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REVIEW ARTICLE

The role of radiotherapy in epithelial ovarian cancer: a literature overview

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Abstract

Ovarian cancer (OC) accounts for 3% of all cancer in women and for 5% of all cancer-related deaths. Epithelial Ovarian Cancer (EOC) is a radiosensitive malignancy with a poor prognosis. In the pre-chemotherapy era, radiation therapy (RT) delivered to the abdominopelvic region (whole abdominal irradiation, WAI) has historically played a role in the adjuvant and consolidation setting. Specific cluster of patients with early-stage disease and definite histologies may take advantage of RT. Platinum-based chemotherapy (CT) has replaced RT and plays a major role in most of the clinical settings. Radiation Therapy for palliation is recommended in patients with localized symptoms. Nevertheless, modern RT represents a reliable treatment option, with a mild toxicity profile, particularly effective for oligo-recurrent or progressive disease. The present literature review aims to highlight the historical role of RT in EOC, the actual lines of evidence, and the future perspectives.

Keywords Epithelial ovarian cancer · Radiotherapy · Radiation · Stereotactic ablative radiotherapy

Introduction

Ovarian cancer (OC) accounts for 3% of all cancers diagnosed in women and for 5% of all cancer-related deaths. Approximately, 295.414 new cases per year are estimated worldwide for OC, corresponding to more than 184.000 deaths every year [1]. Ovarian cancer is rare in women before the age of 40, with a median age at diagnosis of 63 years. The histological classification comprises epithelial (EOC, approximately 90% of all OC), sex cord, stromal, and germ cell tumors. Epithelial ovarian cancer accounts for 25% of all gynecological malignancies, including high- and low-grade serous tumors (respectively, 70% and 5% of all EOC), endometrioid (10%), mucinous (3%), and clear cell (10%) histology. The pathogenetic mechanism underlying the carcinogenesis of ovarian cancer is still unclear. Hormonal (e.g., reproductive history), patient's specific (e.g., endometriosis, diabetes mellitus, obesity, dietary habits, sedentary behavior, smoking status, high alcohol intake), genetic (e.g., BRCA genes), environmental (e.g., exogenous hormone use, exposure to ionizing radiation) risk factors have been identified [2]. Recurrent ovulation, with repeated breakdown and repair of the ovarian surface epithelium (or recurrent exposure to hormone), may increase the likelihood of DNA damage and neoplastic transformation [3]. Therefore, more ovulations a woman experiences in her lifetime and higher the risk of developing EOC. Moreover, high hormonal levels stimulate proliferation of the epithelium within cortical inclusion cysts (probably fallopian tube epithelium invaginations into the stroma) resulting in greater potential for neoplastic transformation [4]. The mechanisms of EOC spread includes direct contiguous infiltration of adjacent organs, lymphatic, transcoelomic dissemination in the peritoneal cavity, and hematogenous spread (infrequent). Ovarian cancer is staged surgically according to the International Federation of Gynecology and Obstetrics (FIGO) staging system based on the patterns of spread [5]. In almost all cases, an exploration of the abdomen and pelvis to determinate the stage is needed, because the extent of disease drives subsequent treatments [5]. More than 75% of EOC are diagnosed when disease has spread throughout the abdominal

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cavity and pelvis (advanced-stage disease). Five-year overall survival (OS) is approximately 45% in patients with EOC overall. The survival rate is significantly better in localized disease, with 5-year OS of 93%. Conversely, for advanced-stage disease, 5-years OS is 25%. Age is a prognostic factor, since women aged below 65 have higher 5-year OS (65.8%) compared to those > 65 (32.9%) [6, 7]. Surgery is the primary approach. Generally, surgery for early-stage disease consists of total extrafascial hysterectomy with bilateral salpingo-oophorectomy and pelvic and para-aortic lymph node dissection together with omentectomy. Patients with early-stage disease (except in case of low-grade EOC) benefit from adjuvant combination taxane and platinum-based chemotherapy (CT). For patients with advanced stage, the standard approach comprises combined modality treatment including cytoreductive surgery and post-operative taxane and platinum-based CT [8]. Up to 70% of advanced ovarian cancer patients experience recurrence during the course of disease, most frequently with peritoneal carcinomatosis and/or distant metastases [9, 10]. Nevertheless, a small but not negligible proportion of patients do experience exclusive locoregional recurrence [10, 11]. Another possible clinical presentation is 'oligometastatic disease,' a transitional condition characterized by 1-5 detectable metastases, with an intermediate prognosis between localized and widely disseminated cancer, in which local control may lead to improved survival [12].

