

Gynecologic Cancer Treatment: Risk Factors for Therapeutically Induced Neoplasia

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Therapeutic intervention in a course of illness, while producing the desired result, also may have some adverse long-term effects on the patient. Second malignancies are one of the known complications of therapy. The treatments of gynecologic cancers by surgery, irradiation and chemotherapy have been associated with subsequent neoplasms. Care must be exercised in associating previous therapy and a subsequent malignancy. "Naturally" occurring second cancers must be separated from those which are iatrogenic. Associations in the literature have been made involving malignancies as a sequelae of prior gynecologic therapy. The use of normal skin from the thigh to fabricate an artificial vagina has resulted in more squamous cell carcinomas than expected. Alkylating agents used in the treatment of ovarian cancer and other diseases have been shown to lead to an increased risk of leukemia. Irradiation therapy, however, has not yet been shown to be related to leukemia in cervical cancer patients. The incidence of lymphoma and uterine, urinary bladder and colon carcinomas has been associated with prior irradiation for gynecologic disease. The literature regarding the therapeutically induced risk factors in gynecologic therapy is reviewed and areas of our knowledge that require more investigation are identified.

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IN MEDICINE, the treatment of every disease has been associated with some adverse effects. The more serious the illness, the more accepting physicians are of therapeutically-related toxicities. As the therapy available for particular diseases improves, the long-term survival of many patients begins to unmask late complications. Long-term survival has been achieved for many gynecologic malignancies,¹⁻³ and with increased survival, late side effects have been recognized, which serve to influence our consideration of future therapy.

It is important that the risk of late complications be seen in the proper perspective. If initial treatment of the primary malignancy is not successful, and survival is not prolonged, latent side effects of therapy will be masked by the patient's death. It is only with the success of primary curative therapies that the issue of therapeutically induced risk factors becomes important.

Acute toxicities are often obvious and bothersome,

whereas long-term complications require careful monitoring of high risk populations over many years. When such monitoring is performed, second malignancies occurring as a result of a variety of cancer therapies have been well documented.⁴ Nevertheless, because these second tumors occur often years after initial treatment, they must be differentiated from the random occurrence of second malignancies in cured patients and from the natural predilection some patients have for certain other tumor types.⁵ These distinctions are often difficult and sometimes impossible to unravel. When ascribing a second malignancy to previous treatment, care must be taken to ensure that what is observed is not the natural occurrence in the population at risk.^{5,6} For example, in the field of gynecologic malignancies, ovarian cancer patients have a higher risk of developing breast cancer (relative risk 4.4),⁶ thyroid cancer (relative risk 20.0),^{6,7} endometrial cancer (relative risk 2.9),⁸ and lung cancer (relative risk 2.0),⁸ which appear to be largely independent of therapy. Patients with endometrial carcinoma have been reported to have an increased incidence of second tumors of the breast, ovary, oral cavity, and thyroid not related to their primary treatment.^{6,7,9} Also, non-therapeutically related increases in lung cancer (relative risk 6.3), oral cavity (relative risk 5.3), skin, and thyroid cancer have been observed in cervical cancer patients.⁷⁻¹¹ Possible explanations for these associa-

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tions include a common hormonal etiology in ovarian, breast, and endometrial cancers. Smoking, an environmental factor, common among women with cervical cancer, has been suggested as a link to the increased incidence of carcinoma of the oral cavity, bladder, and lung in these patients.¹¹ Other possible explanations are discussed in more detail elsewhere.^{6,7,11}

Throughout this text, we will be using the term "relative risk." This term refers to the ratio of the observed to expected (O/E) numbers of cases. In general, when this ratio is large, and the 95% confidence intervals around the estimate of relative risk do not include 1.0, then the estimate of relative risk is often statistically significant at the 5% level (P less than 0.05). When published materials fail to include confidence interval information, the statistical significance of any increase in relative risk cannot be assumed.

