



# Radiotherapy in women with epithelial ovarian cancer: historical role, current advances, and indications

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**Abstract:** Epithelial ovarian cancer (OC) is known to be a neoplasm responsive to radiotherapy (RT). Nevertheless, the role of RT in the management of this disease represent a topic of controversy, and the indications for its use are not fully established. Initial studies suggested that the addition of RT in the form of intraperitoneal (IP) radioisotopes was useful. Indications for this treatment were peritoneal cytology with tumor cells, peritoneal implants, and capsule rupture. The instillation of radioisotopes was contraindicated when macroscopic residual disease was present. Pelvic RT was used after surgery in patients with an absence of gross residual disease. Early studies established the inadequacy of this technique and the need for treating the whole abdomen. Whole abdominal irradiation (WAI) was a therapeutic tool used in the prechemotherapy era to eradicate large amounts of microscopic peritoneal disease. Ideal candidates for WAI were stage I patients with grade 2 or 3 tumors; stage II patients with grade 1 or 2 tumors and residual disease, and stage III, grade 1 patients with <2 cm residual disease. The disadvantages of WAI were the dose-limiting toxicities, which were predominantly acute hematologic and late gastrointestinal. The era of aggressive debulking and platinum agents made WAI fall out of favor as a treatment of OC. Selective approaches with highly conformal radiotherapy (CRT) have been used in case of limited recurrent or unresectable disease with the potential for long-term disease control. Currently, the role of RT in OC applies for patients with recurrent oligometastatic or oligoprogressive disease and in the palliative setting for symptom control. We performed a nonsystematic review and included data from both retrospective and prospective studies focusing on the use of RT for OC and its biological rationale. Furthermore, ongoing trials on this issue are reported.

**Keywords:** Immunotherapy ovarian cancer (immunotherapy OC); radiosensitizers; radiotherapy (RT); stereotactic body radiotherapy (SBRT)

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## Introduction

Ovarian cancer (OC) is one of the most common malignancies around the globe, with 295,414 newly diagnosed cases and 184,799 deaths registered in 2018, according to Globocan (1). Because of a silent spillage OC is mainly diagnosed as an advanced disease (the most common

stage at presentation); being the most lethal gynecological malignancy (2,3). The World Health Organization histological classification for ovarian tumors separates ovarian neoplasms according to the probability of origin: Surface epithelial (65%), germ cell (15%), sex cord-stromal (10%), metastatic (5%) and miscellaneous (5%). Surface epithelial tumors are further classified by cell type (serous,

mucinous, endometrioid) and atypia [benign, borderline (atypical proliferation, low malignant potential)] or malignant (4). The hallmark of OC biology is intraperitoneal (IP) dissemination. Early OC stages may present with an ovarian tumor in nearly 30% of cancer cases (5). Once the tumor mass overpasses the ovarian surface, tumor cells disseminate through the IP fluid and transports malignant cells in a diffuse peritoneal distribution (5).

Once OC is diagnosed, treatment is based on the stage of disease, age, performance status, life expectancy, and comorbidities. Staging is performed with hysterectomy, bilateral salpingo-oophorectomy, pelvic and paraaortic lymph node dissections, omentectomy, peritoneal washings, and peritoneal biopsies (6). Therapeutic options include surgery, chemotherapy with novel targeting molecular therapies, radiotherapy (RT), or a combination of these modalities (7). Treatment with chemotherapy depends on surgical staging findings, the grade and the histology of disease. Complete surgically staged patients with grade I tumors can be observed with no additional treatment, whereas for patients with grade II and grade III or advanced ovarian carcinoma a comprehensive debulking surgery is the mainstay of management followed by adjuvant platinum/taxane-based chemotherapy for 3 to 6 cycles (5,8).

The role of RT in the management of OC continues to represent a topic of controversy, and the indications for its use are not fully established. Thus, to assess the use of RT in OC, we conducted a literature search of all publications written in English language through the PubMed/Medline central database at the National Center for Biotechnology Information (NCBI) website (9) searching by the terms “ovarian cancer”, “radiation therapy”, “radiotherapy”, “whole abdominal irradiation”, “intraperitoneal radionuclides”, and “stereotactic body radiotherapy”. The last search date was December 16, 2019.

