

Changing Perspectives in Gynecologic Oncology Diagnosis and Treatment

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Abstract

Gynecologic oncology has a unique status in the field of oncology. Due to easy accessibility, early detection by cytology and first successful radiotherapy were achieved in cancer of the cervix. In addition, the first successful radical surgery, and the first successful chemotherapy were in the field of gynecologic oncology.

Gynecologic oncology is always in evolution and our aim in this article is to review the new approaches to diagnosis, staging, and treatment.

Key words: Papanicolaou smear, gynecologic oncology, colposcopy, radiation, radical surgery, cervix, endometrium, ovary.

Gynecologic oncology occupies a strategic position in the general field of oncology. This unique status is related to:

1. Easy accessibility of the female genital organs for examination/evaluation, leading to:
 - a. early diagnosis, e.g., through cytology, and
 - b. the first successful use of total irradiation in treatment of cancer of the cervix;
2. The first successful use of chemotherapy with complete control of the disease in trophoblastic disease.

Gynecologic oncology is always in evolution, aiming at early diagnosis, correct mapping of the disease for correct and adequate treatment. Our aim in this article is to review the new approaches to the main

gynecologic oncologic disease from the point of view of diagnosis, staging and treatment

1. Cancer of the cervix

a. Diagnosis:

In the United States of America fewer women die annually from carcinoma of the cervix today than in any period in modern history. Areas of progress include:

- 1) Increased utilization of cervical cytology.
- 2) Better assessment and evaluation of the patient with an abnormal Papanicolaou smear.
- 3) Better primary therapy.
- 4) A better understanding of the spectrum of cervical intra-epithelial neoplasia (CIN).

The Papanicolaou stained cytology smear is an invaluable tool for detecting cervical carcinoma. However, in recent years the significant incidence of false negative smears has been recognized. The incidence varies from 15-20%.¹ This incidence of false negative smears emphasizes the need for histologic study of the abnormal cervix before therapy is started, regardless of the findings from the cytology smear.

In order to fill this serious gap in screening for cervical cancer and its precursor, created by the high incidence of false negative smears, colposcopy is utiliz-

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ed.² The basic idea behind colposcopy is that neoplastic changes are associated with changes in the vascular pattern. By detecting the abnormal vascular pattern, one can predict the most appropriate area for biopsy, i.e., targeted biopsy. The introduction of colposcopy has accomplished the following:

- 1) Complemented cytology and reduced the undiagnosed cases.
- 2) Eliminated the need for cone biopsy in pregnancy.
- 3) Reduced significantly the need for diagnostic cone biopsy (10% or less)
- 4) Made it feasible to treat selective cases of intra-epithelial neoplasia by cryosurgery.

b. Treatment:

The most important prognostic factor in carcinoma of the cervix is the stage of the disease. The stage correlates well with incidence of lymph node metastasis both in and outside the pelvis. In stage I the correlation between the clinical stage and the surgical stage is reasonably accurate. However, when the lesion is larger than 1-2 centimeters or the stage is II or higher, the clinical staging is inadequate. In several recent studies the incidence of lymph node metastasis outside the pelvis was 16% in stage II, and 48% in stage III. This means that if the treatment is limited to the pelvis, there will be outright failures in 16% of stage II and 48% in stage III, as their disease is outside the field of treatment.^{3,4} Several attempts were made to extend the field of radiation to the periaortic areas. However, statistically this did not increase the survival of those patients, but increased the incidence of morbidity, especially intestinal damage.

Research is continuing to find better means for treatment of advanced disease of the cervix through chemotherapy and/or immunotherapy. For these reasons, we have to continue to map the disease carefully as well as selectively consider doing surgical staging for advanced stages, in order to be able to cover every area of the disease by different modalities for treatment. In advanced stages of the diseases (II B, III, IV) the main modality of treatment is irradiation; however, studies have shown that some patients may benefit from combined treatment, i.e., irradiation plus surgery:

- 1) Patients with endocervical lesions, as they tend to have enlarged barrel-shaped cervixes.
- 2) Patients with adenocarcinoma of the cervix, as it tends to invade the myometrium.