The use of a relative risk ratio is a commonly used method to assess treatment risks in epidemiologic studies. This ratio assumes comparability of the observed and expected populations. In such studies, patients with a specific primary malignancy should be compared to other such patients, and not to the general population, of which only a very small portion has cancer.⁵ Many studies upon which our understanding of therapeutically induced neoplasms is based have inadequate or noncomparable populations as controls or estimates of expected values. This makes conclusions of significance often difficult. We have presented in this review a number of well-executed studies; however, many studies are not of optimum caliber. It is our intention to point out not only significant but also suggested associations of therapy and subsequent malignancy. Only with many well-designed and carefully analyzed future studies can our understanding of cancer induction by therapy be broadened.

Therapeutically Induced Risk Factors

Surgery, radiation therapy, and chemotherapy, either alone or in a variety of combined modality approaches, have been used in the management of gynecologic malignancies. Each of these approaches appears to have some risk.

Surgery

Surgery has been, and still is, the mainstay of therapy in the majority of gynecologic neoplasms. In general, surgery is considered not to be oncogenic, and there is little information to suggest significant late oncologic risk. However, a few case reports have been published of carcinomas developing in artificial vaginas reconstructed after cancer operations or for benign congenital conditions.¹²⁻¹⁴

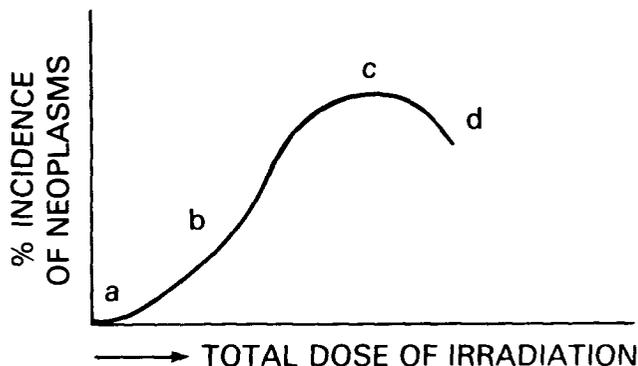


FIG. 1. Diagrammatic relationship of radiation dose and subsequent neoplasms.

In the reconstruction of a vagina, skin is often taken from the thigh and molded into a new vaginal pouch. This once normal skin subsequently has been shown to lose hair follicles, sweat glands, and many long elastic fibers.¹⁵ Rete pegs are shortened and glycogen storage occurs. The pH and flora of the artificial pouch become very similar to those of the normal vagina.¹⁵ As a result of these changes, vaginal examination is usually normal.¹⁵⁻¹⁷ These alterations appear to be changes in the transplanted skin and not regrowth of the original vaginal mucosa.¹⁸ There have been two reported cases of subsequent squamous cell carcinoma arising in previous thigh skin transplanted to the vaginal position, with about 700 operations performed.^{12,13} This incidence has been suggested to be greater than the random incidence of epidermoid carcinoma of the thigh.¹³ An additional case of carcinoma has been reported following vaginal replacement by an intestinal graft.¹⁴ These reports and the histologic changes in the transplanted skin suggest a regional predisposition to malignant transformation. This evidence is only suggestive as a therapeutically induced risk. The exact role of surgical transplantation, if any, can only be elucidated with further studies in this patient population.

Irradiation Therapy

Irradiation has long been known to be oncogenic.¹⁹ In the 1930's and 1940's, many investigators showed that irradiation was carcinogenic in animals.²⁰⁻²² In general, these animal experiments showed tumorigenicity varied with dose, tissue irradiated, and the type of irradiation used.²³⁻³² Figure 1 shows the relationship of dose and subsequent tumor development in many animal systems. At low levels of irradiation, relative to the specific tissue being considered, little or no increase in tumor formation is seen. This may be due to the fact that chromosomal DNA damage is not extensive and/or is repairable. Radiation chromosomal