### Role of adjuvant radiation therapy for early-stage OC

Epithelial OC is known to be a radiosensitive tumor. Initial studies suggested that the addition of RT in the form of IP radioisotopes and whole abdominal irradiation (WAI) to chemotherapy for subsets of patients was useful.

#### *IP instillation of radioisotopes*

Because of the risk of IP dissemination and before the platinum-based chemotherapy era, the benefit of adjuvant

peritoneal administration of radionuclides, such as gold ( $^{198}\text{Au}$ ) and chromic phosphate ( $^{32}\text{P}$ ), was evaluated in a group of studies (10-15). Indications for this treatment were peritoneal cytology with tumor cells, peritoneal implants, and capsule rupture. The instillation of radioisotopes was contraindicated when macroscopic residual disease was present. The first studies were performed using colloidal gold, because of its short half-life (2.697 days) and decay properties. The radiation was mainly negative beta decay with a mean energy of 0.316 MeV and a maximum energy of 0.96 MeV. The gamma decay energy was 411 keV. The therapeutic effect was due to the short-range beta radiation according to physical properties (its 3.8 mm penetration range in water/soft tissue destroyed tumors without nearby healthy tissue being irradiated). The handling of  $^{198}\text{Au}$  was complicated because of higher risks of exposure for the staff and the need to separate the patients from one another (16). In addition, the physical properties of  $^{32}\text{P}$  were more convenient because of higher beta energy (mean energy of 0.69 MeV) with a maximum energy of 1.709 MeV, and a maximum penetration in tissue of 7.6 mm, longer half-life than  $^{198}\text{Au}$  (14.29 days), easier handling, lack of gamma radiation, and a relatively low complication rate (17).

Three trials evaluated IP  $^{32}\text{P}$  or adjuvant chemotherapy in patients with high-risk, early-stage tumors. IP  $^{32}\text{P}$  resulted in increased bowel toxicity and not superior than chemotherapy in survival outcomes (Table 1) (18-20). The use of  $^{32}\text{P}$  for early-stages of OC was abandoned due to the new platinum agents. A better understanding of the physiopathology of OC led to a better classification of early-stage patients in whom close observation could be feasible instead adjuvant therapy (21). For patients with advanced-stage OC,  $^{32}\text{P}$  in combination with WAI was attempted but found to be excessively toxic with no difference in relapse rates or survival (22-24). At present, IP instillation of radioisotopes is no longer a therapeutic strategy for OC.

#### *Adjuvant pelvic RT*

Before WAI, pelvic RT was used after surgery in patients with an absence of gross residual disease (25). Early studies established the inadequacy of this technique and the need for treating the whole abdomen. Patients with microscopic residual disease after initial debulking surgery experienced 10-year disease-free survival (DFS) rates of 42% to 62% in two randomized trials evaluating pelvic RT (26,27). A trial from Dembo *et al.*, randomized 147 women with OC in stages I-III to either abdominopelvic

**Table 1** Prospective studies of adjuvant  $^{32}\text{P}$  IP instillation in high-risk ovarian carcinoma

Author	Year	Stage	Study design	N	Comments
Young <i>et al.</i> (18)	1990	I, II	Adjuvant melphalan vs. single dose IP $^{32}\text{P}$	141	5-year DFS 80% melphalan vs. 80% IP $^{32}\text{P}$ . 5-year OS 81% melphalan vs. 78% IP $^{32}\text{P}$
Bolis <i>et al.</i> (19)	1995	I	Cisplatin vs. IP $^{32}\text{P}$	152	5-year DFS 65% $^{32}\text{P}$ vs. 85% cisplatin. 5-year OS 79% $^{32}\text{P}$ vs. 81% cisplatin
Young <i>et al.</i> (20)	2003	IA or IB grade 3 or IC or II, no residual disease	IV CP and cisplatin vs. IP $^{32}\text{P}$	251	Recurrence at 10 year 35% for $^{32}\text{P}$ vs. 28% for CP arm

IP, intraperitoneal; DFS, disease-free survival; OS, overall survival; CP, cyclophosphamide.

