MINI-REVIEW

Radiotherapy for Ovarian Cancers - Redefining the Role

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Abstract

Radiation therapy in ovarian cancers has been considered an outdated concept for many years, mainly due to its toxicity and failure to show benefit in terms of survival. Chemotherapy has been extensively used after surgery for these cancers and it has almost replaced radiation therapy as an adjuvant treatment. Nevertheless, failures in ovarian cancers continue to occur even with the use of newer and effective chemotherapy regimens. About 70% patients demonstrate recurrence in the abdomen or pelvis after first line chemotherapy in ovarian cancers. With advances in technology and sophistication of radiation techniques, along with the molecular and biological knowledge of distinct histological subtypes, there is a need to redefine the role of radiation therapy. This review article focuses on the literature on use of radiation in ovarian cancers and its rationale and indications in the present day. For this, a literature pub med/medline search was performed from January 1975 to March 2014 to redefine the role of radiotherapy in ovarian cancers.

Keywords: Ovarian cancer - radiation therapy - chemotherapy

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Introduction

Ovarian cancer is the fourth most frequent fatal malignancy in women and the leading cause of death from gynecological malignancies. A disease that was initially thought to be predominant in the western countries is now showing an increasing trend even in the developing countries (Murthy et al., 2009; Bhurgri et al., 2011). A large majority of ovarian malignancies, 85% to 90%, arise from the surface layer or epithelium (Gocheva, 2003).

The modern management of ovarian carcinoma is the aggressive surgical removal of tumor masses (debulking) and platinum-based chemotherapy (Ozols, 2003). Although important advances have been made during the last three decades in surgery and chemotherapy, overall survival (OS) for patients with ovarian cancer has not changed significantly. A high proportion of patients (60-80%) with advanced ovarian epithelial cancer initially respond to first-line chemotherapy, but ultimately majority of these patients (about 70%) recur either in the abdomen or pelvis. Despite the improved surgical techniques and use of platinum based chemotherapy, as many as 20% of women with early stage disease eventually relapse and die from their disease. The 5-year survival rate for FIGO stage III disease is approximately 20-25% and the median time to recurrence is less than 2 years. The relapses are associated with low response rate to further chemotherapy and subsequent poor prognosis, (Bristow et al., 2002; Suprarest et al., 2014). With these not very satisfying results achieved during the last decade with chemotherapeutic regimens, there has been resurgence of interest in the use of radiotherapy in ovarian cancers. The role of radiotherapy in the management of ovarian cancers is still not clearly established despite its long history in the treatment of the disease and its role in the present day continues to remain controversial. Thus, in order to evaluate the role of radiotherapy in ovarian cancer, we conducted a literature search from January 1975 to March 2014, through the pub med/medline central database at National center for biotechnology information (NCBI) website (http://www.ncbi.nlm.nih.gov/pmc) using the search terms, "Ovarian cancer", "radiation therapy", "whole abdomen radiotherapy", "involved-field radiotherapy" so as to discuss the present day role of radiation in ovarian cancers in this review article.

Role of Radiotherapy - Literature Review

Radiotherapy has been tried in ovarian cancers in the literature as a single curative modality, as part of a combined modality approach in early and advanced stage cancers as adjuvant and consolidative therapies respectively, as salvage therapy for patients with small volume persistent disease after primary cytoreductive surgery and chemotherapy, and as palliative therapy in metastatic settings. Radiation in ovarian cancer patients has been delivered to either whole abdomen or to pelvis alone. The present article discusses the role and the evidence for the use of radiotherapy in ovarian cancers (Figure 1).