Epithelial ovarian cancer is a radiosensitive tumor and in the past radiotherapy (RT) main role was in the adjuvant setting. However, this role has evolved during the years. Nowadays, due to the contradictory clinical results and the consistent toxicity in the adjuvant clinical setting, RT has been replaced by highly effective taxane and platinum-based CT [10]. Nevertheless, modern RT can still play a role in specific clinical scenarios, especially in the oligometastatic and oligo-recurrent setting.

Moreover, there is a renewed interest in whole abdominal RT, taking advantage of modern RT delivery techniques, such as IMRT [13]. Given the paucity of data available in the literature regarding this clinical setting, the present study was structured as a narrative review on the topic. The workflow included a literature review of all indexed reports written in English. The search was based on the following keywords: ovary AND (Radiotherapy[MeSH Terms]) AND (Ovarian Cancer[MeSH Terms]) AND (Radiation[MeSH Terms]). The last search date was April 1, 2019.

The present review aims at highlighting the historical role of RT in EOC, the actual lines of clinical evidence, and the future perspectives.

Historical role of whole abdominal irradiation (WAI)

Early-stage and adjuvant RT

Patients affected with localized EOC (stage I and II localized to the ovaries and pelvis according to the 2014 update of the FIGO classification) are one-third of cases. The treatment of early-stage EOC is predominantly surgical, since surgical staging and debulking is a crucial step in the treatment of this disease. Adjuvant CT is more beneficial than observation in patients with early-stage EOC [14, 15].

The role of adjuvant RT in this clinical setting has changed during the years since RT has been replaced by highly effective taxane and platinum-based CT.

Both whole-abdominopelvic irradiation (WAI) and intraperitoneal installation of radiocolloids (radioactive chromic phosphate suspension) were used [16, 17].

Radiation therapy was historically used to manage early-stage patients with low residual volumes of disease in all histological subtypes.

In particular, WAI was usually employed in the post-operative setting in case of either macroscopically radical resection or residual pelvic disease smaller than 20 mm [18]. When compared to radiocolloids, WAI has the advantage to deliver a homogeneous dose to the target. The limit is represented by the toxicity profile which includes hematologic and gastrointestinal events. In the late seventies, a randomized trial by Dembo et al. compared WAI + pelvic RT to pelvic RT with or without chlorambucil and showed that chlorambucil added to pelvic irradiation delayed the time to treatment failure without reducing the absolute number of treatment failures [18].

While no survival difference was found by Smith et al. [19] between post-operative whole abdominal/pelvic RT and melphalan in early-stage patients, a trial by Hreshchyshyn et al. [20] showed a survival benefit for Melphalan. Women with Stage I EOC were initially treated surgically and subsequently randomized to either no further treatment, RT, or CT. The lowest incidence of recurrences was observed in the CT arm (6%), while the highest rate was observed for patients in the RT arm (30%) [20].

As a consequence, during the 80 s, WAI was almost abandoned, given the recognized achievements of systemic treatments.

However, certain histologic subtypes seem to have a particular benefit from the use of RT. Clear cell carcinomas are generally resistant to CT, and may consequently take advantage of adjuvant RT in terms of locoregional control [21]. In a prospective study by Dinniwell et al. [22], combined modality treatment (cytoreductive surgery, CT, and sequential consolidative WAI) provided consistent clinical outcome among women affected with clear

cell carcinoma and endometrioid histologies compared to patients having serous subtype histology.

Thus, histological type is able to predict the curative potential of RT [23]. Clear cell, endometrioid, and mucinous histotypes, with a very frequent presentation of confined pelvic disease, may be cured with limited surgery and can benefit from the sterilization of microscopic disease with adjuvant regimens, including RT.

Particularly, clear cell cancers are usually confined to the pelvis and improved locoregional control within the pelvis, provided by the use of RT, can translate into a lower rate of relapse in this patient population and is worth further investigation [24].

On the other hand, serous disease is usually disseminated at diagnosis and hence does not take advantage of local treatments [23].

For details of the main studies regarding *Early-Stage and Adjuvant RT*, see Table 1.

Advanced-stage and consolidation RT

The standard management for advanced EOC is staging laparotomy with resection of gross disease, followed by first-line adjuvant CT.

