings

Stage II. Growth involves one or both ovaries, with pelvic extension.

- Stage IIA Extension of metastases to the uterus or tubes
- Stage IIB Extension to other pelvic tissues
- Stage IIC Tumor either stage IIA or IIB, but with ascites* present or with positive peritoneal washings

Stage III. Growth involving one or both ovaries with intraperitoneal nodes, or both. Tumor is limited to the true pelvis but with histologically proven malignant extension to small bowel or omentum.

Stage IV. Growth involving one or both ovaries with distant metastases. If pleural effusion is present there must be positive cytology to allot a case to stage IV. Parenchymal liver metastasis equals stage IV.

Special Category. Unexplored cases that are thought to be ovarian carcinoma are included here.

*Ascites is peritoneal effusion that, in the opinion of the surgeon, is pathologic or clearly exceeds normal amounts, or both.

Table 1. FIGO Stage Grouping for Primary Carcinoma and Borderline Tumors of the Ovary.

is two-fold. First, surgery is performed to evaluate the extent of cancer within the pelvic and abdominal cavities. Second, all grossly apparent tumors are extirpated. Therefore, surgery is the first stage of treatment delegated to the patient. According to Smith and Day (as cited in Devita, 1981), the single most important prognostic factor is a residual tumor less than one centimeter. So important is this factor that patients who left after surgery with either no residual disease or tumors less than one centimeter, have essentially the same prognosis regardless of the initial tumor stage (Devita, et al., 1982).

When an exploratory laparotomy is performed, the abdominal incision should be vertical and long enough to allow proper examination of the abdomen. The presence and amount of ascites should be noted and sent for cytologic examination. The status of the tumor capsule and presence of a rupture or excrescence should be noted. The upper abdomen, especially the diaphragm, must be properly explored for the presence of tumor nodules. If nodules are present, biopsies should be taken to check for malignancy. The omentum should be biopsied also as it is an area of high metastatic spread. Para-aortic lymph nodes should be biopsied next to prove the absence or presence of cancer in the upper abdomen (Devita, et al., 1982).

For women under 35 years of age, where disease is limited to one ovary, unilateral adnexectomy and contra-

lateral ovarian wedge resection is advised (Nikrui, 1981).

For women near or past menopause, total abdominal hysterectomy and bilateral salpingo-oophorectomy should be performed. If extensive residual disease is still present adjuvant chemotherapy or radiation therapy is advised (Anderson, et al., 1983).

Treatment

Once the surgery has been performed, the tumor staged, and further therapy is warranted, the decision must be made to determine which treatment would be most beneficial. For Stage I patients, adjunctive therapy in the form of chemotherapy or pelvic irradiation is deemed unnecessary (Creasman, et al., 1982).

In a study by Genadry, et al., 154 patients were reviewed. Of these 154 patients, 108 were diagnosed Stage I; 21 Stage II; 24 Stage III; and one Stage IV. Of these, 28 received adjuvant therapy following surgery. Twenty patients had died during the time span of the study, 18 died of unrelated causes, whereas only two deaths were related to intra-abdominal neoplasm. It was concluded that adjuvant therapy was unwarranted for any borderline ovarian tumor regardless of stage (Genadry, et al., 1981).

On the other hand, Nikrui reviewed 62 cases of borderline tumor cases. Forty-three Stage I, seven Stage II, five Stage III, one Stage IV, and six recurrent cases were reported. From the results compiled, Nikrui concluded

that for advanced stages, where bulky disease was left behind, adjuvant radiation therapy and/or chemotherapy should be administered (Nikrui, 1981).

If adjuvant therapy is advised for the patient, radiation treatments may be chosen. The principles of radiation therapy are as follows. Ionizing radiation includes high energy (short wavelength) electromagnetic radiation (X, gamma rays) and high speed subatomic particles. These high energy particles interact with molecules through two mechanisms, excitation and ionization. When atoms become excited, electrons are shifted to higher orbitals making the atoms more reactive. In ionization, electrons are removed from atoms leaving free radicals and broken chemical bands. Because ionization is a random process, some molecules will escape being ionized. However, these nonionized molecules may undergo radiation-related changes which are brought about by energy transfer from ionized molecules to the undamaged ones. There are two methods by which this energy is transferred between irradiated and unaffected molecules: direct effect and indirect effect. Direct effect is the release of energy into the structure of the molecule under discussion, while indirect effect is the absorption of initial energy by one molecule which is then transferred to another. Energy is passed between molecules via special structures such as tryptophan, benzene rings, alpha helices, and DNA double helices (Rubin, et al., 1978).