RT without chemotherapy, pelvic RT alone or pelvic RT followed by adjuvant daily chlorambucil therapy. For analyzing survival characteristics patients were divided in two groups according to complete or incomplete debulking surgery. The 5-year actuarial survival rate after complete debulking surgery was 81% among patients treated with abdominopelvic RT and 51% in patients treated with pelvic RT plus chlorambucil ( $P=0.019$ ). This benefit appeared to be independent of stage. Poor prognosis for patients with incomplete debulking surgery was not different for any of the tested therapies. Serious gastrointestinal toxicity was uncommon in the abdominopelvic RT arm with one patient requiring bowel surgery. The pelvic RT only and pelvic RT and chlorambucil arms had eight cases of gastrointestinal toxicity (abdominal cramps and rectal bleeding) (28). A trial from Hreshchysyn *et al.* randomized 86 stage-I OC patients to pelvic RT, melphalan, or no additional treatment. A survival difference between no additional treatment and pelvic RT could not be demonstrated but a benefit for melphalan was obtained (29). Sell *et al.* published a study of 118 patients randomized to WAI or pelvic RT with cyclophosphamide (CP). There was no difference between the regimens with respect to recurrence-free survival (RFS) (55%) and 4-year overall survival (OS) (63%). At routine second-look laparotomy (SLL), 16% of patients without clinical detectable tumor showed recurrence (30). These trials validated RT as an effective adjuvant modality in patients with OC. They also established that WAI is better than pelvic RT alone or in combination with chemotherapeutic agents for patients with microscopic or no residual disease.

### Adjuvant WAI

Adjuvant WAI was a therapeutic tool used in the prechemotherapy era to eradicate large amounts of microscopic peritoneal disease. Ideal candidates for WAI

were stage I patients with grade 2 or 3 tumors; stage II patients with grade 1 or 2 tumors and residual disease, and stage III, grade 1 patients with <2 cm residual disease (26). Its advantage in comparison to  $^{32}\text{P}$  and pelvic RT was the ability to deliver a homogeneous radiation dose to all areas of the abdomen and pelvis encompassing pelvic and paraaortic lymph nodes. The disadvantages of WAI were the dose-limiting toxicities, which were predominantly acute hematologic and late gastrointestinal. The total dose in WAI technique was limited to 25–30 Gy, owing to the radiation tolerance of organs within the field (31). Vergote *et al.* randomized 347 patients, stages I to III (no macroscopic residual disease), to cisplatin (50 mg/m<sup>2</sup>) every 3 weeks for six cycles or  $^{32}\text{P}$ . Patients with intraabdominal adhesions initially randomized to IP administration of  $^{32}\text{P}$  received WAI followed by pelvic RT instead. The 5-year OS for patients with stage I disease was 82%, 94%, and 79% for the  $^{32}\text{P}$  arm, WAI and cisplatin arms respectively. Bowel obstruction was frequent in patients treated with  $^{32}\text{P}$  (9%) and WAI (21%) when compared with to cisplatin arm (2%) (32). Because no survival benefit was shown with RT, cisplatin was recommended as the standard treatment for this subset of patients (Table 2) (33–35).

### Role of consolidative radiation therapy for advanced-stage ovarian carcinoma

The role of consolidative RT in OC besides surgery and chemotherapy has been controversial. Several publications addressed the benefit of RT in this scenario.

### Consolidative WAI

Consolidative WAI was used after SLL in patients with minimal residual disease and without prior abdominopelvic RT to eradicate subclinical residual disease in women

**Table 2** Prospective studies of adjuvant WAI in ovarian carcinoma

Author	Year	Stage	Study design	N	Comments
Redman <i>et al.</i> (33)	1993	IC–III	WAI vs. cisplatin	40	5-year survival rates were 58% WAI arm and 62% in cisplatin arm
Chiara <i>et al.</i> (34)	1994	I–II	Cisplatin + CP + WAI vs. WAI alone	70	5-year survival was 71% and 53%, relapse-free survival was 74% and 50% for chemotherapy and WAI, respectively
Kojs <i>et al.</i> (35)	2001	IA, IB grades G2–3, IC, IIA	WAI + pelvic boost vs. cisplatin, CP, adriamycin	150	5-year survival rates were 81% for both arms. Patients with grade G3 tumors had the worst survival

WAI, whole abdominal irradiation; CP, cyclophosphamide.