The role of "consolidation" RT as a sequential approach to surgery and CT has always been controversial. The best option for patients with EOC with no or minimal residual disease at second-look laparotomy after surgery and consolidation CT has been investigated. In this setting, a comparative evaluation between CT and RT was evaluated within a randomized trial by Bruzzone et al. [25], closed early considering the higher survival rate for patients treated with three additional cycles of platinum-based CT compared to WAI (total dose: 43.2 Gy/24 fractions to the pelvis and 30.2 Gy to the upper abdomen).

Lambert et al. investigated whether consolidation therapy with WAI after CT could improve outcomes compared to continued CT. Women with advanced EOC (stages IIB to IV) were treated with 5 monthly courses of carboplatin. Patients with ≤ 2 cm residual disease at second-look laparotomy or laparoscopy were then randomized to receive consolidation therapy, including either five further courses of carboplatin at the same dosage or WAI (24 Gy). No statistical difference was found in terms of DFS and OS between consolidation WAI and continuation of the same CT regimen even in the presence of macroscopic residual disease at second-look surgery [26].

In 1993, a review from Thomas et al. including 28 studies and a large number of patients (713 considering all series), showed how controversial is the role of sequential CMT in advanced EOC. Disappointingly, considering the remarkable amount of studies and patients analyzed, no definitive conclusion or final evidence was drawn on such a therapeutical strategy. Overall, this review showed no benefits from WAI in the setting of consolidation or salvage therapy in advanced EOC. [27].

However, encouraging results were shown in two subsequent randomized trials [28, 29].

In 1999, Pickel et al. published a randomized study evaluating the effect of additional WAI in patients with no evidence of clinical disease after surgical staging (stage IC-IV) and platinum-based CT. The 5-year DFS and OS were significantly higher in the RT arm, particularly in case of stage III [28].

In 2003, a Scandinavian prospective trial randomized patients with EOC stage III disease after primary cytoreductive surgery and CT followed by second-look surgery. Patients with microscopic disease were randomized to CT or WAI, and no beneficial differences were found. Women with no microscopic disease were randomized to CT, WAI, or observation. A PFS benefit was observed for the RT arm. Treatment-related side effects were most frequent in the RT arm, with severe intestinal late toxicity reported in 10% of patients [29].

Historically, also intraperitoneal installation of radiocolloids was used, but this treatment did not decrease the risk of relapse or improve survival after surgery and CT in advanced-stage ovarian cancer [30].

For details of the main studies investigating *Advanced-Stage and Consolidation RT*, see Table 2.

WAI: toxicities, techniques, and perspectives

Historically, the use of large fields during WAI (open-field plan, AP-PA technique) in the management of OC has shown a consistent rate of toxicity, including acute events such as diarrhea, fatigue, nausea, and hematologic effects and even more long-term toxicity. Generally, treatment volumes during WAI delivered with external beam radiation comprised all peritoneal surfaces. Long-term toxicities included pneumonitis in up to 20% of patients, liver damage, and bowel toxicity (10–15% of patients) [31].

Dembo et al. [18] highlighted the importance of ensuring adequate margins to the diaphragm to take into account of all phases of normal respiration.

More recently, the possibility of better organs–at-risk (OARs) sparing and dose-distribution homogeneity given by modern RT delivery techniques, such as IMRT, renewed the interest for this treatment modality.

Interestingly, Rochet et al. [32] published in 2015 the results at 4-year of 16 women with optimally resected FIGO stage III OC, treated with consolidation WAI (total dose 30 Gy, 1.5 Gy per fraction), delivered with IMRT technique (step and shoot and helical tomotherapy), following adjuvant carboplatin/taxane-based CT. No grade 4 toxicities occurred during IMRT-WAI and no toxicity-related treatment break