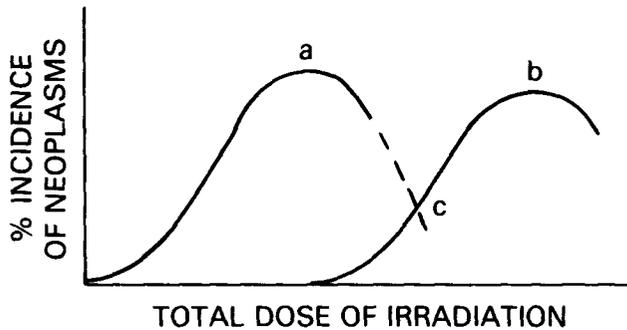


FIG. 2. Diagrammatic relationship of radiation dose and subsequent neoplasms in two different tissues.

mutation experiments indicate that more than one chromosomal event is required to produce tumors.³³ As the dose is increased, chromosomal damage by irradiation increases, and tumor formation becomes more prevalent, often in a linear fashion. However, as the dose is increased further, cell death occurs, eventually balancing the mutagenic effects and the curve plateaus. Still higher doses produce more cell death than sublethal injury, and carcinogenic measurable end points decrease.¹⁹

The level at which tumorigenicity increases, plateaus, and decreases appears to be a function of the tissue irradiated.^{23,26} Rodent myeloid leukemia increases and plateaus with doses less than 500 rads total, whereas kidney neoplasms do not begin to rise until doses are well over 500 rads and peak near 1500 rads.²³ Therefore, it is possible to have two tissues within a radiation port so that the dose given kills most of one tissue and is tumorigenic to the other tissue (Fig. 2).

Review of human exposure to irradiation and subsequent malignancy is difficult to interpret but appears to be consistent with this theory of varying tumorigenicity with dose and tissue. Thymic irradiation in childhood with doses of 200–500 rads has resulted in a linear increase in thyroid cancer at about two cases per million per rad per year.^{34,35} Irradiation to the chest for tuberculosis and mastitis has also shown a linear dose-effect relationship in subsequent breast cancer.^{35–37} Low dose (500–1000 rads) irradiation to the pelvis and therefore the pelvic bone marrow for benign gynecologic conditions has resulted in a three-fold excess of leukemia in this population.^{35,38–40} A linear slope again has been shown relating the leukemia incidence to these doses.³⁵

The type of irradiation and dose rate (time needed to administer a dose) are also of importance in tumorigenicity. Animal studies suggest that neutrons are equally or slightly less leukemogenic than x-rays or gamma rays at high dose rates (large amounts of irra-

diation per unit time); however, at low dose rates (lower amounts of irradiation per unit time), neutrons appear to be several times as leukemogenic as gamma rays.³⁰ Because of differences in types of irradiation, radiation biologists use the term "relative biological effects" (RBE). By this characterization and an accurate reporting of the type of irradiation used, comparisons can possibly be made of tumorigenicity in humans.

In 1944 and 1950, March first linked radiation exposure in radiologists with the development of leukemia.^{41,42} Subsequent studies in atomic bomb survivors,^{43,44} ankylosing spondylitis patients treated with irradiation,⁴⁵ and other nonmedically exposed groups^{46,47} confirmed the leukemogenic effect of radiation in humans.

Though cases have been reported, leukemia has not been clearly linked with therapeutic doses of radiation in gynecologic tumor treatment. Zippin *et al.* reviewed 497 patients treated with irradiation for cervical carcinoma.⁴⁸ Follow-up ranged from 17–36 years, and no increased incidence of leukemia could be demonstrated.⁴⁸ In 1960, an international study, eventually involving 31 institutions, was begun to study the incidence of leukemia in irradiated cervical carcinoma patients. The early report⁴⁹ and a recent ten-year update,⁵⁰ covering more than 31,000 patients followed for more than 140,000 women-years, failed to show an increase in the incidence of leukemia, lymphoma, multiple myeloma, or Hodgkin's disease.⁵⁰ The observed and expected frequencies did not differ significantly among patients treated with external irradiation, internal implantation, or both.⁵⁰ The explanation for this lack of radiation risk in light of other studies showing some leukemogenic risk with pelvic irradiation in the treatment of other diseases is of importance in a discussion of therapeutically induced risk factors.