**Table 3** Prospective studies of consolidative WAI in ovarian carcinoma

Author	Year	Stage	Study design	N	Comments
Lawton <i>et al.</i> (40)	1990	Surgery → cisplatin → SLL	WAI vs. chlorambucil	109	2-year OS 35% for both groups. Important toxicity in both arms, almost 50% of patients did not complete the planned treatment in both arms
Lambert <i>et al.</i> (41)	1993	IIB–IV	Carboplatin vs. WAI	254	Median survival 25 months for both groups. No statistical difference in OS or DFS between groups
Bruzzzone <i>et al.</i> (42)	1990	III, IV minimal residual disease	WAI vs. chemotherapy	41	3-year OS rate of 45% in WAI arm and 85% for chemo arm
Pickel <i>et al.</i> (43)	1999	IC–IV	WAI vs. observation	64	5-year OS rate of 59% in WAI arm and 33% for observation arm
Sorbe and Swedish-Norwegian Ovarian Cancer Study Group (44)	2003	III without residual disease. Macroscopic disease	WAI vs. chemotherapy vs. no further therapy. WAI vs. chemotherapy	172	5-year PFS rate 56% WAI arm vs. 36% chemotherapy arm vs. 35% no treatment group. No significant differences in survival between arms. Late severe intestinal radiation reactions in 10%

WAI, whole abdominal irradiation; SLL, second-look laparotomy; OS, overall survival; DFS, disease-free survival; PFS, progression-free survival.

who remained at high risk for relapse following surgical cytoreduction and adjuvant chemotherapy. Published data demonstrated 3-year progression-free survival (PFS) rates of 50% to 67% (36,37) and 5-year OS rates of 40% to 66% (38,39). A few early, prospective randomized trials evaluated the role of consolidative WAI compared to extended chemotherapy in patients with advanced-stage disease (stage III/IV) after initial surgical cytoreduction, adjuvant chemotherapy, and SLL. In all of these trials, DFS and OS rates were not found to be significantly different between WAI and chemotherapy (*Table 3*) (40–44).

### Consolidative IP <sup>32</sup>P

Randomized data evaluating IP <sup>32</sup>P as consolidative treatment following SLL are limited. Vergote *et al.* randomized 50 patients with negative second-look findings

to receive <sup>32</sup>P or no treatment. PFS was 95% in the <sup>32</sup>P arm vs. 82% for the observation arm. <sup>32</sup>P therapy was associated with bowel complications (45). A trial of the Gynecologic Oncology Group randomized 202 patients with a negative SLL to receive <sup>32</sup>P or no additional therapy. With a median follow-up of 63 months in living patients, the 5-year RFS rate was 42% and 36% for the IP <sup>32</sup>P and no further therapy groups, respectively; the difference was not statistically significant, 61% of stage III OC patients had tumor recurrence within 5 years of negative SLL (24). These data did not support the use of <sup>32</sup>P for consolidative treatment in OC.

### Role of RT for clear-cell and mucinous histologies

Clear-cell carcinoma (CCC) of the ovary is a different histologic subtype of OC that is associated with worse

outcomes when compared with other subtypes of epithelial OC of a similar stage. Given the relatively chemotherapy-resistant nature of ovarian CCC to standard therapy with paclitaxel and carboplatin, different treatment strategies have been evaluated. Because of the modest response rates seen with platinum-based chemotherapy, RT has also been evaluated as a component of treatment in both the first-line and the recurrent setting (46).