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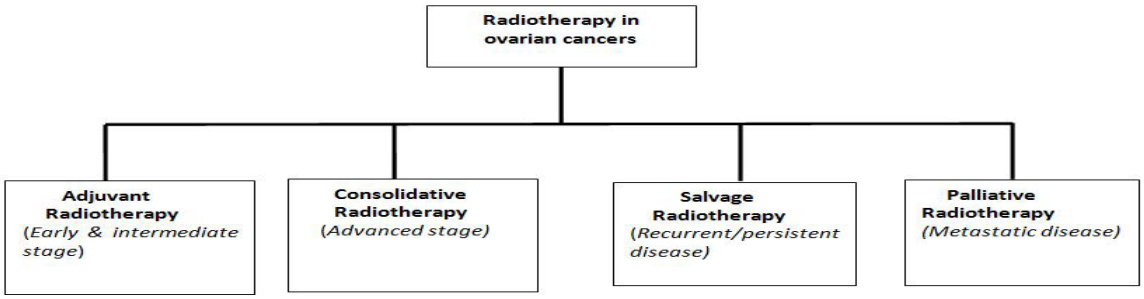

Figure 1. Radiotherapy in Ovarian Cancers

Radiotherapy as an adjuvant treatment

The superiority of radiotherapy as compared to chemotherapy and the fact that radiotherapy may be curative has been well documented in various trials in the past. Trials in the past have shown that radiotherapy to the whole abdomen following surgery is more effective than certain chemotherapy and pelvic radiation. In the early 1980's Dembo et al, categorized ovarian cancers into distinct groups of low, intermediate and high risk depending on the stage of the disease, postoperative residual disease and tumor grade (Dembo and Bush, 1982). Studies have shown that whole abdomen radiotherapy may be an option in early and intermediate stage disease with minimum postoperative residual disease.

Dembo and colleagues analyzed five published trials in patients who underwent surgery followed by whole abdominal radiotherapy Approximately 40-50% of these patients with minimal residual (<2cm) disease after surgery were cured. The proportion of survivors was directly related to the stage of the disease and the extent of residual disease (Dembo et al., 1979).

In another study by the Princess Margaret Hospital, 147 patients with stages I-III disease were randomized to, pelvic radiotherapy plus chlorambucil chemotherapy compared to whole abdomen radiotherapy. 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). However, the survival benefit was only seen in patients with small macroscopic residual tumor (<2cm) or no tumor residual. In the presence of extensive tumor residual, no benefit was seen with whole abdomen radiation therapy compared to the other treatment methods (Dembo, 1992). In a prospective randomized study, Kojs et al, randomized 150 patients of stage IA, IB grades G2-3, and all patients with stage IC and IIA, without any post operative residual disease to whole abdomen irradiation of 30 Gy in 24 fractions over 5 weeks, with a pelvic boost to 50 Gy versus chemotherapy with cisplatin, doxorubicin and cyclophosphamide for six cycles. Similar outcomes were reported for both the groups and the actuarial five year disease free survival was 81% for both the arms. Grade 3 bowel toxicity was observed in three patients (Kojs et al., 2001).

These trials validated that radiation therapy is an effective adjuvant therapy in selected patients with ovarian cancer. They also revealed that whole abdomen radiation therapy is superior to pelvic radiotherapy alone or with certain chemotherapeutic agents in patients with minimal residual or no residual disease. Although the above studies demonstrated comparable benefits with chemotherapy, the role of radiotherapy gradually diminished with the advent of platinum and taxane based chemotherapy and more aggressive surgical techniques.

Consolidative radiotherapy after chemotherapy

In the present day, primary cytoreductive surgery (with or without neoadjuvant chemotherapy) followed by adjuvant chemotherapy is the standard practice in ovarian cancers. However, there are high rates of recurrence as well as residual gross disease after chemotherapy. Many consolidation therapies like intraperitoneal chemotherapy/ radiotherapy have been tried in the literature. Consolidative radiotherapy may offer the possibility of improving tumor control in selected patients.

Sorbe and colleagues conducted a trial with 98 patients with stage III ovarian cancer who had initial cytoreductive surgery followed by chemotherapy with complete pathologic response. They were randomly assigned to receive either chemotherapy, whole abdominal radiotherapy, or no further treatment. The patients who had whole abdominal radiotherapy had a significantly better progression-free survival rate (56%) compared to chemotherapy (36%) and no further treatment (33%). At 5 years, the overall survival rates were 69%, 57%, and 65% for radiation, chemotherapy, and no treatment respectively (Sorbe, 2003).