Analysis of port size and tissue dose may explain the lack of correlation. Irradiation field size in cervical cancer patients is localized to the pelvis, whereas most associations of radiation with leukemia have been after total body exposure.^{43–47,51} Diagnostic radiologists exposed to irradiation without protection before the 1950's and the atomic bomb survivor studies initially alerted investigators to the association of total body irradiation (TBI) and subsequent leukemia.^{41–44} The development of leukemia and myeloproliferative disorders following total body irradiation for relapsing non-Hodgkin's lymphoma is being recognized with increased frequency.^{52,53} Similar reports from nuclear fallout victims and industrial nuclear exposure show TBI to be a common factor.^{44,46,51} Nevertheless, Court-Brown and Doll reported leukemia following irradiation for ankylosing spondylitis.⁴⁵ With follow-up

averaging 13 years and greater than 14,500 patients studied, death from leukemia was 1.8 times higher than the general population.⁴⁵ Though exact ports and doses are not known, many of these patients may have received total or near total bone marrow exposure, *i.e.*, spine and pelvis that contain 40–80% of an adult's active marrow. Thus, the lack of correlation between irradiation for cervical cancer and subsequent leukemia can possibly be explained by the limited portion of marrow irradiated.

The dose to the marrow may also be of importance as a leukemogenic risk factor. Animal studies show that doses less than 500 rads are associated with the development of leukemia, but higher doses show a decrease in leukemia probably due to myeloid cell death rather than development of sublethal mutation.³¹ In the treatment of cervical cancer, a localized port with high doses is the rule. This high dose may reiterate the animal studies and cause myeloid cell death within the localized port, to such an extent that sublethal events are not manifested in this population. Though high dose and limited ports in cervical cancer patients may not lead to an increase in the risk of leukemia, prolonged follow-up time of treated patients is crucial to resolve this controversy. Second malignancies may arise years after irradiation. Data from the atomic bomb survivor studies show a latency associated with age. The majority of patients under 15 years of age at the time of exposure had leukemia less than ten years later.⁴⁴ However, patients over 45 years of age at exposure continued to have significant risks of developing leukemia 15–25 years later.⁴⁴ In the international study of cervical carcinoma patients treated by irradiation, 66% of the patients were over 45 years of age at the time of treatment.⁵⁰ Follow-up has been less than ten years in 79% of these women. Therefore, it is possible that longer follow-up may show an increased incidence of leukemia.⁵⁰

Ovarian cancer patients treated by irradiation, like cervical cancer patients, do not appear to have a significant increase in subsequent leukemia.⁸ Again, high doses to a localized port are given.

The exact mechanisms of leukemia development after irradiation are unclear. Low total body dose either as one single exposure or multiple exposures are well documented as leukemogenic in the lymphoma studies, atomic bomb survivors, and nuclear accident victims.^{43–47,52,53} Higher total body doses over prolonged periods of time, as in radiologists in the 1930's and 1940's, also produce leukemia at an increased rate.^{41,42} Extensive marrow and/or total body exposure appears to be the common link. Much more investigation is needed to unravel these complex relationships.

As mentioned earlier, tissues seem to vary in the

amount of irradiation needed for carcinogenesis. While in the preceding discussion, pelvic irradiation has not been associated with leukemia, it is clear that it is not innocuous. Reimer *et al.* have suggested a relationship between pelvic irradiation and the subsequent development of lymphoma in ovarian cancer patients.⁸ In 6596 irradiated patients, six subsequently had lymphoma.⁸ The expected number with lymphoma in the general population was 2.2 for a relative risk of 2.7 (95% confidence intervals 1.0–5.9).

