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Scientific Article

Palliative Radiation Therapy for Metastatic, Persistent, or Recurrent Epithelial Ovarian Cancer: Efficacy in the Era of Modern Technology and Targeted Agents

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Abstract

Purpose: Metastatic, persistent, or recurrent epithelial ovarian cancer (MPR-EOC) remains a significant threat to patient mortality despite advances in novel targeted agents. Radiation therapy (RT) is often used as a palliative option. We report outcomes of a large series of MPR-EOC patients treated with modern palliative RT (PRT) in an era of novel systemic therapies.

Methods and Materials: A retrospective review was conducted of women treated with PRT for MPR-EOC between 2007 and 2019 at an academic institution. Clinical response rates were recorded at <1 month, 1 to 3 months, and >3 months. Radiographic responses were categorized by RECIST 1.1 criteria. Overall response rate (ORR) was the sum of complete and partial response. Linear regression analyses of baseline characteristics were conducted for statistical testing.

Results: Eighty-six patients with PMR-OC received 120 courses of palliative RT. Median follow-up was 8.6 months. Median age was 61 (range, 22-82). Thirty-six percent of women received central nervous system (CNS)-directed RT. In addition, 43% received targeted therapies before RT. Clinical ORR within 1 month and at last follow-up for non-CNS lesions was 79% and 61% (69% and 88% for CNS lesions, respectively). High-grade serous lesions were more likely to have clinical response ($P = .04$). Biologically effective doses (BED) >39 Gy were associated with improved clinical response in CNS lesions ($P = .049$). Bony sites were associated with worse clinical ($P = .004$) response in non-CNS lesions compared with soft tissue or nodal sites. Acute or late grade 3+ toxicities with bevacizumab were low (8.7%/4.3%).

Conclusions: PRT offers excellent rates of response for symptomatic patients with MPR-EOC within 1 month of treatment, with durable responses beyond 3 months. High-grade serous lesions were associated with improved response in all patients. Higher BED and soft tissue or nodal sites were associated with improved response in CNS and non-CNS patients, respectively. Acute or late toxicities with bevacizumab and PRT were low. Prospective investigation is warranted to determine the optimal PRT regimen.

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Introduction

Ovarian cancer (OC) is a highly aggressive gynecologic malignancy, with the majority of patients presenting with advanced disease at diagnosis. The general treatment paradigm for advanced OC is maximal cytoreductive surgery with platinum-based chemotherapy.[1] Recent literature has also reported a progression-free survival benefit with maintenance inhibition of poly (adenosine diphosphate-ribose) polymerase (PARP) in women with partial or complete response to platinum-based regimens.[2,3]

Whole abdominal radiation therapy was historically indicated as adjuvant therapy to address microscopic residual disease.[4] However, due to its considerable toxicity and the development of platinum-based chemotherapy, whole abdominal radiation therapy is no longer included in primary OC treatment paradigms.[1]

Despite advances in cytoreductive strategies and frontline systemic therapy, >70% of women relapse within 3 years of diagnosis.[5] As such, many patients with OC benefit from palliative care referrals to assist with symptom management, goals of care discussions, and complex medical decision making at the end of life.

There is a growing body of evidence to support the incorporation of palliative services in cancer care. In 2010, a seminal randomized trial[6] reported early palliative care among patients with metastatic non-small cell lung cancer significantly improved quality of life, led to less aggressive care at the end of life, and resulted in longer overall survival. Furthermore, both the American Society of Clinical Oncology and the Society of Gynecologic Oncology have published official practice guidelines recommending the routine and early integration of palliative services.[7,8]

Radiation therapy (RT) is often used as an effective therapeutic option in the palliation of patients with metastatic, persistent, or recurrent epithelial OC (MPR-EOC) as a means for symptomatic relief and local control. This includes oligometastatic disease or symptomatic disease causing pain, bowel or ureteral obstruction, or bleeding. Despite their rarity in OC (2% incidence[9]), brain metastases can also cause significant morbidity and can be treated with palliative RT to reduce the risk of progression and neurocognitive deficits.[10,11]

As patient survival improves with modern systemic agents, there is a growing need to understand the efficacy of palliative RT regimens for MPR-EOC in the same era. Although radiation therapy has traditionally been delivered for symptomatic control in MPR-EOC, the recognition of the biologically distinct (and potentially curable) oligometastatic state[12,13] is expanding the scope of RT indications. Data from phase 2 trials in other malignancies evaluating the effect of locally directed therapy to oligometastatic lesions has demonstrated improvements in overall survival.[14,15]

We therefore conducted, a large contemporary retrospective analysis of palliative RT in MPR-EOC. This patient cohort is highly relevant to modern practice given the number of patients who received novel systemic agents, the prominent usage of advanced RT technology, and the representation of patients with BMs from OC (an area with limited data but increasing prevalence in practice). The analysis will report the outcomes and durability of palliative RT in MPR-EOC and delineate factors predictive of response in the modern era.