Table 1 Early stage ovarian cancer and radiotherapy

Author and year	Type of study	Years	Reported stage	Trial design	Population	Radiation therapy dose	Radiation therapy volumes/radiation shielding	Toxicity	Outcomes
Smith et al. [19]	Randomized trial	1969–1974	Stage I–III	Primary surgery (residual tumors < 2 cm) and randomization to: Post-OP WAI followed by additional pelvic RT Post-OP CT (Melphalan)	149 patients 70 patients 79 patients	Moving strip technique - Entire abdomen: 2.600-2800 rads to each strip in about 2 and half weeks, followed by 2.000 rads to the pelvis.	Moving strip technique: the abdomen is divided into 1-inch strips beginning at the pelvic floor and extending to the dome of the diaphragm. Liver shielded front and back and kidneys shielded from the back.	Chronic small bowel injury requiring surgery: 10%	5-year OS: 71% 5-year OS: 72%
Dembo et al. [18]	Prospective, stratified, randomized study	1971–1975	Stages 1b–III asymtomatic	Post-OP Pelvic RT + Abdominopelvic RT Post-OP Pelvic RT + Chlorambucil	147 patients 76 patients 71 patients	Abdominopelvic RT: 2.250 rads to the midplane in 10 fr. to the pelvis, followed immediately by 2.250 rads to the midplane in 10 fr. to the whole abdomen and pelvis. Pelvic RT dose: 4.500 rads to the midplane in 20 fr.	The upper border of the abdominal held was at least 1 cm above the domes of the diaphragm, and no liver shielding was employed. The lower border was below the obturator foramen. The kidneys were shielded from the posterior beam throughout treatment.	Pelvic + Abdominopelvic irradiation complications (% of patients) Acute Nausea and vomiting 54% Acute Cramps and/or diarrhea 64% Acute myelosupression 66% Chronic radiation bowel damage: 12%	5-year OS: 81%; 10-year OS: 64% ($p < 0.05$) 5-year OS: 51%; 10-year OS: 40%
Hreshchyshyn et al. [20]	Randomized trial	1971–1978	Stage I	Extirpative surgery and randomization to: observation adjuvant RT (Pelvic irradiation) Adjuvant CT (Melphalan)	86 patients 29 patients 23 patients 34 patients	5.000 rads with a daily dose of 160 to 200 rads, 5 times a week.	RT-portals margins: (1) superior-the upper margin of the sacroiliac joint; (2) inferior-the upper third of the obturator foramen; and (3) lateral- 1 cm beyond the lateral margins of the bony pelvis at the widest plane of the pelvis.	Not assessed	Recurrence Observation arm: 17% Recurrence RT arm: 30% Recurrence CT arm: 6% ($p < 0.05$)

Table 1 (continued)

Author and year	Type of study	Years	Reported stage	Trial design	Population	Radiation therapy dose	Radiation therapy volumes/radiation shielding	Toxicity	Outcomes
Dinniwell et al. [22]	Prospective study	1998–2000	Stage I–III	Cytoreductive surgery+ adjuvant CT (carboplatin/paclitaxel) + Abdominopelvic RT	29 patients	Abdominopelvic RT: 2300 cGy in 100 cGy daily fr. The pelvis received a concurrent boost of 1150 cGy in 23 fr and a further 1050 cGy in 7 fr after completation of the abdominal treatment.	The field borders extended from 1.5 cm above the diaphragms in quiet expiration, to 1 cm below the inferior aspect of the obturator foramen. Laterally, the fields extended 2 cm beyond the peritoneal reflection. Posterior kidney shields. No hepatic shielding. The pelvic fields margins were typically positioned at the sacral promontory, the inferior aspect of the obturator foramen, and 2 cm lateral to the inlet of the true pelvis on each side.	Acute G3 Gastrointestinal events: 6.9% Acute G3 Myelotoxicity: 31% Late side events: 17.2%	4-year DFS: 57%; 4-year OS: 92% 4-year DFS clear cell and endometrioid tumors: 77% ($p < 0.05$) 4-year DFS serous tumors: 27%
Swenerton et al. [23]	Review of a population-based experience	1984–2003	Moderate risk group (Stage I, grade 2; II, grade I, II) High risk group (Stage I-II, grade 3; III)	Primary surgery (without macroscopic residuum) + adjuvant platin-based CT ± sequential RT	703 patients	2250 cGy to the whole pelvis in 10 fr over 2 weeks, followed by 2250 cGy to the whole abdomen and pelvis in 22 fr.	There was no shielding of the liver, and the kidneys were typically shielded with posterior blocks.	Chronic G3–G4 events: 4%; G5 events: <1%	Stage I–II tumors (clear cell, endometrioid, mucinous) who received adjuvant RT: 40% reduction in disease-specific mortality 43% reduction in overall mortality

Table 1 (continued)