In these patients, it is difficult to control the central disease. Therefore these patients, even when the rest of the disease appears to be controlled, are liable to have persistent disease which ultimately is the cause of death. Therefore, it is recommended that if such patients respond to the irradiation treatment, they ought to be subject to hysterectomy in order to remove the central persistent cancer.^{5,6}

Radiotherapy and radical surgery are both excellent modalities for treatment of early stages of carcinoma of the cervix with equal survival results. Attempts to choose between these two modalities on the basis of sensitivity testing by cytology, histology and DNA content have proven futile. Recent studies have shown clearly that the degree of tumor differentiation has no influence on the radiation response, nor on the incidence of lymph node metastases.³

Recent evidence shows that radiation therapy may be carcinogenic. Patients who were treated solely by irradiation for carcinoma of the cervix, and survived long enough, had a higher incidence of adenocarcinoma of endometrium, sarcoma of uterus, sarcoma of the pelvic bone, and carcinoma of vagina, than the normal population. In addition, radiation damage which is usually very severe and difficult to treat, can occur several years later. Also, the ovarian and vaginal function after irradiation is inadequate. Early stages of carcinoma of the cervix comprises more than half of all cases, and they tend to occur in younger patients. Therefore, in such patients radical surgery would be preferable for the following reasons:

- 1) Preservation of the ovaries.
- 2) Adequately functioning vagina.
- 3) To avoid late complications of irradiation.
- 4) To avoid the carcinogenic effect of irradiation to the pelvis and genital organs.

With the addition of the colposcope to the armamentarium of the gynecologic oncologist, patients can be selected with intra-epithelial neoplasia ranging from dysplasia to carcinoma in situ, to be treated with cryosurgery or laser surgery.⁶ The latter is too expensive and does not have any advantage over the former. This treatment is specially suitable for the younger patient desiring to preserve her genital organs. Patients suitable for these modalities are those in whom the diagnosis is accurate, the lesions are small, well-defined and confined to the ectocervix. They should be very reliable for follow-up. The advantages of this treatment are the following:

- 1) Outpatient procedure.
- 2) Does not require anesthesia
- 3) Eliminates the cost of hospitalization.
- 4) Minimal complications, much less than the complications of cone biopsy.

2. Carcinoma of the endometrium

Diagnosis:

Cytology has a very low yield in detecting adenocarcinoma of the endometrium.¹ The main reasons are that the majority of the cells are well-differentiated, and also the majority of cases occur in postmenopausal patients whose cervixes are stenosed. Therefore, it is imperative to define groups of patients who are considered at high risk for adeno-

carcinoma of the endometrium:

- 1) Hypertensive, obese, diabetic patients.
- 2) Strong family history of carcinoma of the endometrium.
- 3) History of adenocarcinoma of the breast, thyroid, colon, etc.
- 4) Long history of infertility.
- 5) Irregular bleeding.
- 6) Stenosed cervix.
- 7) Pyometra.
- 8) Prolonged untreated anovulation.
- 9) Prolonged estrogen treatment.

By sampling the endometrium of the suspected cases, early diagnosis can be accomplished and correct treatment instituted.

b. Treatment:

Unfortunately, physicians have taken a somewhat complacent attitude toward adenocarcinoma of the endometrium. This may be due to the fact that most of the lesions are diagnosed as stage I and because there is a feeling that it can be treated easily with reasonable results. However, when one reviews the survival data as noted in the most recent annual report, any complacency should disappear rather rapidly. The five year survival rate gathered from leading medical centers around the world is only 72%.^{7,8}

There are several important prognostic factors in this malignancy. The international staging has utilized the differentiation of the tumor, the size of the cavity of the uterus, and cervical involvement. All these factors determine the incidence of lymph node metastasis. However, the best single prognostic factor which correlates better with lymph node metastasis, is the myometrial invasion. Unfortunately, this cannot be ascertained except after removal of the uterus. For this reason it was not included in the clinical staging. Cooperative studies were performed where surgical staging with periaortic and pelvic lymphadenectomy were performed. The data showed clearly that even though myometrial invasion is a reasonable parameter for lymph node metastasis, it is not adequate. The only way to be truly accurate is by sampling the lymph nodes.

Consequently, it seems that our first endeavor should be to determine the full extent of the disease process before giving any adjunctive therapy. By mapping the extent of the disease the extent and type of irradiation and chemotherapy can be ascertained with accuracy. In addition, some patients may prove not to be in need for additional therapy, thus avoiding the complications in some patients and providing better control in other patients.

3. Carcinoma of Ovary

a. Diagnosis:

Although carcinoma of the ovary represents the third most frequent gynecologic malignancy, it is now the number one killer. Pap smears are of no value in its detection. Efforts to study cul-de-sac cytology proved to be unsuccessful. There is a flurry of activity with a variety of immunologic investigations being undertaken concerning a screening diagnostic serologic test which is based on the identification and purification of one or several specific ovarian cancer-associated antigens. At best, this must be regarded as hopeful at this time. Carcinoembryonic antigen (CEA) initially reported with colon cancers has been found in association with a variety of cancers, including ovarian cancers and can be useful only for follow-up of response to treatment. CA 125 is more hopeful but as yet nonspecific as it occurs with other benign diseases as endometriosis and myomas.