Methods and Materials

We conducted a retrospective chart review of women treated with palliative radiation therapy for metastatic ovarian cancer from 2007 through 2019 at [University of Pennsylvania] and affiliate sites. Institutional review board approval was obtained before conducting this review. Patients were included in this analysis if they were treated for palliative intent, including treatment of oligometastatic disease. All patients had MPR-EOC ovarian cancer and received anywhere from one to 5 courses of radiation treatment.

Given the poor prognosis of patients with metastatic ovarian cancer, clinical and radiographic response rates were categorized in intervals of <1 month, 1 to 3 months, and >3 months after the end of radiation treatment to indicate acute and durable responses. Clinical responses were categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Pain scores were classified using the Bone Metastases Consensus Working Party guidelines[16] (indeterminate responses, which are neither PR nor PD per BMWCP guidelines, were classified as SD to maintain consistency with other clinical response categorizations). Radiographic responses were categorized as CR, PR, SD, or PD based on the RECIST 1.1 criteria.[17] Overall response rate (ORR) was the sum of CR and PR in a given patient. Given the large subset of patients with brain metastases (BMs), courses were stratified by central nervous system (CNS) and non-CNS anatomic locations. Acute (during RT and within 3 months of completion) and late (>3 months after completion of RT) toxicities were recorded with concurrent and prior bevacizumab using Common Terminology Criteria for Adverse Events version 5.0[18] classification.

Rates of response (CR or PR at any point) were compared with demographic and treatment characteristics. χ^2 ($n \geq 20$) or Fisher exact ($n < 20$) tests were used for such comparison with variables for race, histology, platinum chemotherapy, or targeted therapy before RT, RT

Table 1 Patient characteristics and treatment details

No. of courses	105
No. of patients	76
Median age	61
Ethnicity	
White	82.9% (63/76)
Black	9.2% (7/76)
Asian	3.9% (3/76)
Hispanic	2.6% (2/76)
Unknown	1.3% (1/76)
Histology	
High-grade serous	59.2% (45/76)
Adenocarcinoma, other	13.2% (10/76)
Low grade serous	9.2% (7/76)
Clear cell	5.3% (4/76)
Other	7.9% (6/76)
Endometrioid	3.9% (3/76)
Carcinosarcoma	1.3% (1/76)
Anatomic site	
Soft tissue/organ	35.2% (37/105)
Lymph node	21.0% (22/105)
Bone	11.4% (12/105)
CNS	36.2% (38/105)
Indications	
Clinical symptoms	59.0% (62/105)
Progressive/metastatic	33.3% (35/105)
Postoperative	7.6% (8/105)
Systemic therapy before RT	
Platinum chemotherapy	27.6% (29/105)
Nonplatinum chemotherapy	61.9% (65/105)
Targeted therapy	42.9% (45/105)
None/other	1.0% (1/105)
Technique	
2D/3D CRT	53.3% (56/105)
SRS	21.9% (23/105)
VMAT/IMRT	16.2% (17/105)
SBRT	4.8% (5/105)
Proton	3.8% (4/105)
Non-SRS dose	14-63 Gy in 4-35 fractions
SBRT dose	24-50 Gy in 3-5 fractions
SRS dose	15-25 Gy in 1-5 fractions

Abbreviations: 2D = 2-dimensional; 3D CRT = 3-dimensional conformal radiation therapy; CNS = central nervous system; IMRT = intensity modulated radiation therapy; RT = radiation therapy; SBRT = stereotactic body radiation therapy; SRS = stereotactic radiosurgery; VMAT = volumetric modulated arc therapy.

technology, RT location, and biologically effective dose (BED) >39. Binary logistic regression analyses were used for comparison with continuous variables (age and BED). Covariates with $P < .1$ were included in multiple logistic regression modeling to assess for independent effect. Additionally, χ^2 analyses were used to compare rates of radiographic response between patients treated for clinical symptoms and asymptomatic progression. Statistical analysis was conducted using IBM SPSS Statistics, version 26 (IBM Corporation, Armonk, NY).