Pelvic irradiation has also been associated with second solid tumors. Adenocarcinoma of the colon related to irradiation was first reported by Slaughter and Southwick in 1957.⁵⁴ Two of the original nine cases who had colon cancer were patients with carcinoma of the cervix treated by irradiation.⁵⁴ Fehr and Prem found an association between irradiation in cervical carcinoma and the subsequent development of carcinoma of the uterus.⁵⁵ In a population of 2294 patients treated, 12 cases of endometrial cancer occurred 5–18 years after irradiation, average 10.9 years.⁵⁵ This observed frequency is twice the expected annual spontaneous incidence.⁵⁵ It is of interest that eight of these patients had no vaginal bleeding, though blood was found in the uterus. The absence of blood was attributed to stenosis of the cervical canal that resulted from the radium implant treatment.⁵⁵

For 20 years, cancers of the urinary bladder have been recognized after irradiation to the pelvis.⁹ Duncan *et al.* reported eight cases in 2675 patients irradiated for cervical carcinoma (relative risk 57.6).⁵⁶ The interval between irradiation and the development of bladder tumors ranged from six months to 20 years with a mean of nine years.

The Institute of Oncology in Warsaw studied 8043 patients after irradiation therapy for cervical carcinoma.⁵⁷ Statistically significant increases of second malignancies were found for uterine sarcoma (O/E 4.3/0.8, relative risk 5.38) and skin within the radiation port (O/E 5.8/0.4, relative risk 14.5).⁵⁷ Palmer and Spratt studied 721 patients followed 12 or more years after pelvic irradiation for benign gynecologic disease.⁵⁸ Observed to expected risks of subsequent malignancies were elevated for endometrial carcinoma (O/E 29/4.86, relative risk 5.95), cervix (O/E 11/6.53, relative risk 1.68), ovary (O/E 8/2.58, relative risk 3.1), and rectal (O/E 7/2.11, relative risk 3.32) carcinoma. This data should be viewed with the knowledge that follow-up was obtained by questionnaire 12 or more years after treatment. Only 43% of the original patient population returned an adequate reply, and this may represent patient population selection. Many second malignancies may have been missed in the population not returning statements. On the other hand, those

with a second malignancy may be more motivated to return a questionnaire, thus making the incidence appear higher than is true for the entire population of 1670 patients who were initially treated. The relatively small numbers of patients who had second malignancies must be kept clearly in mind. If the expected rate is less than one, significance of one or two cases observed is doubtful. Therefore, large numbers of patients without selection are needed to define relationships between second solid tumors and irradiation.

Reimer, Hoover, Fraumeni and Young examined, in a retrospective but comprehensive study, second neoplasms after treatment for ovarian cancer.⁸ Irradiated patients had a statistically significant increase compared with the general population in endometrial carcinoma (O/E 56/12.4, relative risk 4.5, 95% confidence interval 3.4–5.9), colon carcinoma (O/E 33/17.0, relative risk 1.9, 95% confidence interval 1.3–2.7), bladder carcinoma (O/E 9/3.2, relative risk 2.8, 95% confidence interval 1.3–5.3), and lymphoma (O/E 6/2.2, relative risk 2.7, 95% confidence interval 1.0–5.9).⁸

Separation of the risk of second solid tumors resulting from therapeutic irradiation and those tumors that are the natural predilection in ovarian cancer patients is difficult. Reimer *et al.* evaluated 6713 nonirradiated ovarian cancer patients from the End Result Program (1935–1972), which showed elevated relative risks compared with the general population for endometrial carcinoma (O/E 40/13.6, relative risk 2.9, 95% confidence interval, 2.1–4.0, *P* less than 0.05), colon carcinoma (O/E 30/23.3, relative risk 1.3, 95% confidence interval 0.9–1.8), and lymphoma (O/E 6/3.7, relative risk 1.6, 95% confidence interval 0.6–3.5).⁸ These natural increased risks suggest factors other than radiation may also be playing an important role.⁸ A predisposition to bladder cancer, however, was limited to irradiated patients.⁸

Osteosarcoma resulting from exposure to irradiation was first recognized in 1929.⁵⁹ Case reports of sarcoma following irradiation in gynecologic cancer are few and suggest that the incidence must be low.⁶⁰ In a large retrospective study of ovarian cancer, irradiated patients had more second neoplasms involving connective tissue than nonirradiated patients. However, the number of patients is small (3 vs. 1), and significance cannot be placed on this finding.⁸ A large series of cervical cancer patients treated with irradiation has failed to show a significant increase in sarcomas.⁵⁷

In the treatment of gynecologic malignancies, associations between irradiation and subsequent cancers of the bladder, colon, uterus, and lymphoid tissues have been suggested.^{8,58} However, the role of irradiation is unclear at therapeutic doses in the treatment of ovarian cancer.