Author and year	Type of study	Years	Reported stage	Trial design	Population	Radiation therapy dose	Radiation therapy volumes/radiation shielding	Toxicity	Outcomes
Hoskins et al. [24]	Retrospective study	1984–2008	Stage I–II clear cell carcinoma	Surgery + Adjuvant CT (3 cycles of carboplatin and paclitaxel) + Abdominopelvic RT	241 patients	22.5 Gy to pelvis in 10 fr over 2 weeks followed by 22.5 Gy to whole abdomen and pelvis in 22 fr over 4.5 weeks.	No liver shielding.	Not assessed	Stage IA/IB:5-year DFS: 84%; 10-year DFS:70%; Stage IC: 5-year DFS: 67%; 10-year DFS: 57% Stage II: 5-year DFS 49%; 10-year: DFS:44%

RT radiation therapy; *CT* chemotherapy; *post-OP* post-operative; *WAI* whole abdominal irradiation; *fr* fractions; *OS* overall survival; *DFS* disease-free survival; *G* grade

was necessary. Given the promising toxicity profile and the encouraging median recurrence-free survival (RFS) of 27.6 months, consolidation IMRT-WAI was further evaluated in a subsequent trial, with promising toxicity and tolerability preliminary results [32, 33]. Other clinical series evaluated modern irradiations techniques in this setting [9, 34, 35].

Recurrent ovarian cancer

Abdominopelvic relapse is the predominant pattern of treatment failure in EOC patients treated with definitive and adjuvant therapy. Intra-abdominal recurrences are usually symptomatic.

The prognosis of failures after first-line therapy is rather dismal, particularly for those who relapse less than 6 months from the completion of treatment (so called platinum-resistant disease). Symptom palliation is the main goal of treatment in this setting.

Salvage WAI as well (30–35 Gy, followed by a pelvic boost) has been employed in this subgroup of patients [36].

Of interest, selective approaches with volume-directed involved field radiotherapy (IFRT) were used in case of limited recurrent disease, with no disease dissemination. In a series by Albuquerque et al., patients who received tumor volume-directed IFRT for localized extraperitoneal recurrences (either as a consolidation approach after cytoreductive surgery (CRS) or as attempted salvage in case of unresectable disease) achieved 10-year DFS, OS, and local recurrence-free survival rates of 20, 19, and 60%, respectively [8].

In a series by Brown et al. [10], at the MD Anderson Cancer Center, patients were treated mostly with conventional fractionation up to a median dose of 59.2 Gy (range: 45–68.2 Gy), directed to localized nodal or extranodal recurrences.

When the recurrence is localized in the pelvic wall or para-aortic/pelvic lymph nodes, excellent results were observed with intra-operative radiotherapy (IORT), as shown in series from both the Mayo Clinic Rochester [37] and Stanford University [38].

For details of the main studies reporting on *Recurrent Ovarian Cancer and Oligometastatic Disease*, see Table 3.

Oligometastatic disease

Another scenario in which RT has been employed is the oligometastatic state, a transitional condition characterized by 1–5 detectable metastases, with an intermediate prognosis between localized and widely disseminated disease, in which local control may lead to improved survival [12]. Stereotactic ablative radiotherapy (SABR) allows for the delivery of a high-dose per fraction with

Table 2 Advanced stage ovarian cancer and consolidation radiotherapy

Author and year	Type of study	Years	Reported stage	Population	Trial design	Radiation therapy dose	Outcomes	Toxicity
Bruzzone et al. [25]	Randomized trial	1985–1988	Stage III–IV (minimal residual disease)	41 patients 21 patients 20 patients	No or minimal residual disease at second-look laparotomy after front-line platinum-based CT and randomization to: CT arm (three additional course of the same front-line CT) WAI arm	43.2 Gy in 24 fr to the pelvis and 30.2 Gy to the upper abdomen	3-year OS: 85% 3-year OS: 45%	CT arm - Grade 3 N/V events (WHO): 36.9% CT arm - Grade 3 Leukopenia (WHO): 10.5% RT arm - Grade 3 N/V events (WHO): 14.2% RT arm - Grade 3 Leukopenia (WHO): 7.2% RT arm - Bowel obstruction: 5%
North Thames Ovary Group Study. [26]	Randomized trial	1985–1989	Stage IIB–IV	117 patients 59 patients 58 patients	≤ 2cm residual disease at second-look surgery after front-line Carboplatin based-CT and randomization to: CT arm (five additional course of Carboplatin based-CT) WAI arm	24 Gy in 20 fractions, four time a week for 5 weeks. Pelvic boost no routinely administered. In case of pelvic residual disease (at second look-surgery) boost up to a dose of 40 Gy	5-year OS: 30% 5-year OS: 25%	CT arm - Grade 4 N/V events (WHO): 2% RT arm - Grade 3 myelotoxicity (WHO): 5% RT arm - Bowel obstruction (WHO): 1.7%
Thomas et al. [27]	Review of 28 studies	1975–1992	Advanced stage (variable residual disease)	713 patients	Role of consolidation or salvatage WAI after sequential surgery and CT	The planned WAI dose varied between 20 and 30 Gy. In many studies: pelvis boost to bring dose to 45 or 50 Gy. Several also employed a boost to the para-aortic nodes	No residual disease - DFS: 76% Residual disease <5 mm DFS: 49% Residual disease >5 mm DFS: 17%	Bowel obstruction variable. In 13 series: < 10%
Pickel et al. [28]	Randomized trial	1985–1992	Stage IC–IV (no clinical disease)	64 patients 32 patients 32 patients	Surgery (no residual disease) and adjuvant platinum-based CT and randomization to: WAI arm Observation arm	WAI: 30 Gy (1.5 Gy/5 treatments per week). Additional boost of 21.6 Gy to the pelvis and boost of 12 Gy to paraaortic region	5-year OS: 59% 5-year OS: 33%	Treatment breaks: 37.5% Bowel obstruction: 3.1%

Table 2 (continued)

Author and year	Type of study	Years	Reported stage	Population	Trial design	Radiation therapy dose	Outcomes	Toxicity
Swedish-Norwegian Ovarian Cancer Study Group. [29]	Prospective randomized trial	1988–1993	Stage III	172 patients 98 patients 74 patients	Complete surgical and pathologic remission of disease at second-look surgery after induction CT. Randomization to: Consolidation with RT (WAI) Consolidation with CT (6 courses) Observation Complete surgical but not pathologic remission of disease at second-look surgery after induction CT. Randomization to: Consolidation with RT (WAI) Consolidation with CT	Abdominal RT dose of 20 Gy (1 Gy, 5 days a week, 20 fr) + abdomino-pelvic boost dose of 20.4 Gy (1.7 Gy per fraction, 12 fractions) WAI: 20 Gy (1 Gy, 5 days a week, 20 fraction) + pelvic boost of 20.4 Gy (1.7 Gy per fraction, 12 fractions)	5-year PFS: 56.3%; 5-year OS: 68.8% 5-year PFS: 36%; 5-year OS: 57.1% 5-year PFS: 35.5%; 5-year OS: 64.5% 5-year PFS: 16.7%; 5-year OS:32.4% 5-year PFS: 25.3%; 5-year OS: 40.5 %	Early side events radiotherapy group: Grade 3 myelotoxicity: 4.4% Grade 3 bowel events: 4.4% Late side events radiotherapy group: Grade 3 intestinal obstruction: 10%

RT radiation therapy; *WAI* whole abdominal irradiation; *CT* chemotherapy; *fr* fractions; *OS* overall survival; *PFS* progression-free survival; *DFS* disease-free survival; *G* grade; *N/V* nausea and vomiting

Table 3 Recurrent ovarian cancer and oligometatastic disease –the role of radiotherapy

Author and year	Setting	Type of study	Population	Tumor site	Treatment	Radiation therapy dose	Toxicity	Outcomes
Brown et al. [10]	Recurrent	Retrospective	102	Nodal or extranodal recurrence	Involved field RT	≥ 45 Gy conventional fractionation	G3–G4 events: 0%	5-year LC: 71% 5-year PFS: 24% 5-year OS: 40%
Albuquerque et al. [8]	Recurrent	Retrospective	27	Nodal, pelvis Retroperitoneal	Involved field RT	Median dose: 50 Gy conventional fractionation	≥ G3 late effects: 7.5%	5-year LRFS: 70% 5-year DFS: 33%
Yap et al. [38]	Recurrent	Retrospective	22	Pelvis, paraaortic and paracaval lymph node beds, inguinal region, or porta hepatitis	IORT/ orthovoltage X-rays (200 kVp)	9–14 Gy (median, 12 Gy)	G3 events: 41%	5-year OS: 22% median OS: 26 months * LRR 32%
Lazzari et al. [40]	Oligometastatic	Retrospective	82	Nodal or metastatic sites	SABR	24-30 Gy/3 fr 25 Gy/5 fr	G3–G4 events: 0%	Systemic-treatment free interval: 7.4 months
Kunos et al. [41]	Oligometastatic	Phase II	50 Ovary:50%	Nodal or metastatic sites	SABR	Median dose: 24 Gy/3fr	Fatigue G2 events: 16% Nausea G2 events: 8% Diarrhea G2 events: 4%	Median DFS: 7.8 months Median OS: 20.2 months

RT Radiotherapy; *SABR* Stereotactic ablative radiotherapy; *IORT* Intra-operative radiotherapy; *LC* Local control; *PFS* Progression free survival; *OS* Overall survival; *LRFS* Local recurrence free survival; *DFS* Disease free survival; **median OS* 26 months from the time of IORT

steep dose-gradient and ablative intent and is particularly suitable as local treatment in oligometastatic disease [39].

Lazzari et al. reported on oligo-recurrent or oligo-progressive ovarian cancer patients (during or after systemic treatment) treated with SABR with a median dose of 24 Gy in three fractions (82 patients and 156 lesions). Up to 67% of the treated lesions were comprised within lymph nodes. Objective response rate (including complete and partial responses and stable disease) was 93% with a complete response rate of 60%. No major toxicity was observed. Median time to a new systemic treatment was 7.4 months and 1/3 of patients were free from disease at 1 year after treatment. Actuarial local PFS and OS were 68% and 71%, respectively, with a prevalent pattern of failure out of the radiation field [40].

In order to deliver SBRT in oligometastatic women affected with gynecological malignancies, Cyberknife has been tested in a phase II study. Half of the population enrolled was affected with an ovarian primary (68% with nodal lesions). The dose, prescribed at the 70% isodose line, was 24 Gy in 3 daily doses. Local control was 96% at 6 months [41].

Further results of ongoing trials exploring the role of SBRT in the recurrent setting are soon expected [42], Table 4.

For details of the main studies exploring the clinical scenario of *Recurrent Ovarian Cancer and Oligometastatic State*, see Table 3.

Palliative radiation therapy

Palliative RT, although frequently neglected in this setting, can have a major role in managing symptoms. Due to its capacity to lead to remarkable shrinkage of abdominal masses, RT provides opportunities for symptom relief [43].

High chances to control vaginal bleeding and pain were reported by Gelblum et al [44]. In a series by Adelson et al. [45], 42 patients received single or multiple 10 Gy fractions (three at maximum) to the pelvis. Bleeding decreased or stopped in 15/21 patients, and pain at least decreased in 11/20.

Table 4 Ongoing clinical studies

ClinicalTrials.gov identifier and trial title	Type	First submitted date	Estimated primary completion date	Recruitment status	Estimated enrollment	Setting	Age eligible	Tumor/RT site	Treatment	Radiation therapy dose	Primary outcome
NCT03325634 Stereotactic body radiation therapy in treating patients with recurrent primary ovarian or uterine cancer [42]	Phase I study	October 20, 2017	July 21, 2020	Recruiting	18 participants	SBRT in Recurrent disease	18 Years and olde	Three or fewer total sites of active disease (at least one site of active disease to be treated on study must be confined to the abdomen or pelvis excluding liver and must be < 5 cm in greatest dimension as determined by pre-screening cross-sectional imaging).	SBRT	3 fractions	MTD [Time Frame: After the completion of SBRT treatment through 3 months of follow-up.]

Table 4 (continued)

ClinicalTrials.gov identifier and trial title	Type	First submitted date	Estimated primary completion date	Recruitment status	Estimated enrollment	Setting	Age eligible	Tumor/RT site	Treatment	Radiation therapy dose	Primary outcome
NCT03283943 PDL-1 inhibition and focal sensitizing radiotherapy in recurrent ovarian/primary peritoneal/fallopian tube cancers. [52]	Phase I study	June 30, 2017	December 16, 2020	Recruiting	22 participants	PDL-1 Inhibition and Focal Sensitizing RT in Recurrent patients	19 Years to 99 Years	Such as CT scan, MRI, or radiograph for each lesion, partial treatment of a tumor mass is permitted, but the treatment volume cannot be less than the equivalent of a 2cm sphere (4cc) and the two targets cannot be part of the same contiguous mass.	Focal sensitizing radiotherapy/SBRT	Focal sensitizing RT will be given at a starting dose level of 24 Gy (6 Gy x 4 fractions), and may be escalated to 32 Gy (8 Gy x 4 fractions).	Determine the MTD of durvalumab combined with focal RT for use in recurrent OC [Time Frame: First 4 weeks of therapy]