Two studies have evaluated surgery plus either chemotherapy and RT or RT alone for upfront treatment of CCC. In a retrospective cohort of 241 patients with stage I and II ovarian CCC treated with surgery followed by platinum/taxane chemotherapy with or without RT, patients with stage IC to II disease had an improvement in DFS that favored RT [risk ratio, 0.54; 95% confidence interval (CI), 0.33–0.95;  $P=0.02$ ], and a 20% increase in DFS at 5 years (47). A second cohort of 28 patients with stage IC to III ovarian CCC treated with surgery followed by either platinum/taxane chemotherapy or WAI showed an improvement in both 5-year OS and DFS in patients who received surgery plus RT (OS: 81.8% *vs.* 33.3%,  $P=0.031$ ; DFS: 81.2% *vs.* 25%,  $P=0.006$ ) (13). RT has also shown to improve outcomes when used to treat advanced or recurrent ovarian CCC. In a retrospective cohort of 158 patients with stage I to IV ovarian CCC that included recurrent disease, 17 patients received RT either alone or with chemotherapy. In this cohort, 70.6% of the patients had a treatment benefit when adjuvant treatment included radiation compared with only 27.3% of the patients treated with chemotherapy alone (48). In another more recent cohort, definitive RT was used to treat 102 women with recurrent OC and included all epithelial histologic subtypes. Subgroup analysis showed that patients with CCC had higher 5-year OS and PFS rates than patients with other histologies (OS: 88% *vs.* 37%,  $P=0.05$ ; PFS: 75% *vs.* 20%,  $P=0.01$ ) (49). Similar results were also seen for patients with stage I or II OC of endometrioid, clear cell, and mucinous subtypes in a population-based study, which reported a 40% reduction in disease-specific mortality and 43% reduction in overall mortality with the addition of consolidative RT (14).

Mucinous ovarian cancer (MOC) is a rare subtype of OC. It has a distinct natural history, molecular profile, chemosensitivity, and prognosis in comparison to other histologies of OC. Recently, a study published by Patel *et al.*, analyzed incidence, survival, and treatments from the Surveillance, Epidemiology, and End Results (SEER) Program for clear cell, mucinous, and endometrioid histologies of the ovary

receiving adjuvant RT. For stage I and II patients OS was higher in individuals who did not receive RT at 5 years (76% *vs.* 70%) and 10 years (65% *vs.* 49%,  $P=0.036$ ) whereas in stage III patients there was an improvement with RT in OS at 5 years (53% *vs.* 36%) and 10 years (45% *vs.* 26%,  $P=0.052$ ) suggesting RT could be useful in this setting (50).

### Reasons WAI is no longer a standard treatment in OC

The toxicity of WAI technique is not negligible. During treatment, patient complaints were about diarrhea, fatigue, nausea, and hematologic effects (mainly thrombocytopenia). More concerning, however, used to be long-term toxicities (51). A study published by Thomas *et al.* analyzed 1,098 patients from 10 prospective series with WAI as OC treatment. Fatigue was the most common complaint. Approximately 75% of patients had mild diarrhea, 67% were nauseous and 15% of patients had bloating. Basal pneumonitis or fibrosis was evident in chest radiographs in up to 20% of patients. Transient elevation of alkaline phosphatase levels occurred in 50% of patients. The necessity for bowel surgery for treatment complications was 5.6%. Four patients died as a result of bowel damage (52). The era of aggressive debulking and platinum agents made WAI fall out of favor as a treatment of OC (51).

### Current scenarios for RT in OC

#### Salvage RT for recurrent disease

Abdominopelvic relapse is the main pattern of failure in OC patients treated with definitive and adjuvant therapy. The response rates to second-line chemotherapy in patients with relapsed OC are poor. Salvage WAI (30–35 Gy, followed by a pelvic boost), has been employed in an effort to improve outcomes (53). Selective approaches with highly conformal radiotherapy (CRT) have been used in case of limited recurrent disease (nodal or extranodal non-debulkable disease) with no disease dissemination, a subset of these patients may have oligometastatic or oligoprogressive disease that may benefit from RT instead of surgery with the potential for long-term disease control (Table 4) (54–58).