In the future, special attention needs to be paid to the organs within the irradiation port.

Radioisotopes

Irradiation in the form of isotopes was first used intraperitoneally in ovarian cancer by Muller in 1945.⁶¹ Intraperitoneal isotopes are still in use, and there is little evidence relating intraperitoneal administration to subsequent malignancies. However, the *intravenous* administration of isotopes has been reported to be leukemogenic and carcinogenic.^{62–66} Though not used in gynecology, the injection of radioactive thorium (thorotrast) for diagnostic evaluation of vessels, liver, and spleen, 35–45 years ago, resulted in sarcomas and carcinomas of the reticuloendothelial tissues.⁶⁵ Thorium has also been reported to cause carcinomas after intracavitary instillation. When injected into maxillary sinuses, subsequent squamous cell carcinomas have developed 15–25 years later.⁶⁷ Exact doses are not known, but radioactive thorium was identified in some of these tumors.⁶⁷

Carcinoma and leukemia have also been associated with the use of radioactive iodine (¹³¹I) and ³²P.^{64,68} Pochin studied 200 patients treated for thyroid carcinoma and found 12 malignancies (O/E 12/5.2, relative risk 2.3).⁶⁴ Total dose and exposure may be important as they are with external beam irradiation discussed earlier. Thyroid cancer patients are treated with high doses of ¹³¹I to destroy the gland and malignant tissue. Lower doses are used in the treatment of hyperthyroidism, and evidence now shows no significant increase in leukemia or carcinoma in these populations treated with lower doses.^{69–71}

In gynecologic malignancies, ³²P is currently the most commonly used isotope. There have been no reported cases of a second malignancy following treatment with Cr³²PO₄ for a gynecologic tumor; however, the literature reflects a paucity of data on this agent in humans. Based upon evidence from the use of elemental ³²P in other diseases, more data are required to evaluate Cr³²PO₄ properly. Leukemia was first associated with systemic ³²P in polycythemia vera in 1947.⁷² Much debate centered around the issue of whether ³²P was the cause of the leukemia or merely an “innocent bystander.” Evidence is mounting that implicates ³²P as a major contributor to subsequent leukemic development.⁶² The usual dose given in these cases is 3–5 mCi intravenously. In ovarian cancer, Cr³²PO₄ is given intraperitoneally in a dose of 10–15 mCi. This is given as a colloidal suspension to confine the isotope to the abdominal cavity. Nevertheless, the isotope can escape the peritoneum and gain access into the systemic circulation.^{73,74} Animal kinetic stud-

ies show that particulate material, *i.e.*, colloidal ^{32}P , is moved by normal respiration and intestinal peristalsis toward the diaphragm. From the diaphragm the particles pass through lymphatic channels to the mediastinal lymphatics and enter the blood stream. This pathway accounts for approximately 80% of particulate matter clearance from the intraperitoneal cavity and occurs in a matter of hours after intraperitoneal injection.⁷⁵ The significance of these data to human treatment is unclear. Chromium phosphate is a different compound than elemental ^{32}P , which has been associated with leukemogenesis. Chromium phosphate is rapidly absorbed by the liver once it gains access into the circulation, and the lack of count suppression suggests that bone marrow exposure is minimal. However, human kinetics of intraperitoneally administered colloidal ^{32}P is virtually unknown. The distribution within the body needs further definition to assess the potential for risk of this treatment. A multi-institute study to investigate the absorption and distribution of intraperitoneal ^{32}P is now being organized (Alan Lichter: personal communication).

Chemotherapy

Disseminated malignancies often are not manageable by surgery or radiation therapy. Chemotherapy used to treat systemic or disseminated disease in gynecologic cancers has improved survival in many instances.^{2,3} Concomitant with improved survival is the recognition of long-term side effects.

Chemicals have been known to cause cancer since the turn of the century. Workers handling coal tars, certain aromatic amines, and chromium compounds have increased incidences of skin cancer, bladder cancer, and lung cancer, respectively.⁷⁶ Alkylating agents, the most commonly used chemotherapeutic agents in gynecologic cancer, have had their mutagenic effects demonstrated in viruses, bacteria, fungi, plants, insects, and mammals.⁷⁷ The mechanism of action is not completely understood, but DNA binding and subsequent mispairing leading to abnormal DNA sequences appears to be a major pathway to mutagenesis and cell death.⁷⁶ These agents were first associated with malignancy in humans over a decade ago.^{78,79} Alkylating agents used in ovarian cancer and multiple myeloma have been implicated in the development of acute non-lymphocytic leukemia.^{80,81} Soon after these initial reports, alkylating agents were also implicated in the development of leukemia after treatment of various other malignant⁸²⁻⁹³ and nonmalignant^{82,94-96} disorders.

Casciato and Scott reviewed the literature on leukemia development after alkylating agent treatment of a variety of underlying diseases.⁸² They found leukemias

after chemotherapy in multiple myeloma (33 cases), Hodgkin's disease (seven cases), lymphoproliferative disorders (six cases), macroglobulinemia (four cases), solid tumors (eight cases), and nonneoplastic conditions (16 cases). Melphalan, chlorambucil, and cyclophosphamide accounted for 70% of the chemotherapeutic agents used.⁸² The average duration of therapy was 41 months, and leukemia became evident on an average of 59 months after the diagnosis of the underlying disease.⁸²

The role of alkylating agents in the development of leukemia in ovarian cancer patients has recently been studied by two groups.^{90,97} Reimer, Hoover, Fraumeni, and Young conducted a 70-institute survey of a population of 5455 ovarian cancer patients in 1977.⁹⁰ Fifteen cases of leukemia were found compared with 1.62 expected cases (relative risk 9.3, 95% confidence interval of 5.2-15.3). In those patients treated with alkylating agents for two years or more, the relative risk increased to 66.7 times the expected rate.⁹⁰ They also compared the risk of leukemia in 4324 historical controls and found the risk of leukemia for those recent patients treated for two years or more increased to 171 times the risk of ovarian cancer patients in the past (95% confidence interval 88.5-299.5).⁹⁰ Leukemia in the recent group was only observed in patients who received alkylating agents at some time in their course; however, nine patients (69%) also received radiation therapy, though its role in leukemogenesis could not be ascertained.⁹⁰ Leukemia developed a mean of 41.5 months after the initiation of chemotherapy (range 30-90 months) and an average duration of continuous therapy of 24 months. At autopsy, six of nine patients who died of leukemia as a result of treatment for ovarian cancer had no evidence of the gynecologic malignancy.⁹⁰ Pederson-Bjergaard *et al.* have recently reported on 553 ovarian cancer patients treated with dihydroxybusulfan.⁹⁷ In this group, seven patients had leukemia (O/E 7/0.04, relative risk 175). The average duration of therapy was 26 months.⁹⁷

Erythroleukemia has also been described after prolonged treatment of ovarian cancer with alkylating agents.^{90,98} Duration of therapy and time to onset is not different from acute non-lymphocytic leukemia.⁹⁰

Though all risk factors have not been delineated, low doses of chemotherapy for a protracted period of time appear important. Most reports suggest that the dosages of chemotherapy used did not cause substantial acute leukocyte count suppression. After prolonged therapy, anemia, thrombocytopenia, and/or neutropenia, often developed even months after discontinuation of treatment. This prodromal pancytopenia often heralded the onset of leukemia.^{82,90,92}