Table 4 (continued)

ClinicalTrials.gov identifier and trial title	Type	First submitted date	Estimated primary completion date	Recruitment status	Estimated enrollment	Setting	Age eligible	Tumor/RT site	Treatment	Radiation therapy dose	Primary outcome
NCT03277482 Durvalumab, Tremelimumab + Radiotherapy in gynecologic cancer [53]	Phase I study	September 7, 2017	January 1, 2020	Recruiting	32 participants	Two immunotherapy drugs in combination with radiation therapy in Ovarian (including ovarian epithelial, fallopian tube, primary peritoneal) cancer that is metastatic or unresectable and for which standard curative or palliative measures do not exist or are no longer effective	18 Years and older	At least 1 lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm with conventional techniques or as ≥20 mm with spiral CT scan, MRI, or calipers by clinical exam.	SBRT	RT will begin on the same day as the first immunotherapy infusion or on the following day. RT course is either 1 day or 5 days.	MTD of RT with durvalumab and tremelimumab [Time frame: 8 weeks]

RT Radiotherapy; *SBRT* Stereotactic body radiotherapy; *IMRT* Intensity-modulated radiation therapy; *PDL-1* Programmed death-ligand; *MTD* Maximum tolerated dose; *CT scan* computed tomography scan; *MRI* Magnetic resonance imaging; *CTCAE* Common terminology criteria for adverse events; *OC* Ovarian cancer

Discussion and future perspectives

The role of RT in the management of EOC patients has changed during the years. In the past, RT was mainly used in the adjuvant setting, but nowadays, due to the contradictory clinical results and the consistent toxicity profile, it has been replaced by highly effective taxane- and platinum-based CT. Radiation therapy was used to manage early-stage patients and low residual volumes in all histological subtypes. During the 80 s, WAI was abandoned, given the recognized achievements of systemic treatments. Treatment-related toxicity, mostly due to the large-field employed, particularly with respect to small bowel, and the unfavorable effect on bone marrow reserve, precluding maximal CT administration, contributed to this shift of treatment strategies [46].

More recently, the possibility of a better organs-at-risk (OARs) sparing and dose distribution homogeneity offered by modern RT delivery techniques, such as static and dynamic IMRT, renewed the interest in this treatment modality [13].

The use of IMRT to deliver WAI showed a feasible and manageable toxicity profile with promising results in terms of recurrence prevention [32]. Robust clinical data are needed to eventually (re) establish RT indication in this setting [33].

A "modern" clinical scenario in which radiation has been employed is oligometastatic disease. In the oligometastatic setting, modern RT represents a reliable and effective treatment option with a mild toxicity profile for ovarian cancer patients. Palliative RT, given its capacity to lead to a remarkable shrinkage of abdominal masses, can offer valid opportunities of symptom relief, with particular regards to vaginal bleeding and pain control.

Novel therapies, such as PARP inhibitors and antiangiogenic drugs, are promising and more encouraging results are awaited [47]. For instance, PARP inhibitors represent an interesting category of radiosensitizers, that can potentially enhance the effect of radiation. Tumor cells can exploit avoidance of apoptosis caused by DNA damaging agents via increased PARP. Thus, PARP inhibitors may interrupt the catalytic effects of PARP. Moreover, the DNA damage induced by radiation may destabilize DNA repair systems within the cancer cell, allowing for enhanced activity of PARP inhibition. Particularly in cancers with defects in homologous recombination, such as ovarian cancers with BRCA mutations, PARP inhibitors showed major activity [48–50].

The analysis of the molecular signature underlying this tumor pathogenesis can lead to combine novel therapies and eventually RT together in the treatment algorithm [51].

Ongoing studies are evaluating the safety and effectiveness of immunotherapy drugs (single or double agents) combined with RT in recurrent or metastatic gynecologic cancer, including ovarian cancer [[52], [53]]; Table 4.

Thus, we believe that new lines of evidence are eagerly awaited to redefine the role of RT in EOC, regarding both WAI and modern irradiation techniques, to fully exploit all the potentials of this locoregional treatment in such a clinical setting.

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Compliance with ethical standards

Conflict of interest We declare that we do not have any conflict of interest.

Ethical approval The present study has been reviewed and approved by the Internal Review Board of the Department of Oncology of the University of Turin at AOU Citta' della Salute e della Scienza, Turin, Italy.

Research involving human and animal participants No human participants were involved in the present study.

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