#### Symptom control in the palliative setting

Palliative RT in OC is effective in patients with symptomatic localized disease. For patients with vaginal bleeding, pain resulting from retroperitoneal masses, or



**Table 4** Studies of RT in recurrent ovarian carcinoma

Author	Year	Stage	Study design	N	Comments
Albuquerque <i>et al.</i> (54)	2016	Nodal, pelvis Retroperitoneal	Retrospective IFRT median dose: 50 Gy conventional fractionation	27	5-year LRFS: 70%; 5-year DFS: 33%
Choi <i>et al.</i> (55)	2017	Nodal and extranodal disease	3D-CRT	44	The 1- and 2-year in-field LC rates were 66.0% and 55.0%, respectively. BED $\geq$ 50 Gy showed better outcomes
Chang <i>et al.</i> (56)	2018	Nodal and extranodal disease	Prospective phase II; IFRT-IMRT, 3D-CRT or brachytherapy	–	Overall and CRRs were 85.7% and 50%, respectively. The 2-year PFS rate was 39.3%. The 3-year LC and OS rates were 84.4% and 55.8%, respectively
Komura <i>et al.</i> (57)	2019	Nodal or extranodal recurrence	Retrospective 3D-CRT	24	In-field overall response of 58.3%, median regression was 40.2%. The 1-year survival and local PFS rates after RT were 66.7% and 45.8%, respectively
Smart <i>et al.</i> (58)	2019	Peritoneal, nodal, vaginal	Retrospective IFRT 3D-CRT	40	At 3 years, DFS and OS were 18% and 80%, respectively. Non-serous histology and platinum sensitivity were associated with lower relapse risk

IFRT, involved-field radiotherapy; LRFS, local recurrence-free survival; DFS, disease-free survival; 3D-CRT, three-dimensional conformal radiotherapy; LC, local control; BED, biological equivalent dose; CRR, complete response rate; PFS, progression-free survival; OS, overall survival; IMRT, intensity-modulated radiation therapy.

metastatic disease (e.g., brain metastases, voluminous or painful nodes), RT can induce tumor regression and provide symptom relief. Bansal *et al.* (59) analyzed abdominal pain and vaginal bleeding control in a group of 23 patients with metastatic OC treated with pelvic RT. After finishing RT, abdominal pain was controlled in 88.2% and vaginal bleeding in 80% with doses ranging from 46–50 Gy. Jiang *et al.* (60) published a study of 64 patients with symptomatic OC recurrence who received RT for pain, bleeding, and obstruction. Overall response rates were higher for bleeding control in 93% and for pain control in 87% than for obstruction in 62%. Patients treated for pain at nonbony sites had higher pain control (96%) compared with those treated at bony sites (75%). When delivered locally to symptomatic sites, RT appears to be of significant and durable benefit and should be considered for palliative purposes in select patients with symptomatic relapses, particularly in those who are refractory to chemotherapy.