No alkylating agent appears to be risk free. Reports

have implicated phenylalanine mustard, chlorambucil, cyclophosphamide, thio-tepa, melphalan, and hexamethylmelamine.^{82,90} It is unclear whether the production of chromosomal abnormalities as discussed earlier is etiologic or if prolonged therapy causes immunosuppression and the subsequent surfacing of a malignant clone.¹⁰⁰⁻¹⁰³ Though no safe dose or duration of alkylating agent therapy can be absolutely stated, rarely has leukemia developed with less than 10-12 months of therapy.^{82,90} In a recent follow-up of 746 colorectal cancer patients treated adjuvantly between 1958 and 1964 with thio-tepa or 5-fluoro-2-deoxyuridine for less than one month after surgery, no measurable leukemogenic or carcinogenic effect could be demonstrated.¹⁰⁴

Risk appears to increase with the duration of continuous therapy. Ovarian cancer patients who were treated with alkylating agents for more than two years have over 170 times the risk of patients never exposed to alkylating agents.^{90,97} Those patients treated for intermediate time periods have an intermediate risk of developing leukemia.⁹⁰ Additional studies may help define a dose and duration of therapy that can achieve acceptable responses while minimizing the risk of subsequent leukemia.

Inducement of solid tumor by chemotherapy has not been substantiated in gynecologic malignancies or other cancers.^{8,82,105} There is a suggestion in Hodgkin's disease that solid tumors may be increased (O/E 3/0.7, relative risk 4.3), but the increase does not reach statistical significance.¹⁰⁵ Colon cancer is possibly increased by chemotherapy in ovarian cancer treatment, though separation from irradiation effects and the known risk of colon cancer independent of therapy is difficult. Elucidation of the role that chemotherapy plays in the induction of solid tumors can only be evaluated with further studies.

Combined Modality Therapy

Combination chemotherapy and radiation therapy may be a very important risk factor in second malignancies induced by therapy. Animal studies show the combination to be synergistic.¹⁰⁶ Hodgkin's disease patients treated by intensive irradiation alone had second tumors 3.8 times more frequently than the normal population. With intensive chemotherapy alone, these patients had 3.2 times the incidence of second malignancies. However, with both modalities, the risk of developing a second malignancy increased to 29 times control values.¹⁰⁵ There are no specific data presently available on the oncogenic role of combined radiotherapy and chemotherapy in gynecologic malignancies. However, the two modalities are being used more frequently in combination, and investigators should try to assess the risks of second malignancies after these combined modality approaches.

Summary

Long-term survival has been achieved with present therapy for many gynecologic malignancies.¹⁻³ Concomitant with this increased survival has been the recognition of second neoplasms as a late side effect of therapy. Reports associate vaginal reconstruction with local carcinoma, irradiation for gynecologic cancer with subsequent cancers of other tissues within the radiation port, and alkylating agent administration with the development of leukemia.

Care must be exercised in performing and interpreting studies that associate second malignancies with treatment of a primary cancer. Controls need to be appropriate for the study, and large numbers need to be reviewed to make significant conclusions.

Based upon present available information, there is a suggestion that fabrication of normal skin into a vaginal pouch is associated with subsequent squamous cell carcinoma. Irradiation in therapeutic doses for ovarian or cervical cancer has not been shown to lead to subsequent leukemia; however, there is some evidence that solid tumors and lymphoma may be increased within the radiation port. Intraperitoneal administration of isotopes requires further study of kinetics and distribution before risk evaluation can be attempted, but no instances of second malignancies have been reported. Chemotherapy has been significantly associated with subsequent development of leukemia, particularly after long-term therapy. Associations with solid tumor development have not been well documented. Combinations of chemotherapy and radiation are particularly oncogenic in the treatment of Hodgkin's disease. Their combined use in gynecologic malignancies is increasingly prevalent, but with present data no estimate of risk can be established.

It is in part the measure of the success of present therapy that we now concern ourselves with the long-term complications of our treatments. As primary therapy continues to improve, second neoplasms may become a more profound problem. Only through well-designed and analyzed studies can we optimize primary therapy while minimizing potential late risks.

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