Results

We identified 86 patients with PMR-OC that received 120 combined courses of palliative radiation treatment. Median follow-up was 8.6 months (range, 0.5-119 months). Excluding 10 patients (15 courses) with no evaluable clinical or radiographic follow-up, 51 patients (58 courses) were treated to non-CNS locations and 18 patients (25 courses) were treated to CNS locations; 7 patients (22 courses) received palliative RT to both CNS (13 courses) and non-CNS (9 courses) locations.

Table 1 describes baseline patient characteristics and details related to patient treatments. The median age of patients in this cohort was 61, with a range of 22 to 82. Patients were most commonly white (83%) and black (8%). Tumor histologies were primarily high-grade serous (HGS, 59%), although adenocarcinoma (undifferentiated or unspecified), low-grade serous, clear cell, endometrioid, and carcinosarcoma were also observed.

Non-CNS treatment locations included tumors in soft tissue or organs (35%), lymph nodes (21%), and bone (11%); 4 patients were treated simultaneously to adjacent soft tissue and lymph nodes. Treatment for CNS metastases comprised the remaining 36% of patients.

Most patients were treated for clinical symptoms (59%). Pain and bleeding were the most common clinical indications. Others included neurologic deficits, spinal cord compression, airway compression, and bowel obstruction. A large cohort of patients were treated for asymptomatic progressive or metastatic disease (33%) with a small cohort treated adjuvantly after surgery (eg, metastasectomy or palliative debulking; 7.6%).

Almost all patients (90%) received chemotherapy immediately before radiation therapy. The most common systemic therapy regimens were platinum-based (ie, carboplatin) followed by taxanes and doxorubicin. Many patients (43%) also received treatment with targeted therapy agents before radiation treatment. Bevacizumab was the most commonly used targeted therapy agent (20%), although patients also received PARP inhibitors (9%) and immune checkpoint inhibitors (5%).

A wide range of palliative radiation regimens were delivered across several modalities. Nonstereotactic treatment regimens to both CNS and non-CNS locations ranged from 14 Gy in 4 fractions to 63 Gy in 35 fractions. Common palliative doses were 30 Gy in 10 fractions (14%), 20 Gy in 5 fractions (8.6%), and 35 Gy in 14 fractions (7.6%). Nonstereotactic modalities included 2-dimensional or 3-dimensional (53%), intensity modulated radiation therapy (IMRT) or volumetric-modulated arc therapy (16%), and proton therapy (3.8%). Stereotactic body radiation therapy (SBRT) was less commonly used (4.8%) with treatment regimen ranging from 24 Gy in 3 fractions to 50 Gy in 5 fractions. Lastly, patients with BMs commonly received stereotactic radiosurgery (SRS,

Table 2 Response rates (all lesions)

	<1 mo	1-3 mo	>3 mo
Clinical response			
CR	32.8% (19/58)	45.0% (18/40)	48.4% (15/31)
PR	43.1% (25/58)	35.0% (14/40)	19.4% (6/31)
SD	12.1% (7/58)	2.5% (1/40)	0.0% (0/31)
PD	12.1% (7/58)	17.5% (7/40)	32.3% (10/31)
ORR	75.9% (44/58)	80.0% (32/40)	67.7% (21/31)
Radiographic response: symptomatic patients			
CR	15.2% (5/33)	16.7% (5/30)	25.9% (7/27)
PR	24.2% (8/33)	30.0% (9/30)	22.2% (6/27)
SD	51.5% (17/33)	43.3% (13/30)	40.7% (11/27)
PD	9.1% (3/33)	10.% (3/30)	11.1% (3/27)
ORR	39.4% (13/33)	46.7% (14/30)	48.1% (13/27)
Radiographic response: asymptomatic patients			
CR	39.4% (13/33)	47.1% (16/34)	53.1% (17/32)
PR	9.1% (3/33)	8.8% (3/34)	6.3% (2/32)
SD	45.5% (15/33)	41.2% (14/34)	34.4% (11/32)
PD	6.1% (2/33)	2.9% (1/34)	6.3% (2/32)
ORR	48.5% (16/33)	55.9% (19/34)	59.4% (19/32)

Abbreviations: CR = complete response; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease.
Excludes patients treated with postoperative palliative radiation.
Denominator reflects evaluable patients.

22% of all courses) with doses ranging from 15 Gy in 1 fraction to 25 Gy in 5 fractions. Nearly half of the patients who underwent SRS received 21 Gy in 1 fraction.

Across the entire cohort, the clinical ORR was 76% within the first month after treatment and 67% at least 3 months after treatment (Table 2). Radiographic ORR between patients treated for clinical symptoms (symptomatic) and asymptomatic progression (asymptomatic) were 48% and 59%, respectively. Although patients treated for asymptomatic progression had higher rates of response, no significant differences were observed between the 2 cohorts ($P = .23$).