In a recent study by Beiet et al, ten patients with ovarian cancer who had undergone optimal cytoreduction and were categorized under "intermediate risk" were treated with whole abdomen radiotherapy along with platinum based chemotherapy (9/10). A dose of 22.5Gy was delivered to the abdomen and the dose per fraction was 1.25Gy. An additional boost of 40-45Gy was delivered to the pelvis. At a median follow up of 8 years the five-year acturial disease free survival and overall survivals were 60% and 70% respectively and only one patient developed significant bowel toxicity requiring surgery (Beiet et al., 2010).

Rochet et al studied the feasibility and toxicity of consolidative whole abdomen intensity modulated radiotherapy after optimal cytoreduction and chemotherapy in ten patients with high risk advanced ovarian cancers. A dose of 30Gy in 1.5Gy per fraction was delivered to the planning target volume (PTV) and all the patients completed the planned treatment without any interruptions. Four patients recurred after a median follow up of 23

months and three patients had treatment related bowel obstruction (Rochet et al., 2010). Based on these results, a phase II trial, The OVAR-IMRT-02 study has been initiated to evaluate the toxicity in patients with stage III ovarian cancer undergoing optimal cytoreduction and complete response after chemotherapy (Rochet et al., 2011).

In a recent study, Chang et al, analyzed the patterns of abdominopelvic failures in patients with stage III ovarian cancer inorder to define a subgroup that would benefit from the use of radiotherapy. Of the 149 patients reviewed, 70 (53%) had abdominopelvic failures in whom abdominopelvic radiation was indicated. The author's concluded that abdominopelvic radiation could be helpful in reducing failures in stage III patients with intermediate risk (Chang et al., 2013).

Salvage with radiation therapy (recurrent/persistent disease)

The response rates to second line chemotherapy in patients with relapsed ovarian cancers are poor despite the availability of newer chemotherapeutic agents. In patients with platinum refractory disease the response rates to chemotherapy varies between 10-20%. (Eltaabbakh and Goodrich, 2006). Since, the results, with chemotherapy alone for recurrent disease are dismal; adding radiotherapy for localized disease after chemotherapy or after a complete remission may help in improving the outcome in selected patients. Brown et al reviewed 102 patients who received involved- field radiotherapy for recurrent nodal and extranodal ovarian cancers. At a median follow up of 38 months, 35 patients had no evidence of disease. Higher responses were seen in patients sensitive to platinum chemotherapy and in 8 patients with clear cell histology (Brown et al., 2013).

In another study by Yahara et al, the efficacy and toxicity of radiotherapy was analyzed in 27 patients with limited recurrences after complete remission with first line chemotherapy. Twenty (74%) patients received chemotherapy for recurrences followed by radiotherapy. Of the 22 (82%) patients who had an objective response, complete response was observed in 11 patients and 11 patients had a partial response. No grade III toxicities were reported. The two-year progression free survival was 39% and local control rates were 96% (Yahara et al., 2013). Thus, the above two studies clearly demonstrate the benefit of radiotherapy in reducing the loco-regional recurrences with limited toxicity and thus may help in improving survival in selected patients.

Palliative radiation therapy

Approximately 66% of women with ovarian cancer develop recurrent or metastatic disease. As tumor spreads systemically, women may often present with pain, bleeding, abdominal symptoms which are usually unmanageable with chemotherapy alone. Radiotherapy has been used in the palliation of symptoms in advanced recurrent ovarian tumors.

Fox Chase Cancer Center palliatively treated 33 women with ovarian cancer who were having pain and bleeding. The complete palliative response rate was 51% and overall (complete and partial) response rate was 79%. Patients were found to have good symptom control for an average of 4 months (Corn et al., 1994).

