Section 11

OVARIAN CANCER

Summary and Conclusions

This synthesis of the literature on radiotherapy for cancer originating in the ovaries is based on 74 scientific articles, including 12 randomized studies, 18 prospective studies, and 36 retrospective studies. These studies involve 6 140 patients.

- Treatment for patients at early stages of ovarian cancer (stages I and II) is surgery. The value of adjuvant treatment, ie, chemotherapy or radiotherapy, is not demonstrated.
- Tumor volume is decisive to the success of radiotherapy. Microscopic or small macroscopic cancer residuals, remaining after surgery, may respond to radiotherapy, thereby promoting survival.
- The importance of radiotherapy for advanced ovarian cancer is controversial, and studies frequently show contradictory results.
- Two studies have shown the favorable role played by radiotherapy in consolidation treatment of patients if they become cancer-free at advanced stages.
- The role of radiotherapy in treating larger volumes of residual cancer has not been demonstrated, except for strictly palliative treatment.

Introduction

In 1992, 876 new cases of ovarian cancer (II) were diagnosed in Sweden, making it the fifth most common cancer in women. The median age of newly diagnosed patients was between 65 and 69 years. The Nordic countries have the highest incidence of ovarian cancer in the world, and it is increasing. Mortality from the disease is high, with 607 deaths reported in 1992 (III).

Histologically, ovarian cancer is divided into many prognostically important types. The different types are grouped. Epithelial tumors comprise the largest group, representing 95% of all ovarian malignancies. The literature review is limited to this group. As with many other tumors, ovarian cancer is divided into poorly, moderately, and well-differentiated tumors. The differentiation grade is also prognostically important. Some studies report 100% 5-year survival in patients with well-differentiated tumors (1).

Staging[1] (XII) plays a major role in treatment and prognosis. Tumor symptoms are vague, hence ovarian cancer is often detected late. Approximately two thirds of all ovarian cancer cases are not diagnosed until the disease has spread beyond the genital organs.

The stage distribution of ovarian cancer patients, in percent, for the Stockholm region in 1988 was:

Stage Ia 25%
Stage Ib 6%
Stage Ic 4%
Stage II 14%
Stage III 33%
Stage IV 18%

Treatment, General

The first published report appeared already in 1912 on 8 patients who were successfully treated with radiotherapy. The quality of irradiation at that time was insufficient to penetrate deep lying tumors such as ovarian cancer. Many earlier studies used methods and doses which, based on current knowledge and standards, cannot be considered adequate. Since advanced stages often involve the spread of cancer throughout the abdomen, problems arise since the whole abdomen comprises the target volume for radiotherapy. The upper abdomen contains radiosensitive organs such as the kidneys and liver. Therefore, the radiation doses to the upper abdomen are substantially lower than those delivered to the lower abdomen, and less than needed for meaningful treatment of larger-volume, solid tumors. Meaningful radiotherapy for ovarian cancer requires small tumor volumes.

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[1] Staging categories are:
Stage I = Tumor limited to the ovary. A = tumor limited to one ovary; capsule intact, b = tumor limited to both ovaries, capsule intact, and c = tumor limited to one or both ovaries with any of the following: capsule ruptured, and/or malignant cells in ascites.
Stage II = Tumor involves one or both ovaries with pelvic extention. Divided into a, b, and c.
Stage III = Tumor involves one or both ovaries with extention to the abdomen beyond the true pelvis. Divided into a = microscopic metastases only, b = macroscopic metastases beyond the pelvis <2 cm, c = macroscopic metastases >2 cm and/or regional lymph node metastases.
Stage IV = Distant metastases.

Treatment results for ovarian cancer have been poor. Due to the high frequency of advanced stages, total 5-year survival has been around 30%. Radiotherapy was used earlier to a large extent, even to treat the most highly advanced tumors. Ovarian cancer was one of the first solid tumors to be treated by chemotherapy, already in the 1950s. A model has since been developed whereby primary "debulking" surgery, with maximum reduction in tumor volume, is followed by intensive chemotherapy and often second-look laparotomy for confirmation and possible resection of residual tumors. This treatment approach has resulted in approximately 30% to 40% complete tumor remission. However, more than 50% of these patients experienced relapse. Contrary to expectations, new chemotherapy drugs, like cisplatin and its analogues, have not greatly influenced long-term survival. Tumor-free survival has been extended, but 5- and 10-year survival remain essentially unchanged.

With the development of chemotherapy, radiation therapy has become subject to re-evaluation. This is reflected by the numerous articles that focus on radiotherapy's relevance as adjuvant treatment in early stages of ovarian cancer, and whether radiotherapy in advanced stages can improve the outcome, and, if so, when during the treatment process it should be initiated.

Early stages: stages Ia through IIa

The definition of "early stages" means that the tumor is confined to the gynecologic organs, and can be radically removed by macroscopic surgery. The issue at these stages is whether postoperative adjuvant treatment can be meaningful. Several studies have addressed this issue, but with contradictory results. This literature review presents 10 randomized studies addressing the issue. Unfortunately, several studies recruited too few patients, making it difficult to draw definitive conclusions.

Several studies compared adjuvant treatment with no treatment in patients at early stages (Ia, Ib) and/or with well- to moderately differentiated tumors after surgery. These patients are expected to have a very good prognosis, and no significant gain in survival was found in the treated group, regardless of whether treatment was chemotherapy or radiotherapy (2–5). A possible tendency toward lower recurrence rates could be observed among chemotherapy patients (2, 4). Modern chemotherapy was used in only one of the studies. In that study, the treatment group had a longer disease-free interval than the untreated control group, and recurrence could be treated successfully (4).

Several studies compared chemotherapy with radiotherapy after normal primary surgery. No significant differences were observed, regardless of whether the studies used older anti-cancer drugs such as melphalan (1, 2, 6) or modern therapy including cisplatin (7), or whether or not the entire abdomen was irradiated (2, 6, 7), or only the lower abdominal field (1). A tendency toward better results in patients at stage Ic has been observed with combination therapy using anticancer drugs and irradiation of the lower abdomen (1). A tendency for lower toxicity among chemotherapy patients was also observed (7).

Several studies tested the value of postoperative instillation of phosphorus 32 in the abdomen. Randomized studies have compared phosphorus 32 treatment with chemotherapy (3, 4, 8) and with external radiotherapy to the whole abdomen (8). No method appeared to be superior to any other, neither in the studies with patients at stage Ic (3, 4) nor in the study where external radiotherapy was directed at the true pelvis in patients prior to randomization (8). Initial radiotherapy of the true pelvis followed by phosphorus 32 injections was excessively toxic.

Radiotherapy of the whole abdomen was compared with radiotherapy of the pelvis in combination with chemotherapy in patients at stage Ib–II. One study observed no differences (9), however, the second study, in the group of patients with minimal or no residual tumor following surgery, found a significant survival advantage among those given whole abdomen irradiation (10).

Retrospective studies addressing the value of radiotherapy, including early stages of ovarian cancer, have been conducted by several groups, using either external whole abdominal irradiation (11–16) or intraperitoneal phosphorus 32 treatment (17). These studies observed no distinct superiority over chemotherapy or observation alone. However, the studies clearly show that it should be possible to treat early-stage patients having good prognostic factors by surgery alone without adjuvant therapy (18). This finding motivated EORTC and GOG to initiate studies to compare chemotherapy with observation alone in patients with poor prognostic factors.

The review shows that the value of treatment other than surgery (ie, chemotherapy or radiotherapy), has not been demonstrated in patients at early stages of ovarian cancer.

Advanced stages: stages IIb through IV

Ovarian cancer has a strong tendency to spread intraperitoneally, hence tumor cells in most newly diagnosed cases have already spread to the abdominal cavity. As noted above, radiotherapy is of limited value in treating large tumor volumes of ovarian cancer, and therefore radiotherapy alone is not often used in advanced stages. Rather, the value of radiotherapy lies with its role in combination therapy.

Substantial remission of advanced tumors has been achieved after primary tumor reduction (as radical as possible) followed by chemotherapy (currently based on cisplatin combinations). The problems at advanced stages are that the response to chemotherapy depends on the remaining tumor volume following primary surgery, and that the recurrence rate is high even after complete remis-

sion. Following chemotherapy, so-called "second-look" surgery is often performed. It has two objectives: a) to thoroughly study the effects of treatment, and b) to further reduce any remaining tumor residuals prior to further treatment. Radiotherapy can be introduced at different points in time, each of which are discussed separately below.

Postoperative primary radiotherapy

Dembo and associates from the Princess Margaret Hospital in Toronto compared whole abdomen irradiation with pelvic irradiation plus chemotherapy (chlorambucil), and with pelvic irradiation alone (10). The study included primary surgery patients, some at early stages, Ib and IIa, but also patients at stages IIb and III, assessed on several occasions. An analysis of all 190 patients (stages Ib through III) found 58% survival for whole abdomen irradiation and 40% survival for pelvic irradiation plus chlorambucil, but the difference was not statistically significant (19).

Another study divided patients into a radical surgery group (bilateral salpingo-oophorectomy and hysterectomy) and a minor surgery group. The radical surgery group showed survival rates of 78% after whole abdomen irradiation and 51% after pelvic irradiation plus chlorambucil. In patients receiving minor surgery, no difference could be observed among the groups. If patients were divided according to whether or not macroscopic residual cancer was present, survival among patients without residual cancer exceeded 80%, minor residual cancer 56%, and major residual cancer 10%. A later analysis of the data showed that patients who had suboptimal primary surgery and/or a large remaining tumor mass did not benefit from whole abdomen irradiation (20). For patients at stage III, 5-year survival was 48% for no, or unconfirmed, residual cancer, 43% for <2 cm residual cancer, and 18% for >2 cm residual cancer. Reanalysis of the same data in 1993 found that in patients without (or with small) macroscopic residual tumors, the benefit of whole abdomen irradiation was about 25% above other methods. In on-going studies, the group has identified three risk groups with 18% relapse risk in the low risk group, 30% in the moderate risk group, and 70% in the high risk group. The conclusion was that whole abdomen irradiation as the only postoperative method should be reserved for patients in the moderate risk group, defined as stages I grades 2 and 3, stage II and stage III all grades with no or <2 cm residual cancer (21, 22).

Four retrospective studies are worth noting, showing that 10-year survival rates of 38% to 62% can be achieved by whole abdomen irradiation following primary surgery in patients with residual tumors <2 cm in diameter in the largest metastasis. These studies also showed that 10-year survival was poor, from 0% to 14% if the diameter was >2 cm (11–14). Another study of postoperative radiotherapy alone found that a tumor diameter of 3 cm was the limit for successfully managing cancer (23). In patients with <3 cm tumor residuals, survival was 40%, and in patients with minimal residual tumors, survival was 70%. It should be noted that 95% of the patients had tumor residuals localized to the pelvis only.

Postoperative primary radiotherapy combined with chemotherapy

Between 1990 and 1993, four studies were published on combination therapy (chemotherapy and radiotherapy) for advanced ovarian cancer following primary surgery (24–27), one of which involved intraperitoneal chemotherapy (26). The findings on toxicity are contradictory. Three publications found insignificant toxicity, while the fourth found serious toxicity. The results of treatment are also contradictory and inconclusive. The Toronto group treated high-risk patients with combined chemotherapy and radiotherapy, comparing them to patients previously treated by radiotherapy alone. This study favors combination therapy, but the findings acknowledge that radiotherapy contributes to the favorable outcome (24). The conclusions were drawn by comparing the study with findings from a Dutch collaborative study where patients at advanced stages were treated by chemotherapy alone. A Michigan group arrived at a contrary opinion, finding that radiotherapy did not contribute toward improving the outcome over chemotherapy alone (27).

Radiotherapy for consolidation following secondary surgery without residual cancer

Two randomized studies compared external radiotherapy in patients who, after intensive chemotherapy, were histopathologically verified as tumor-free by second-look laparotomy and received no further treatment. The first study, conducted in Switzerland, was initiated by the Ludwig Institute in Bern (28). Selection for radiotherapy was determined by the institutes themselves. The results showed 93% survival in patients receiving whole abdomen irradiation and 49% for patients who did not receive radiotherapy. In patients with residual tumors, no significant differences were found among the groups. The second study, yet unpublished, is a collaborative study from Sweden and Norway. Patients at stage III who were tumor free after 4 chemotherapy cycles were randomized to further chemotherapy, whole abdomen radiotherapy, or observation. Survival in patients receiving whole abdomen radiotherapy was statistically significantly better. However, the complication rate was higher, although acceptable.

Four studies reported results on intraperitoneal phosphorus 32 treatment following second-look surgery revealing no tumor residuals. Two of these studies showed better

results in the group which received phosphorus 32 than in the group not receiving phosphorus 32 treatment. The two other studies found the opposite (29–32). Three of the studies are retrospective and only one, with a relatively small patient base, is randomized (32).

Radiotherapy following secondary surgery of small residual tumor volumes, <2 cm

Twenty-three publications reported results from radiotherapy following second-look laparotomy, where either minimal tumor residuals were found or where further reduction of tumor volume was achieved with minimal or no tumor residuals remaining. Most of these studies initially used chemotherapy with cisplatin combinations. Radiotherapy followed second-look, and in some cases third-look, surgery. The remaining tumor volume size varies in the different reports.

Only three of these studies are randomized and compare chemotherapy with radiotherapy following second-look or third-look surgery. The findings from the first study show an advantage with chemotherapy (33) while the other two show no difference in survival (34, 35).

Contrasting conclusions have been drawn from the retrospective studies. Most authors assert that radiotherapy should be placed after surgery and chemotherapy for small residual tumors <0.5 mm or tumors detected microscopically (36–49). However, other reports disagree, particularly when comparing with chemotherapy following secondary surgery (50–56). The problem with many of these studies is that they are often based on small, selected patient data and the patient mix is frequently highly heterogeneous with regard to tumor volume, stages, radiation dosage, and methods.

In summary, the studies suggest that irradiation of the whole abdomen in advanced stages of ovarian cancer may be of value in patients with little or no residual tumor. The value of radiotherapy for residual macroscopic tumors >2 cm is questionable. Most of these studies are retrospective, and many patients belong to the category receiving intensive chemotherapy, and in whom the results of treatment were unsatisfactory. All these studies can be criticized with regard to patient selection, choice of chemotherapy, radiotherapy methods, and deficient staging.

Palliative treatment

Two publications report on palliative radiotherapy for recurrence in ovarian cancer patients who previously received intensive treatment. The radiation dose in one study was differentiated with respect to the site of recurrence (57). The second study used single-dose radiation along with chemotherapy (58). The former study found a substantial palliative effect, but duration was relatively short. The second, found that toxicity outweighed the advantages of treatment.

Radiotherapy methods

Two types of target volumes have been used for radiotherapy in the lower region of the abdomen; either pelvic irradiation with a 15 × 15 cm field, or lower abdominal cavity irradiation where the field covers the entire lower peritoneal cavity with the upper boundary corresponding to the 4th or 5th lumbar vertebra. The methods used most frequently to irradiate the whole abdominal cavity were either the "moving strip technique", or opposing dual-field irradiation. With both of these methods, the kidneys, and sometimes the liver, are partly protected by reducing the radiation dosage to these areas. A comparative study at the Princess Margaret Hospital found that survival was equivalent for both techniques, but opposing dual-field irradiation was less toxic (59, 60). A six-field method has been used, although to a lesser extent, particularly at the Radiumhemmet. This method helps protect radiosensitive organs in the upper abdominal field (61).

One of the most important arguments against radiotherapy is the toxicity observed when combining surgery, chemotherapy, and radiotherapy. Some studies found that the impact of radiation on bone marrow after chemotherapy was so extensive that the treatments could not be concluded. The conflicting reports on toxicity may be due to how primary chemotherapy was given or the fractionation of radiotherapy (62). Apprehensions concerning toxicity have contributed to the uncertain role played by radiotherapy in ovarian cancer treatment.

Experimental methods

Intraoperative radiotherapy (IORT). This method remains experimental. Three studies have been published in recent years. All three address palliative treatment, but the patient database is small with 1, 3, and 5 patients treated by IORT. The studies conclude that IORT may be potentially beneficial for local, surgically inoperable, tumor sites. However, this method requires further assessment (63–65).

Treatment with radiolabeled antibodies involves coupling radionuclides to monoclonal antibodies, and has been used to treat advanced ovarian cancer. Antibodies were injected into the abdominal cavity to provide local irradiation. The antibodies were targeted at various tumor-related antigens, and the radionuclides consisted mainly of iodine 131, but also indium 111 and yttrium 90. The method remains experimental, but encouraging results have been reported. Two conclusions may be drawn from these studies; toxicity is slight, and the method may improve survival (66–74).

Literature

The articles that appear in the reference list were classified and graded as follows: (Number of studies/Number of patients)

	1 = High	2 = Moderate	3 = Low	Total
M	–	–	–	–
C	3/684	3/384	6/409	12/1 477
P	8/220	6/244	4/18	18/462
R	9/3 045	5/160	22/653	36/3 858
L	3	–	–	3
O	3	2/343	–	5/343
Total	26/3 949	16/1 111	32/1 080	74/6 140

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