### Feasibility of modern radiation techniques in ovarian carcinoma

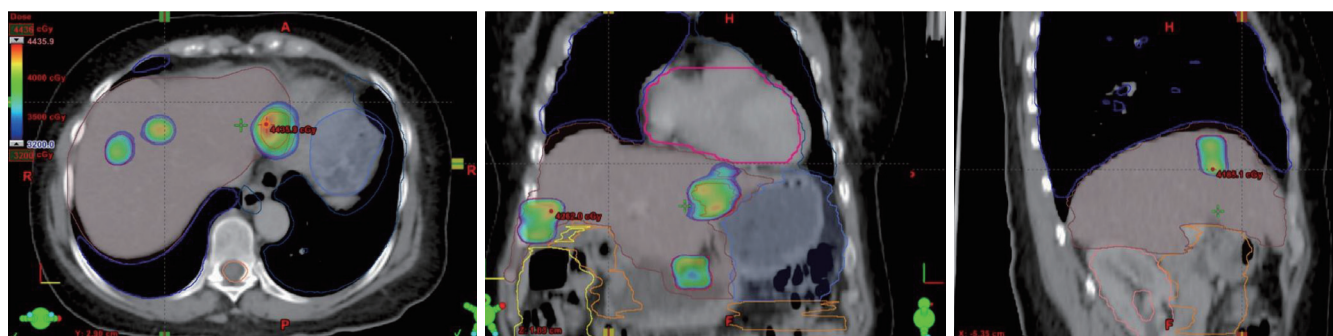
#### Intraoperative RT

Several studies suggested that intraoperative radiation

therapy (IORT) as part of salvage surgery for locally recurrent gynecologic cancers, including OC, may improve local-regional control and OS. However, a few institutions have reported their experiences with IORT for recurrent OC with 5-year OS of 22% with a median survival of 26 months from the time of IORT (61). Barney *et al.* reported a series on 20 women with recurrent OC who were treated with IORT to the pelvis, para-aortic or inguinal lymph nodes. Eighty percent of women also received perioperative external beam RT. Five-year locoregional control was 59%, with 14 and 30 months DFS and OS, respectively (62). Given the propensity of OC to recur in the abdomen, IORT may be suitable for patients with isolated recurrences in the retroperitoneum, in patients with isolated pelvic disease after resection and certain histologic subtypes that may be less sensitive to conventional chemotherapy (63).

#### Intensity modulated-WAI

The use of intensity-modulated radiation therapy (IMRT) to deliver WAI has been proposed as a means of reducing the radiation dose to the bone marrow and kidneys to decrease the incidence of myelotoxicity and renal



**Figure 1** SBRT plan for the treatment of liver metastases in a woman with recurrent MOC is shown. Treatment planning with axial, coronal, and sagittal views is depicted. The PTV is color washed in green, heart is pink, the kidneys are orange and cyan, liver is brown, stomach is blue, and the bowel is orange. The prescription dose was 34 Gy in five fractions. SBRT, stereotactic body radiotherapy; MOC, mucinous ovarian cancer; PTV, planning target volume.

damage. Dosimetric analysis has demonstrated improved planning target volume coverage and significant dose reductions to bones with equivalent kidney-sparing using dynamic multileaf collimator IMRT when compared with conventional fields (64). Recently, the dosimetric advantages of WAI-IMRT and the clinical benefit (CB) of the technique were tested in a prospective phase II study from Arians *et al.* (65). Twenty patients with optimally cytoreduced stage III OC with complete remission after chemotherapy were treated with WAI-IMRT as consolidation therapy. A total dose of 30 Gy in 20 fractions of 1.5 Gy was applied to the peritoneal cavity. WAI-IMRT resulted in good coverage of the peritoneal cavity with effective sparing of all organs within the peritoneum. The tolerability rate of WAI-IMRT was >70%. Side effects mostly consisted of grade 1 or 2 gastrointestinal toxicity with nausea, vomiting or diarrhea with an acceptable quality status of health (65).

### **Stereotactic body radiotherapy (SBRT)**

SBRT is a highly conformal radiation technique that allows doses greater than 5 Gy per fraction to be delivered during a course of 1 to 5 treatments including ablative doses of radiation; these ablative doses of radiation may be used in cases of few metastases or in those with mixed response to chemotherapy, where consolidation treatment can be delivered to the few nonresponding or progressive sites of disease (*Figure 1*) (66). This approach has been validated in multiple disease sites (lung, prostate, breast) for oligometastases with 80% to 90% local control (LC) rates, an improvement in OS, and small risks of significant acute/late toxicity (AT/LT) (67). The few dedicated reports on

SBRT for OC are enlisted in *Table 5* (68-70).

## **The future of RT for OC**

### **RT and poly (ADP-ribose) polymerase (PARP) inhibitors**

PARP inhibitors are oral agents that inhibit PARP enzymes 1, 2, and 3 with clinical efficacy among OC patients. PARP inhibitors were the first United States Food and Drug Administration-approved biological agents for OC based on molecular features of cancer (71). Patients with *BRCA1/2*-mutated or homologous recombination-deficient ovarian tumors can benefit from PARP inhibitors. However, data on safety, tolerability and efficacy in combination with RT are limited (72). Reiss *et al.* tested low-dose WAI with veliparib in patients with peritoneal carcinomatosis adding a dose escalation in ovarian and fallopian cancer patients. Thirty-two patients were treated. Lymphopenia, anemia, and thrombocytopenia were the most common grade 3 and 4 toxicities. After 45 months of follow-up, median PFS was 3.6 months, and median OS was 9.1 months. In OC patients, OS was longer for platinum-sensitive patients (10.9 months) compared to platinum-resistant patients (5.8 months). When combined with WAI, the maximum tolerated dose was determined to be 250 mg twice daily via oral administration (73).

### **RT and immunotherapy combination**

Clinical remission for OC is possible, however, 70% of patients will relapse, with 5-year survival rates of approximately 30% (74), with a proportion of patients

**Table 5** Studies of SBRT/SABR in oligometastatic ovarian carcinoma

Author	Year	Study design	N	Comments
Iftode <i>et al.</i> (68)	2018	Retrospective SBRT (lymph nodes, liver, lung)	26 patients; 44 lesions	1-year PFS: 69.3%, 1-year OS: 100%; 2-year PFS: 38%, 2-year OS: 92.7%; 5-year PFS: 19%, 5-year OS: 61.7%
Lazzari <i>et al.</i> (69)	2018	Retrospective SBRT	82 patients; 156 lesions	Median systemic treatment-free interval after SBRT: 7.4 months, 2-year local PFS: 68%, PFS: 18%, OS: 71%.
Macchia <i>et al.</i> (70)	2020	Retrospective, multicenter study (MITO RT-01) SBRT/SRS	261 patients; 449 lesions	CRR: 65.2%, PRR: 23.8%, SD: 7.4%, PD: 3.6%; 2-year LC: 81.9%, ORR: 89%, CB: 96.4%, AT: 20.7%, LT: 6.1%, 2-year late TFS: 95.1%

SBRT/SABR, stereotactic body radiotherapy/stereotactic ablative radiotherapy; CRR, complete response rate; PRR, partial response rate; SD, stable disease; PD, progressive disease; LC, local control; ORR, objective response rate; CB, clinical benefit; AT, acute toxicity; LT, late toxicity; TFS, toxicity-free survival.

remaining cancer-free at 10 years less than 15% (75). Immunotherapy has emerged as a therapeutic option. Immune checkpoint inhibitors have gained an important place in the treatment of several disease cancer types (76). However, OC remains poorly responsive to immunotherapy (77).

Both SBRT and WAI could be considered as partners for immunomodulatory therapies to improve tumor control in specific clinical scenarios; SBRT has emerged as an important intervention for in-situ vaccination, while low-dose WAI could be used as a means to achieve subdiaphragmatic so-called in-field tumor reprogramming in the context of immunotherapy schemes (78).

Luke *et al.* offered SBRT to 2 to 4 metastases to 79 patients who progressed to standard treatment. Patients with ovarian, endometrial, colorectal, and other cancers received 3 to 5 fractions of 10 Gy. Pembrolizumab was initiated within 7 days after completion of SBRT with a dose of 200 mg every 3 weeks until progression, death, or toxic effects. There were 6 dose-limiting toxicity events. There was 1 complete response; 8 partial responses, and 21 patients with stable disease (SD). Multisite SBRT, followed by pembrolizumab, was well-tolerated with acceptable toxicity (79).

### Ongoing trials

A pilot trial (NCT01989546) of BMN 673, an oral PARP inhibitor, is in progress for patients with advanced solid tumors and deleterious BRCA mutations, including OC patients. A phase I trial (NCT03283943) of durvalumab with focal sensitizing RT in platinum-resistant ovarian, primary peritoneal or fallopian tube epithelial carcinoma is also ongoing. A phase I study (NCT03968406) of talazoparib in combination with RT for locally recurrent

gynecologic cancers is currently in progress, as is a phase I (NCT03325634) dose-escalation study to determine the maximum tolerated dose of 3-fraction SBRT for abdominopelvic recurrences of OC and uterine papillary serous carcinoma. There is also a phase II trial (NCT03618706) aimed to investigate whether the addition of IFRT improves 2-year PFS in patients with recurrent OC after standard primary treatment.

### Conclusions

In the past, RT was frequently used in the management of patients with OC. It was the mainstay of adjuvant treatment for many years but was replaced by cisplatin almost three decades ago. Nevertheless, it remains a useful strategy in patients with recurrent and refractory disease as it can reach a prolonged DFS. The combination of highly CRT techniques with immunotherapy and new radiosensitizers is a paradigm shift for radiation oncology, as the aim of RT is tumor microenvironment reprogramming and immune modulation in addition to tumor ablation. These RT modalities represent new opportunities in OC treatment, promising to enhance the efficacy of new pharmacologic agents in this disease.

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### Footnote

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