Quon et al. (2006) reviewed 53 patients with recurrent symptomatic ovarian cancer who received palliative radiotherapy. The commonly used radiotherapy dose was 30Gy in 10 fractions. Statistically significant complete response rates of 88%, 65%, and 36% were reported for symptoms of bleeding, pain, and "others", respectively and the median duration of response was 4.8 months (Quonet al., 2006).

In a study by Meerleer et al. (2011) whole abdomen pelvic radiotherapy with Intensity modulated arc therapy was used in palliative treatment of bulky recurrent chemo-resistant peritoneal disease in 13 patients. A total dose of 33Gy was delivered to the abdomen and pelvis in 22 fractions and the dose per fraction was 1.5Gy. A complete symptom response was reported in 9/13 patients and in 4/6 patients a complete symptom response in obstruction and sub obstruction was observed lasting for a median duration of 16 weeks. This resulted in a significant improvement in the improvement of quality of life and social life (Meerleer et al., 2011). Thus, radiotherapy has been successfully shown to relieve symptoms of pelvic pain, large bowel obstruction, pulmonary compromise, bone pain, and other symptoms of diffuse disease.

Radiotherapy in non-serous histology

Currently, the standard of care for epithelial ovarian cancers is surgery and chemotherapy with taxane and platinum combination chemotherapy irrespective of the histological subtype. However, it is now evident that ovarian cancers may be represented by distinct histological subtypes depending on various biological and molecular characteristics.

Several studies have demonstrated the lack of improvement in survival in relatively uncommon non-serous variants of ovarian cancer like clear cell carcinoma, endometrioid, and mucinous variants with standard chemotherapy regimens (Sirichaisutdhikorn et al., 2009). Recent hypothesis generating data from the use of adjuvant radiation following adjuvant chemotherapy in these rarer non-serous ovarian subtypes has shown an incremental survival benefit. No incremental benefit was observed for the more common serous subtype.

Nagai et al studied 16 patients between 1996 and 2004, with OCC who underwent initial debulking surgery and whole abdomen radiotherapy (WAR). Patients with clear cell histology, International Federation of Gynaecology and Obstetrics (FIGO) stage Ic–III, no macroscopic residual disease in the upper abdomen and residual disease in the pelvic cavity ≤2 cm, were taken up for WAR which comprised of external beam radiotherapy (EBRT) to the entire abdominal cavity with 22.0-24.0 Gy/22-24 fractions followed by EBRT to the pelvis with 23.4-21.6 Gy/12-13 fractions. Overall survival and disease-free survival were compared with 12 historical control (HC) patients treated with initial debulking surgery followed by platinum-based chemotherapy. Fifteen of the 16 patients (94%) completed the planned WAR. Two patients developed radiation enterocolitis and required bowel surgery. Five-year OS and DFS in the WAR/HC group were 81.8%/33.3% and

81.2%/25.0% (p=0.031 and p=0.006), respectively. This study concluded that postoperative WAR may be effective in selected patients with ovarian clear cell carcinoma (Nagai et al., 2007).

A Population based Outcome data in British Columbia, Canada retrospectively studied the outcomes for 241 patients with stage I or II clear cell ovarian cancer, who underwent complete surgery and given three cycles of carboplatin and paclitaxel for. By a physician choice, 211 were treated with chemotherapy whereas 103 had the addition of pelvic and whole abdominal radiation in a dose of 22.5 Gy in 10 fractions to the pelvis, followed by 22.5 Gy in 22 fractions to the whole abdomen. Overall, 5- and 10-year disease free survival rates were 84% and 70% for stage IA/B, 67% and 57% for stage IC, and 49% and 44% for stage II, respectively.Peritoneal cytological status in patients with stage IC disease was found to be an important prognostic factor. The 5-year DFS was 86% when peritoneal cytology was negative compared with 62% when positive or unknown. When radiation was added to chemotherapy, there was no apparent incremental benefit for stage IA and IC with rupture only. However, for the patients with stage IC disease with cytologic positivity or unknown or surface involvement, the DFS was statistically improved with an absolute increase of 20% at 5 years. This constituted a relative reduction in risk of recurrence of 49% with the addition of irradiation for those with cytologic or surface positivity or in which this was unknown. Therefore, irradiation contributed to improved DFS by reducing pelvic relapse rates from 76% to 62%.Abdominal recurrence occurred in 42% with chemotherapy and only 13% with whole abdominal and pelvic irradiation with 5-year DFS being 25% with chemotherapy and 81% with irradiation. Of note is that even without sophisticated radiation techniques grade 3 and 4 late-radiation toxicities were extremely rare; grade 3 in 3% and grade 4 in 1% of patients, respectively (Hoskin et al., 2012).