Table 3 Response rates (non-CNS lesions)

	<1 mo	1-3 mo	>3 mo
Clinical response			
CR	38.1% (16/42)	44.8% (13/29)	43.5% (10/23)
PR	40.5% (17/42)	31.0% (9/29)	17.4% (4/23)
SD	14.3% (6/42)	3.4% (1/29)	0.0% (0/23)
PD	7.1% (3/42)	20.7% (6/29)	39.1% (9/23)
ORR	78.6% (33/42)	75.9% (22/29)	60.9% (14/23)
Radiographic response: symptomatic patients			
CR	9.5% (2/21)	10.5% (2/19)	18.8% (3/16)
PR	23.8% (5/21)	26.3% (5/19)	18.8% (3/16)
SD	52.4% (11/21)	52.6% (10/19)	50.0% (8/16)
PD	14.3% (3/21)	10.5% (2/19)	12.5% (2/16)
ORR	33.3% (7/21)	36.8% (7/19)	37.5% (6/16)
Radiographic response: asymptomatic patients			
CR	21.1% (4/19)	31.6% (6/19)	41.2% (7/17)
PR	10.5% (2/19)	10.5% (2/19)	5.9% (1/17)
SD	57.9% (11/19)	52.6% (10/19)	41.2% (7/17)
PD	10.5% (2/19)	5.3% (1/19)	11.8% (2/17)
ORR	31.6% (6/19)	42.1% (8/19)	47.1% (8/17)

Abbreviations: CNS = central nervous system; CR = complete response; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease.
Excludes patients treated with postoperative palliative radiation.
Denominator reflects evaluable patients.

Table 4 Response rates (CNS lesions)

	<1 mo	1-3 mo	>3 mo
Clinical response			
CR	18.8% (3/16)	45.5% (5/11)	62.5% (5/8)
PR	50.0% (8/16)	45.5% (5/11)	25.0% (2/8)
SD	6.3% (1/16)	0.0% (0/11)	0.0% (0/8)
PD	25.0% (4/16)	9.1% (1/11)	12.5% (1/8)
ORR	68.8% (11/16)	90.9% (10/11)	87.5% (7/8)
Radiographic response: symptomatic patients			
CR	25.0% (3/12)	27.3% (3/11)	36.4% (4/11)
PR	25.0% (3/12)	36.4% (4/11)	27.3% (3/11)
SD	50.% (6/12)	27.3% (3/11)	27.3% (3/11)
PD	0.0% (0/12)	9.1% (1/11)	9.1% (1/11)
ORR	50.0% (6/12)	63.6% (7/11)	63.6% (7/11)
Radiographic response: asymptomatic patients			
CR	64.3% (9/14)	66.7% (10/15)	66.7% (10/15)
PR	7.1% (1/14)	6.7% (1/15)	6.7% (1/15)
SD	28.6% (4/14)	26.7% (4/15)	26.7% (4/15)
PD	0.0% (0/14)	0.0% (0/15)	0.0% (0/15)
ORR	71.4% (10/14)	73.3% (11/15)	73.3% (11/15)

Abbreviations: CNS = central nervous system; CR = complete response; PD = progressive disease; PR = partial response; ORR = overall response rate; SD = stable disease.
Excludes patients treated with postoperative palliative radiation.
Denominator reflects evaluable patients.

Of patients treated to non-CNS locations, the clinical and radiographic ORR within the first month after treatment were 79% and 33%, respectively (Table 3). Clinical ORR at last follow-up (at least 3 months after treatment) was 61%. Notably, of the patients with a CR (38.1%) within the first month, only 2 went on to have PD at last follow-up (4 were lost to follow-up), indicating durable response to treatment. All but one patient treated for malignancy-related vaginal bleeding (13/14) had a clinical response within 1 month, of which only one patient had recurrence of bleeding at last follow-up. Seventy percent of patients treated for pain (n = 27) had a clinical response within 1 month, of which only 3 patients demonstrated worsening pain at last follow-up. Radiographically, ORR improved to 38% for symptomatic patients and 47% for asymptomatic patients at last follow-up, with no significant differences in response rates between the 2 groups ($P = .44$). All lesions that responded within 1 month of radiation treatment maintained response through last follow-up. Furthermore, only 3 of 22 lesions that were initially SD, progressed over time (1 treated for clinical symptoms, 2 treated for asymptomatic progression).