Since cells are made of at least 70% water, most of the indirect action involves reactive species derived from water molecules. The free radicals formed by these interactions react with one another and solute molecules to form the final stable products (Rubin, et al., 1978).

It now becomes necessary to discuss the changes brought about by ionizing radiation on macromolecules.

1. Nucleic acids: Changes or loss of a base, hydrogen bond breakage between strands, single and double bond breakage, formation of crosslinks with double helices to other DNA molecules and to chromosomal proteins.
2. Proteins: Damage to side chain groups and changes in secondary and tertiary structures occur.
3. Lipids: Formation of peroxides on unsaturated fatty acids.
4. Carbohydrates: Chain breaks (Rubin, et al., 1978).

When a tissue sample is irradiated, certain cells react differently than others to the radiation. This is because cells are in different stages of the cell cycle. The cell cycle consists of four stages M (Mitosis), G1 (Gap One), S (DNA Synthesis), G2 (Gap Two). When cells of mixed stages undergoing exponential growth are irradiated, there is a drop in the mitotic index (i.e., the percentage of cells undergoing mitosis). It will, however, rise up to the pre-exposure level after a short time. The reason for the drop in the mitotic index is due to a complete but temporary block of the G2 stage (G2 block).

It has been hypothesized that chromosome aberrations (an uncoiling of condensed chromosomes), or protein synthesis inhibition causes G2 block. The only other stage that is significantly affected is the early part of S as the rate of DNA synthesis is suppressed (Rubin, et al., 1978).

At the end of the cycle in which irradiation occurred, experiments show that 90% of the mammalian cells will divide. However, during the cycle following the irradiated phase changes will occur. There is a prolongation of generation time, decreased probability of division, frequent appearance of dead and non-dividing cells, and chromosome aberrations (Rubin, et al., 1978).

Cell death from ionizing radiation has been shown to depend on the stage of the cell cycle. Generally, cells are most sensitive at or near M stage. If stage G1 is of appreciable length, a resistant period is usually evident in the stage. However, toward the end of G1, the survival declines considerably and the end of G1 may be as sensitive as M. In most cell lines, resistance rises during S to a maximum in its latter phase. This phase of the cell cycle is the most resistant to ionizing radiation (Rubin, et al., 1978).

Two techniques are used when administering radiation: total abdominal and pelvic irradiation. Total abdominal irradiation can be administered either by Cobalt⁶⁰ or by a linear accelerator. For total abdominal irradiation, a moving strip technique is used which divides the abdomen

into strips 2.5 centimeters in width. Two, three, or four strips are treated daily. After a strip has completed four frontal and four posterior treatments, it is dropped from the irradiation field. This sequence is continued until the entire abdomen has been treated (Devita, et al., 1982).

Radiation is given to the pelvic region when the disease is located only within this area or when abdominal radiation has been completed. X-rays can be focused within the pelvic region so they only hit the tumor, thus sparing the surrounding organs from harmful rays.

The amount of radiation given to the patient must be monitored carefully. The kidneys can tolerate 1800 rad, the liver 3500 rad when given in 200 rad increments per day. If doses exceed these levels, irreparable damage may be done. Small bowel injury and a depression in bone marrow may also occur (Devita, et al., 1982).

An alternative to radiation therapy is chemotherapy. It has been found that chemotherapeutic agents are more toxic to smaller tumors than to large ones. Therefore, to achieve maximal effectiveness for a chemotherapeutic agent, it should be administered following reductive surgery when the tumors are less than one centimeter in diameter.

Cytotoxic chemotherapeutic agents are in general more effective in damaging dividing cells than resting cells. This applies to both normal and tumor cells. These agents can be divided into three categories: (1) there are specif-

ic agents which damage or arrest dividing cells during a specific phase of the cell cycle; (2) there are cycle specific agents which kill proliferating cells more effectively than resting cells; and (3) there are non-specific agents (i.e., those that equally kill resting or proliferating cells) (Rubin, et al., 1978).

Mountain States Tumor Institute uses a wide regimen of chemotherapeutic agents which fall into the preceding subcategories: alkylating agents, antibiotics, antimetabolites, and miscellaneous. Let us now discuss the properties and the side effects of these drugs.

Cytosan, Leukeran, and Melphalan are alkylating agents. Generally, alkylating agents form electrophilic carbonium ions which alkylate (covalent bond) nucleophilic groups such as N7 in guanine of DNA, causing crosslinking and abnormal base pairing, thus interfering with DNA replication. Also alkylating agents react with sulfhydryl, phosphate, and amine groups resulting in multiple lesions in dividing or non-dividing cells (Rubin, et al., 1978).

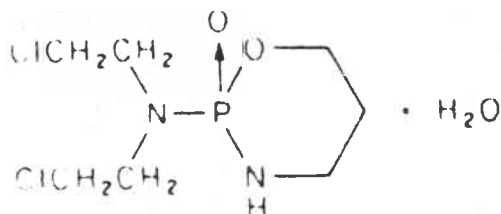


Figure 3. Chemical structure of Cytosan.

Cytosan causes life threatening bone marrow suppression (myelosuppression). Bleeding from the bladder can occur if an increased amount of fluids is not taken during Cytosan therapy. Long-term use is associated with bladder fibrosis and carcinoma. Melphalan causes myelosuppression, leukopenia, thrombocytopenia and anemia. Nausea and vomiting have occurred after large doses (AMA, 1980).

Doxorubicin hydrochloride (Adriamycin) is an antibiotic isolated from Streptomyces peucetius. It is one of the most effective anti-neoplastic agents and works effectively against a wide variety of different tumor types. Adriamycin inhibits DNA dependent synthesis of RNA due to intercalation between base pairs of DNA. It has been determined that Adriamycin is cell cycle specific for the S and/or G2 phase (AMA, 1980).

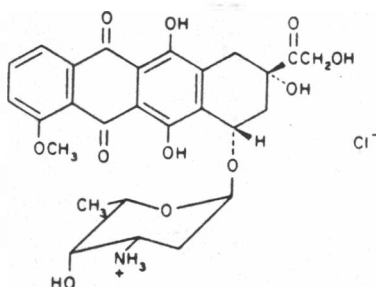


Figure 4. Chemical structure of Doxorubicin hydrochloride.

Side effects of Adriamycin include cardiotoxicity. Therefore, patients with heart problems should be watched closely while taking Adriamycin. Nausea, vomiting, and

alopecia are also common (AMA, 1980).

Flourouracil (5-FU) is a flourinated pyrimidine and acts as an antimetabolite. When used as an antineoplastic agent it was found that tumorous cells utilized uracil for DNA synthesis more effectively than normal cells. 5-FU is converted, in vivo, to the deoxynucleotide which inhibits thymidylate synthetase, thus preventing DNA synthesis. Additionally, 5-FU is incorporated as a nucleotide in RNA which inhibits RNA synthesis by preventing incorporation of uracil and orotic acid into RNA (AMA, 1980).

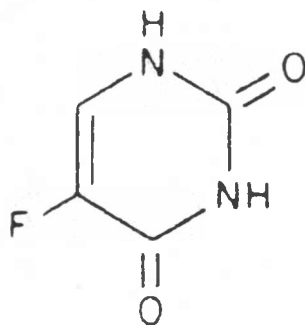


Figure 5. Chemical structure of Flourouracil.

Side effects of 5-FU affect the gastrointestinal and hematological systems. Leukopenia is the major dose-limiting factor. Anorexia, nausea, vomiting, and alopecia are common (AMA, 1980).

Cisplatin falls into the miscellaneous category. It is a heavy metal complex containing a central atom of platinum surrounded by two chloride atoms and two ammonia

molecules in the cis position. Cisplatin produces intra-strand crosslinks in DNA and is cell-cycle nonspecific. Cisplatin and Adriamycin, when administered together, form an effective method for combatting ovarian carcinoma (AMA, 1980).

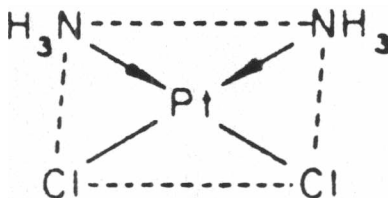


Figure 6. Chemical structure of Cisplatin.

The most serious toxicity problem created by Cisplatin is renal insufficiency which is probably caused by renal tubular damage. Myelosuppression occurs in 25-30% of patients. Nausea, vomiting, and anorexia may persist up to one week following administration. Use of this drug may cause loss of hearing in the high frequency range. Neurotoxicity including loss of taste and seizures does occur and may be irreversible (AMA, 1980).

After treatment has been administered, one way to tell if it has been effective in combatting the cancer is to follow the patients' condition and then determine the survival of the patients. For a treatment to be considered successful, the survival rate must be relatively high.

MATERIALS AND METHODS

A list of 213 patients with malignant ovarian tumors, obtained from the tumor registry at MSTI, was reviewed to determine the number of patients with borderline ovarian tumors eligible for this study. Eligibility was determined by reviewing operative and pathology reports. Tumors with definite histologic features consistent with borderline tumor characteristics were used. A physician also reviewed the cases to confirm the eligibility of the cases. Not all tumors were staged according to International Federation of Gynecology and Obstetric (FIGO) classifications. Therefore, the pathology and operation reports were reviewed and the tumors were staged according to the extent of disease. Once all cases were staged according to FIGO specifications, information pertinent to this study was extracted from the patients' charts and tabulated. Follow-up information concerning the patients' progress following treatment was kept up to date by the Tumor Registry at MSTI. This information was used to determine the survival rate of the patients. Actuarial life table method was used to calculate the survival rates. By using this method, it is possible to determine survival rates five or ten years following treatment without the patients actually being followed-up for that amount of time.

RESULTS

Borderline ovarian tumors occur in seven percent of all ovarian tumors treated at the Mountain States Tumor Institute.

Stage

Of the fifteen patients with borderline ovarian tumors, seven were Stage I, two were Stage II, six were Stage III, and none were Stage IV.

Age

The mean age for patients with Stage I tumors was 49 years, for Stage II the mean age was 42 years, and Stage III patients had a mean age of 30 years. The median age for all borderline patients was 42 years of age.

	Stage I	Stage II	Stage III
Mean	49.4	42.0	30.0
Median	53.0	42.0	24.0
Age Range (years)	25-80	41-42	15-48

Table 2. Mean and median ages of women with borderline ovarian tumors by stage.

Parity

Thirteen of fourteen charts indicated the number of viable offspring the woman has delivered at the time of diagnosis. Twenty-three percent (3 of 13) were nulliparous, while 31% (4 of 13) were nulligravida (never pregnant). Eight percent (1 of 13) had one child, 23% (3 of 13) had two children, and 15% had two children or more.

Family History

Family history for cancer was indicated on ten of fourteen charts. Twenty-nine percent (4 of 14) had one family member or more who had cancer before them. Forty-three percent (6 of 14) had no family history of cancer. In four cases, the family history was unknown.

Histologic Cell Type

Ten of fifteen cases were diagnosed serous cystadenocarcinoma of borderline malignancy. Of these, two were Stage I, two were Stage II, and six were Stage II. Seventy percent (7 of 10) of the serous tumors were bilateral while thirty percent (3 of 10) were unilateral. Five cases of mucinous cystadenocarcinomas of borderline malignancy were diagnosed and all of these were Stage I. All of the mucinous tumors were unilateral.

Tumor Size

Size of the borderline tumors varied from 1.3 centimeters to 34 centimeters, with a mean value of 9 centimeters.

	Stage I	Stage II	Stage III	Stage IV
Serous Tumor	2	2	6	0
Mucinous Tumor	5	0	0	0
Total	7	2	6	0

Table 3. Different histologic cell types of borderline tumors by stage.

Treatment

In all cases surgical removal of the tumor with or without hysterectomy was initiated. In one case, hysterectomy was carried out and only right salpingo-oophorectomy was performed. In six cases, partial or total omentectomy was done. Radiation was administered to six patients. Two were Stage I, two were Stage II, and two were Stage III. Of these, five received Cobalt⁶⁰ radiation and one was administered phosphorus³² radiation. Six patients received chemotherapeutic agents. Two were Stage I and four were Stage III. Two patients received alkylators and four were given combination therapy involving three or more drugs. Three patients did not warrant treatment. They were all Stage I. Second look laparotomies were performed on four patients. Three showed no evidence of recurring disease, while one patient had positive peritoneal washings. She was given eight more courses of combination chemotherapy.

	Stage I	Stage II	Stage III
Radiation Therapy	1	2	1
Chemotherapy	1	0	4
Chemotherapy + Radiation	1	1	1
No Treatment	3	0	0

Table 4. Treatment administered to borderline patients according to stage.

Follow-Up

Follow-up information was available for all patients. One case was lost to follow-up in 1978. Follow-up information for this patient was only until her disappearance from the Tumor Registry. Mean follow-up for all borderline patients was 89 months.

Survival

The five-year survival rate for borderline patients was 100%. In contrast for patients with ovarian carcinoma treated at MSTI, the five-year survival rate for Stage I ovarian carcinoma was 72%. It was 50% for Stage II, 16% for Stage III and 7% for Stage IV. Figure 6 is a graph of the survival rate for borderline tumors compared to survival rates of Stage I-IV.

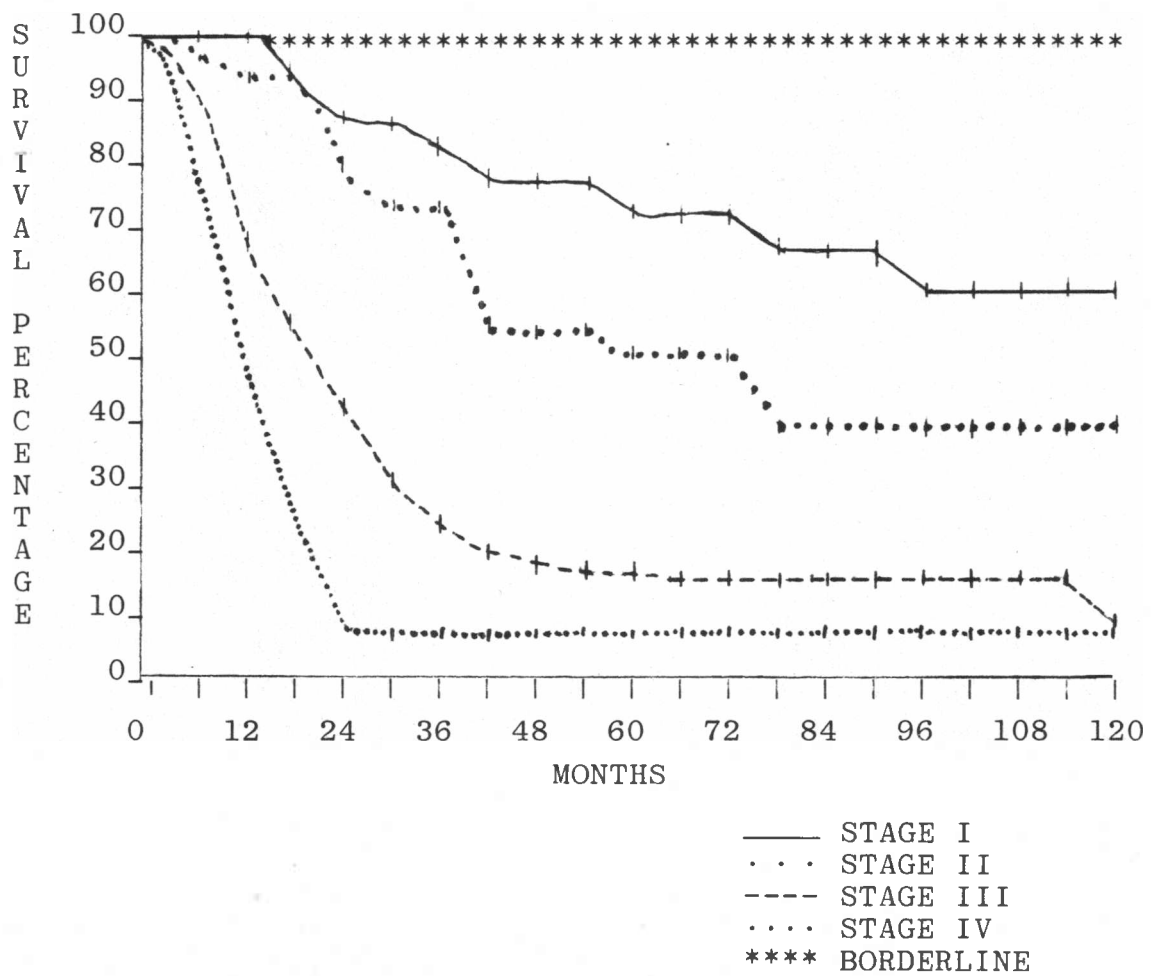


Figure 7. Survival of patients with borderline ovarian tumors, Stage I, Stage II, Stage III, and Stage IV malignant carcinomas.

DISCUSSION

Borderline ovarian cancer is a unique type of cancer in that its progress and metastasis from the initial tumor is relatively slow when compared to definite carcinoma. However, women do die from these slow-growing tumors. Therefore, the disease must be given serious consideration concerning a successful treatment regimen. This is where a difficulty arises. A successful treatment plan has not yet been developed. As I have already stated, some researchers feel that no treatment is necessary to control borderline ovarian cancer, while others feel that both adjuvant chemotherapy and radiation treatment are needed to eliminate the disease from the body. It is obvious that much more research is needed to gain an understanding of this perplexing disease.

The study by Aure, et al., reported the age of patients with borderline tumors to be lower than patients with definite carcinomas. In this study carried out at MSTI, age ranged from 15 to 80 years old for borderline tumor patients and the mean age was found to be 40 years. The mean age of the patients with adenocarcinomas treated at MSTI was 59 years old. Therefore, this information coincides with data already compiled by past studies.

The literature states that 70-80% of all borderline tumors are classified as Stage I tumors. However, in this study it was found that only 47% (7 of 15) were Stage I tumors. This discrepancy could be due to a sampling error because of the small number of patients studied.

Of the seven Stage I tumors examined, five were mucinous and two were serous tumors. Three of the five mucinous tumor patients received treatment. Two were administered Cobalt⁶⁰ radiation therapy and one patient was given combination therapy. The mean follow-up for the patients was 97 months with no evidence of recurring disease. Two of the five mucinous tumor patients received no treatment at all. The mean follow-up of these patients was eleven and one-half months. This figure is seemingly low because the patients have been diagnosed within the last year.

Two of the Stage I tumors were diagnosed as serous carcinomas of borderline malignancy. One of these patients received chemotherapy while the other received no treatment following excision of the tumor. Both of these patients showed no evidence of disease when last reviewed.

Two of the fifteen patients had Stage II tumors. This finding coincides with results of Creasman, et al., Genadry, et al., and Julian, et al. Following excision of the tumor, both patients were given radiation therapy. Both patients have been followed for more than ten years and neither has shown any sign of a recurrence.

According to Creasman, et al., and Genadry, et al.,

Stage III tumors occur with less frequency than Stage I tumors. My findings coincide with their results. Forty percent were Stage II (6 of 15), while 47% were Stage I. All six Stage III tumor patients received adjuvant therapy following excision of the tumor. Radiation therapy was given to two patients, while four patients received combination chemotherapy. Of these patients, three were given second-look laparotomies and only one of these showed any sign of disease. This latter patient was given eight more courses of combination chemotherapy. After two years of follow-up, none of the Stage III patients showed evidence of disease.

The survival rate for all stages of borderline tumors was calculated to be 100%. This is several percentage points higher than other findings as stated by Anderson, et al., 1983; Aure, et al., 1982; Creasman, et al., 1982; Genadry, et al., 1980; Julian, et al., 1972; Tong, et al., 1980. This discrepancy can be explained because of the small number of patients used.

It can be seen from the preceding evidence that a consistent treatment regimen has yet to be established. Patients with Stage I, II, III tumors were either given no treatment or received both radiation or chemotherapy. In all cases, the survival rate was the same. Therefore, there is no way of determining, from this particular study, if receiving treatment is better than receiving no treatment at all.

The purpose of this study was to compile data found in the charts of the fifteen borderline tumor patients. Compiled data may then be added to the small library of literature concerning these tumors, in the hope that some day it might be used to find a proper and satisfactory treatment regimen.

In undertaking this study, the following questions have arisen in my mind. Are borderline tumors an intermediate step in the evolution of a benign adenoma toward a full-blown malignant carcinoma? Or are borderline tumors a unique disease separate from other malignant ovarian tumors? Secondly, if borderline tumors are a separate tumor type, what causes a cell to differentiate, proliferate, and eventually form a malignant ovarian tumor, i.e., one which lacks stromal invasion, rather than forming a tumor that spreads throughout the entire reproductive organ including the connective stroma? When these questions and ones like them have been answered, man will be one step closer to conquering this disease called cancer.

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