In a population-based review, 703 patients without macroscopic post operative residual treated with adjuvant chemotherapy with or without sequential radiotherapy were analyzed. Of the 351 patients who received radiotherapy, those with clear cell, mucinous or endometroid histology showed a 40% reduction in the disease- specific mortality and 43% reduction in overall mortality. The benefit or radiotherapy was not observed for stage III and serous tumors (Svenerton et al., 2011).

In a histopahologic review of complete slide sets of 1009 patients with ovarian cancer, Kobel et al extrapolated the distribution the types of tumor into low stage (I/II) and high stage (III/IV). Of the entire cohort, high stage serous carcinomas constituted 35.5% of stage I/II and 87.7% were stage III/ IV tumors. On the contrary, 26% of clear cell, 27% of endometroid tumors and 8% of mucinous tumors were low stage and only 5% of clear cell, 3% of endometroid and 1% of mucinous were high stage tumors (kobel et al., 2010).

This implies that since 90% of clear cell, endometroid and mucinous tumors are stage I/II, i.e. confined to the pelvis, local treatment in the form of radiotherapy may be of benefit, either alone or in conjunction with molecular target therapy/ chemotherapy in these subset of patients (Thomas et al., 2013).

Reasons for limited use of radiation in ovarian cancers

It is evident from the above-discussed studies that adjuvant radiation therapy is beneficial in ovarian cancers. Although there have been no randomized trials comparing platinum based chemotherapy to radiation therapy worldwide, postoperative treatment with platinum based chemotherapy has become the standard of care irrespective of the histological subtype. There various reasons behind diminished role of radiotherapy in ovarian cancers could be that the majority of trials in the past included largely the patients with serous histology. Another limiting factor could be that radiation can effect on bone marrow reserve, possibly precluding maximal chemotherapy utilization. In addition, wide-field irradiation in tolerable doses is largely ineffective in eradicating bulky residual disease in the peritoneal cavity.

However, in contrary to the above speculations, with the sophistication and advancement in radiotherapy techniques, it is evident that the whole abdominal radiotherapy may be well tolerated with the use of appropriate radiation therapy techniques and patient selection (Mahantshetty et al., 2010; Rochet et al., 2010; Shetty et al., 2013).

Radiotherapy Indications for Ovarian Cancers

Regarding the indications of radiation therapy in ovarian cancers, it is apparent from the studies in literature, that the prerequisite for postoperative adjuvant therapy in early and intermediate stage ovarian cancers, and for consolidation radiotherapy in advanced stage ovarian cancers, is aggressive cytoreductive surgery. It seems clear that aggressive adjuvant combination (radiation and chemo therapy) is not of much benefit in case of large residual tumors. As to the therapeutic sequence, radiation therapy makes sense only after chemotherapy.

Thus, what should be the indications of radiation therapy in ovarian cancers? Although a consensus can be made only after a well organized randomized controlled trial comparing adjuvant chemotherapy and whole abdomen radiation, from the above discussion however, it can be concluded that non serous variants (clear cell, endometrioid, and mucinous), intermediate risk patients (stage I, II, and stage III disease with grades 1, 2, and 3, but no residual disease post-surgery), stage II and stage III disease (with residuum less than 2 cm in diameter and confined to the pelvis), recurrent disease (less than 2 cm in diameter and confined to the pelvis), are the patients that can be considered the potential candidates for radiation therapy. In addition, radiotherapy may also be used in palliation of symptoms which cannot be taken care by chemotherapy alone.

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