Signs and symptoms of ovarian cancer are elusive. The physical findings are the usual method of detection. Clearly, a pelvic mass found in an adolescent or premenarchal child suggests malignancy and warrants further study. The presence of an adnexal mass of almost any size in the postmenopausal patient should lead to suspicion of neoplasm as the postmenopausal ovary should be atrophic. Recent studies have suggested that patients with unexplained postmenopausal bleeding, family history of ovarian carcinoma, and history of adenocarcinoma elsewhere in their body are more susceptible to develop carcinoma of the ovary and ought to be followed closely.

b. Histogenesis and treatment:

In the literature there is support for the concept that ovarian cancer is an environmental and/or cultural disease.^{9,10} The incidence in the United States ranges from 10 to 13 per 100,000, whereas, in Japan the rate is 2.2 per 100,000. The incidence in the northern United States is higher than in the southern part. In addition, blacks living the north have a higher incidence than blacks living in the south, and definitely higher than the blacks living in Africa. Japanese born in America have the same incidence as the white Americans. In addition, females working or living near asbestos mines have a higher incidence of ovarian carcinoma than does the average population. Injecting asbestos into the peritoneal cavity of animals has produced changes similar to ovarian carcinoma and mesothelioma.

Carcinoma of the ovary arises from the surface epithelium which is embryologically similar to the epithelium of the peritoneum, pleura, uterus and fallopian tubes. Ovarian carcinoma tends to spread on the surface epithelium before it metastasizes to the lymph nodes. In stages I and II where the tumor is supposed to be confined to the pelvis, adequate exploration proved that in at least 15-30% of the cases, lesions at the diaphragm were found, i.e., the cases

actually are at stage II.

Females differ from males in one interesting aspect. The female pelvis and abdominal cavity are connected to the environment through the genital tract. Any substance that reaches the vagina can ascend to the peritoneal cavity. For this reason, mesotheliomas are more common in the female and very rare in the male. The carcinogen ascends through the genitalia, and the ovary gets the first brunt or a high concentration. For this reason, it is the organ where the lesion first appears. Then, with lower concentrations, the rest of the peritoneum is affected, depending on the concentration and the susceptibility of the organ.

From the above discussion it becomes clear that there is evidence to suggest that carcinoma of the ovary is a generalized disease of the coelomic cavity. In order to accomplish a better cure we have to treat it as such. Therefore, it is not adequate to concentrate on the pelvis, but we have to use other modalities besides surgery to cover the rest of coelomic cavity. Radiation has been used but has limitations, as one cannot give adequate therapeutic doses to areas of the diaphragm or the gutters, for fear of destroying the liver and the kidneys. In addition, it is more difficult to operate on such patients after irradiation.

For these reasons, the treatment of choice at the present time is as follows:

After adequate mapping and staging of the disease by peritoneal cytology, exploration of the diaphragm and gutters, biopsy of the omentum, lymph nodes, and removing as much as possible of the carcinoma, plus total abdominal hysterectomy and bilateral salpingo-oophorectomy, the patient is started on chemotherapy. Radiotherapy in the form of isotopes is considered only in Stage I cases, or in cases where superficial microscopic neoplastic areas are seen on the surface.

4. Intra-venous Hyperalimentation (IVH) in management of gynecologic cancer patients:

With the advent of aggressive management with chemotherapy, radiotherapy and surgery, there is an increased optimism that many cancers can be cured. Unfortunately, the most effective antineoplastic agents are very toxic to the host. The use of total parental nutrition has provided a means whereby the patient can be maintained and supported for long periods of time at high caloric and nitrogenous in-

takes without the need for oral ingestion.

IVH has two potential problems: (1) tumor growth may be stimulated by the nutritional solution, and (2) septic complications may result from the use of an indwelling catheter in the superior vena cava in patients who have depressed bone marrow and immunocompetence. Data from experimental animals and a large number of patients have shown that stimulation of the tumor growth did not appear to be a problem. On the contrary, the immunocompetence was restored quicker by IVH and the patients were able to withstand the insult of the treatment much better. Sepsis is minimal if aseptic techniques are observed, however, if it occurs, the catheter has to be removed and the patient covered adequately with antibiotics.

The use of IVH has been very helpful and essential in preparing patients for major surgery, radiotherapy and chemotherapy. It enhances the postoperative cure rate and wound healing.

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