Of patients treated to CNS locations, the clinical and radiographic ORR within the first month after treatment were 72% and 62%, respectively (Table 4). No patients with a demonstrated clinical or radiographic response within the first month went on to have documented progressive symptoms or imaging at last follow-up (although 2 patients died and 4 were lost to follow-up). Although clinical responses stayed constant over time, radiographic responses tended to improve, especially in patients treated for clinical symptoms. There was no difference in rates of radiographic responses between CNS patients treated for clinical symptoms and those treated for asymptomatic progression ($P = .41$). All patients receiving SRS responded or had SD at 1 month; only one patient had locally progressive symptoms and disease at last follow-up. Three of the 4 patients with progressive symptoms within the first month were those who received whole brain radiation therapy with more extensive CNS disease before treatment.

Patients in both CNS and non-CNS cohorts tended to have clinical responses early on, with sustained response at last follow-up. Furthermore, if a patient were to have a clinical CR, it most often occurred within the first month. Only 4 patients demonstrated a CR after the first month, and all of these patients had a PR initially; no patients with initially stable disease went on to have a CR. Most patients with radiographic SD at initial follow-up maintained SD over time. The initial responses of patients developing progressive symptoms after 3-month follow-up varied considerably: CR (2), PR (3), SD (2), and PD (3). No patients who progressed within the first month of follow-up went on to have any response.

Eight patients were treated with postoperative RT after surgical resection in the brain (6), mediastinal lymph node (1), and inguinal lymph node (1). Three patients with evaluable clinical symptoms before and after surgery-RT all demonstrated diminished (PR) or complete (CR)

Table 5 Observed toxicities in patients treated with bevacizumab before or concurrent with radiation therapy, by treatment course

	None	Grade 1-2	Grade 3	Grade 4
Acute				
Non-CNS (17)	6	Anorexia (1), depression (1), dermatitis (1), fatigue (5), GI (6), GU (1), odynophagia (1), pneumonitis (1), vaginal hemorrhage (1)	Dermatitis (1), esophagitis (1)	-
CNS (6)	4	GI (1)	Fatigue (1)	-
Late				
Non-CNS (9)	8	GI (1)	-	-
CNS (5)	3	Intracranial hemorrhage (1)	Radionecrosis (1)	Optic neuropathy (1)

Abbreviations: CNS = central nervous system; GI = gastrointestinal; GU = genitourinary.
Toxicities defined according to the Common Terminology Criteria for Adverse Events, version 5.0.
Numbers indicate number of treatment courses; more than one toxicity may be attributed to a single treatment course. Late toxicity data unavailable for 9 treatment courses (all due to patient death).
Late grade 3 and 4 toxicities occurred in the same patient.

resolution of symptoms within 1 month after RT. Of the 6 patients with radiographic follow-up, one recurred 9 months after treatment; the rest maintained stable disease (ie, no recurrence) through last follow-up.

Acute and late grade 3 or higher (G3 +) toxicities with bevacizumab were low (8.7% and 4.3%, respectively). CNS and mediastinal locations were the only treatment sites in which G3 + toxicity occurred. CNS toxicity (acute G3 fatigue, late G3 radiation necrosis, and late G4 optic neuritis) was identified in a single patient who received craniospinal irradiation with prior Gamma Knife irradiation. A second patient treated to the mediastinum had acute but not chronic grade 3 esophagitis. Notably, no acute or late G3 + toxicity was seen in patients treated to the abdomen or pelvis (the most common treatment location; Table 5).

An exploratory analysis examining patient demographics and treatment characteristics was performed to identify predictors of clinical or radiographic response. In all patients (CNS and non-CNS sites), HGS histology was associated with clinical responses (88% vs 64%, $P = .04$). In patients with CNS lesions, BED >39 Gy was associated with clinical response ($P = .049$). In non-CNS locations, bony site was associated with worse clinical (44% vs 89%, $P = .004$) response compared with soft tissue/nodal (STN) sites. Lastly, we compared BED regimens ≤39 Gy versus >39 Gy (assuming an alpha/beta ratio of 10,[19,20] the BED of 30 Gy in 10 fractions is 39 Gy) in non-CNS locations and found no differences in clinical ($P = .10$) or radiographic response rates ($P = .47$). We otherwise compared the most common regimens of 20 Gy in 5 fractions and 30 Gy in 10 fractions and found no significant differences in clinical ($P = .60$) or radiographic responses ($P = .29$; Table E1).[2]

Discussion

We report the outcomes of a large modern cohort of women with PMR-OC who received palliative radiation therapy in an era of novel systemic agents. In a population with poor prognosis, palliative radiation therapy resulted in excellent clinical and radiographic response rates (Table 2) within 1 month of treatment, with many responses durable beyond 3 months. