Review Article

Role of Radiotherapy in Ovarian Cancer

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SUMMARY

Carcinoma ovary is diagnosed at a late stage due to paucity of symptoms and non-availability of any specific screening tools. The available modalities of treatment viz; surgery and /or chemotherapy give only 25-40% survival in advanced stage disease. No large scale randomized trials are available to provide a guidance to role or sequence of radiation therapy in epithelial carcinoma of ovary. The article is a brief attempt to sensitize the readers to the non-utilized application of an effective modality of treatment and gain an audience to find ways of applying radiation in the era of targeted techniques along with conformal avoidance that was not possible in the times of orthovoltage/cobalt therapy.

INTRODUCTION

Ovarian cancer is the fifth most common cancer among women with a lifetime risk of about 1 in 70. It is the leading cause of death with highest fatality to case ratio of all the gynecologic malignancies. 70-75% of the cases are diagnosed at an advanced stage and early detection is difficult. Despite advances in the treatment of epithelial ovarian cancer in the past decade, this disease still poses a great challenge, 5-year survival of advanced stage ranging from 15-25%. Primary surgical cytoreduction followed by paclitaxel plus platinum based chemotherapy (CT) is currently the standard treatment approach.[1] Despite its long history in the treatment of ovarian cancer and its proven curative role in patients with microscopic or minimal residual disease, the proper role of radiotherapy (RT) in the management of ovarian cancer is controversial and not clearly established.[2] Similarly, the potential role of RT in the consolidative treatment and as salvage therapy following CT failure remains controversial. In this review, we have tried to analyze the existing data on the value of radiotherapy in the treatment of epithelial ovarian cancer.

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EARLY STAGE EPITHELIAL OVARIAN CANCER (FIGO STAGE I & II)

Clinical trials have evaluated the postoperative impact of both radiation therapy and chemotherapy upon the survival of patients with early stage disease [3-5]. There have been two randomized studies of external-beam pelvic radiation therapy in patients with Stage I tumours[5,6] A Princess Margaret Hospital randomized trial of 147 patients compared pelvic radiotherapy alone or with chlorambucil chemotherapy to whole abdomen radiotherapy, in patients with stages I-III disease [5]. After a 7 year follow-up, the 10-year difference in survival was significantly higher in the 76 patients treated with pelvis plus whole abdomen radiotherapy compared to the 71 patients treated with pelvic irradiation and chlorambucil (46% vs 31%, p=0.05). The survival benefit was only seen in patients with small macroscopic residual tumour (<2cm) or no tumour residual. In the presence of extensive tumour residual, there was no benefit seen with whole abdomen radiation therapy compared to the other treatment methods In the study of the Gynecologic Oncology Group (GOG),[6] Stage I patients were randomized postoperatively between observation, pelvic radiation therapy, and melphalan. Unfortunately, the elimination of almost half the entered patients from the analysis, as well as the absence of a requirement

for complete surgical staging, makes it difficult to draw conclusions from this study. Both studies failed to demonstrate superiority for any form of therapy. While pelvic radiation produced a reduction in the rate of pelvic relapses, distant relapses occurred throughout the peritoneal cavity, leading to the same overall relapse rate.

Abdominal pelvic radiation therapy has not been the subject of a Phase III trial in patients with Stage I disease but has been retrospectively compared to pelvic radiation therapy or no treatment.[7] No benefit was found in grade 1 patients, where the risk of relapse was under 5% overall. In grades 2 and 3, a statistically non significant reduction in relapse risk was observed. In patients whose tumours were densely adherent, a significant reduction in relapse was associated with the use of abdominal pelvic radiation therapy. These patients are more correctly classified and treated as having Stage II disease.

RADIATION THERAPY

Pivotal to the use of curative radiation in ovarian cancer is recognition that ovarian cancer has a dominant route of dissemination throughout the peritoneal cavity and that tumour remains confined to the abdominal cavity for extended periods of time. In fact, at first relapse, regardless of therapy, tumour is confined to the abdominal cavity in approximately 85% of patients.[8] Thus, for radiation to be of curative benefit, techniques that encompass the whole peritoneal cavity, rather than just the pelvis or lower abdomen alone, are likely to be most beneficial. Several studies have compared treatment using abdomino-pelvic radiation therapy with pelvic radiation therapy alone or combined with single-agent alkylating chemotherapy.[5] These studies demonstrate a superior outcome using abdomino-pelvic radiation therapy for patients with minimal residual disease after primary surgery.

The dose of radiation that can be delivered safely to the upper abdomen is considerably lower than that which would be considered optimal and sufficient for the successful treatment of solid tumours. The efficacy of radiation in eradicating residual tumours is dependent on the number of clonogenic cells present. Thus, the limitations imposed by the tolerance of the normal tissues in the abdomen, particularly the gastrointestinal tract, imply that whole-abdominal irradiation would produce a modest improvement in tumour control in the upper abdomen, but this benefit would be seen only in patients with small numbers of residual clonogenic cells or microscopic disease residuum in the upper abdomen. There is little or no curative potential for abdominal irradiation in patients with bulky disease in the upper abdomen.

CHOICE OF RADIATION TECHNIQUE

Several techniques for delivering radiation to the entire peritoneal cavity have been developed. The two most commonly used are the **moving-strip technique**, in which a small part of the abdomen is irradiated daily sequentially; and the **open-field technique**, in which the whole volume is treated daily. The moving-strip technique was initiated in an era when radiation therapy equipment could not adequately encompass the large volumes required in one portal.[9] It was justified because a biologically higher dose can be delivered sequentially to the smaller volumes than could be delivered simultaneously to the whole volume in the open-field technique. The duration of the entire treatment course, however, using the moving-strip technique was approximately twice that of the open field. Theoretically, the prolonged treatment course might allow accelerated proliferation of tumour [10] and possible reseeding of tumour metastases from the untreated area of the peritoneum back to the previously treated area. Given the movement of the abdominal contents from day to day, there is also some uncertainty about the dose received by mobile organs. These two techniques have been compared with the commonly used radiation doses and fractionation schemes.[9] In both studies the difference in 5-year survival between the two treatment approaches was less than 1%. The analysis of the Princess Margaret Hospital study shows the two techniques to be comparable in all patient subgroups, regardless of stage, histology, grade, or tumour residuum.[11,12] Furthermore, there were no

differences in acute toxicity between the two treatment techniques. Although late complications were infrequent with either method, they were less commonly encountered with the open-field technique. The open-field technique has become the standard in most centers because of shorter duration of treatment, technical simplicity, and reduced toxicity. Variations in the open-field technique including adding T-shaped boost portal to the para-aortic nodes and medial domes of the diaphragm and treating the upper and lower abdomen through separate portals.

While the technique of radiation is likely to continue to be that of the open field, recent radiobiological information suggests theoretical strategies to change radiation fractionation schemes to increase the biologically effective dose delivered without increasing radiation toxicity. The effect of a simple dose escalation using the same 1 Gy dose per fraction of abdominal irradiation was examined in a randomized trial by Morgan et al.[13] Escalation to a total abdominal dose of 27.5 Gy in 27 fractions did not result in improved disease or overall survival nor was toxicity increased. Possible changes in radiation fractionation schemes include delivering two to three fractions per day of fraction size less than 1 Gy. Using such a scheme, with an open-field technique, it was possible to deliver 30.6 Gy in 0.8 Gy fractions twice daily with a pelvic boost of 1,519.2 Gy to the pelvis; treatment was well tolerated and did not appear to result in any increased late toxicity. Authors used this technique to treat 15 patients with known residual disease after induction with cis-platin based regimens. Limiting the kidney and liver doses to 20 Gy and 30.4 Gy respectively ,all patients completed the planned treatment and only two patients required a treatment break for thrombocytopenia. No episodes of small bowel obstruction were reported in the study. Changed fractionation schemes, with or without accompanying "chemotherapy," warrant exploration to determine whether they will be of increased curative benefit in patients with optimal disease or whether they will even be useful treatment for some patients with suboptimal disease.

SELECTING PATIENTS FOR ABDOMINO-PELVIC RADIATION THERAPY

Abdomino-pelvic radiation therapy has been used during the past 15 years in all stages and extents of ovarian cancer.[14] From these randomized and nonrandomized studies, considerable data have defined the patient and tumour factors that will predict a favorable outcome after the use of abdomino-pelvic radiation therapy. Besides the general medical condition of the patients and their suitability for such therapy, the tumour factors that determine suitability include the extent of disease at presentation, the amounts and sites of residual disease in the pelvis and abdomen, and the histopathological findings (grade and type) of the tumour.

A multivariate analysis of pathological prognostic factors was performed for an initial cohort of patients treated between 1971 and 1978.[15] A second cohort of patients treated between 1979 and 1985 was examined to test the validity and reproducibility of the original prognostic classification. The derived prognostic classification has been used to select treatment by classifying patients with ovarian cancer into low, intermediate, or high-risk categories. The low-risk group is composed of patients with Stage I ovarian cancer, who by multifactorial analysis of prognosis within Stage I have been determined to have such a good survival (96% ± 2%) that no postoperative therapy is warranted. These patients at low risk for recurrence after surgery alone are those with Stage I, grade 1 disease, without evidence of dense adherence or ascites. The remainder of patients with Stage I disease, i.e., those with grade 2 or 3, or with dense adherence or ascites, have a significant risk of relapse and fall into the intermediate-risk group. Currently, the randomized studies in the management of Stage I disease have failed to show a significant advantage for treatment.While a curative benefit for abdomino-pelvic radiation therapy has not been established in Stage I disease, except for those with dense adherence, it has been established as curative therapy for a large proportion of patients with Stage II disease whose residuum is less than 2 cm.[16] Thus, it

seems appropriate at this time to consider that abdomino-pelvic radiation therapy or platinum-based chemotherapy are both rational options for management of the high-risk patient with Stage I disease i.e., those with grade 2 or 3 tumours, with large-volume ascites, and/or positive peritoneal cytologic finding, and those with dense adherence.

In selecting patients with Stages II and III disease for whom abdomino-pelvic radiation therapy is appropriate, the amount and site of residual disease and the tumour grade are strong determinants of success of outcome. Given the restrictions on the dose deliverable to the upper abdomen and pelvis, abdomino-pelvic irradiation should be used only in patients with no macroscopic disease in the upper abdomen and with small macroscopic (0 to 2 cm) residual disease in the pelvis. This classification of patients into risk groups has been validated by three other investigators in New Germany[16] Haven[17] and in Denmark.[18] The patients in the intermediate-risk category constitute about 33% of the total patient population with ovarian cancer. It is in this intermediate-risk group that abdomino-pelvic radiation therapy is the most appropriate as the sole postoperative treatment method. These patients are mainly derived from patients with Stages I and II disease, including those with dense adherence. Those with Stage III disease are suitable for this treatment alone if their macroscopic residual tumour is less than 2 cm, is located in the pelvis, and is grade 1. Using abdomino-pelvic radiation therapy, more than 67% of intermediate-risk patients were alive and disease-free 10 years after treatment, with minimal late morbidity. Recognition of this poor outcome led to examine, in a nonrandomized study, the use of six cycles of cisplatin-based combination chemotherapy, followed by abdominopelvic radiation therapy. In these high-risk, optimally cytoreduced patients, the sequential therapy appeared to improve their median survival time and relapse-free rate significantly, compared to that achieved by radiation therapy alone.[19]

Sequential Chemotherapy and Radiotherapy

The similarity of the long-term survivals for patients treated with platinum-containing chemotherapy or radiation therapy should stimulate an interest in the use of radiation therapy in ovarian cancer. While many investigators were quick to discard radiation therapy from the armamentarium for management of ovarian cancer when cisplatin was believed to be a promising agent for improved cure rates, it is now apparent that decision may have been ill-conceived. It would now appear to be appropriate to further investigate the role of radiation therapy, either as a sole agent or as part of a multimodality treatment in the primary management of ovarian cancer. With the demonstration that paclitaxel is a highly active cytotoxic agent in ovarian cancer and that interaction may occur between this agent and radiation it would seem appropriate to explore their concurrent use in ovarian cancer.[20] Kong and colleagues treated patients with sequential chemotherapy, second-look surgery, and whole-abdominal radiation therapy.[21] In that study, a total dose of 30 Gy was delivered to the abdomen in 1 Gy fractions twice daily, and only one patient developed bowel obstruction. To date, no studies have been reported examining either the toxicity or efficacy of salvage or consolidation whole abdomino-pelvic irradiation after paclitaxel-based chemotherapy.

PALLIATION

Recurrent or persistent ovarian cancer after first-line chemotherapy is incurable. Patients are often symptomatic, with generalized or localized abdominal symptoms from intra peritoneal disease. Usually, second, third, or fourth-line chemotherapy is used in attempts to prolong life and palliate symptoms. Reported response rates range between 10% and 43% and are associated with various toxicities.[22] Radiation therapy as a palliative modality in ovarian cancer is often neglected but may be very useful if the sole or dominant symptomatic problem for the patient is localized to a site and volume that may be safely encompassed in a radiation field. For example, a fixed pelvic mass eroding the vaginal mucosa causing bleeding, pain, or bowel or bladder dysfunction may occur without obvious disseminated symptomatic peritoneal disease. Tumour regression or symptomatic relief can often be obtained in

these situations from local irradiation. Similarly radiation may be employed to treat localized masses elsewhere in the abdomen, such as the retroperitoneal nodes. Patients with isolated brain metastasis should be treated with surgical resection followed by whole brain irradiation and chemotherapy when possible. Patients may survive up to 3 years with this combination treatment.[23]

CONCLUSION

There is paucity of data on definitive role of radiation for management of carcinoma ovary till date. The advent of organ sparing radiotherapy techniques in the last decade along with a better understanding of ovarian cancer's natural history can be translated into prospective trials with/without chemotherapy. These trials may be able to harvest the benefits for carcinoma ovary over and above achieved by improved surgical techniques and the available chemotherapy agents.

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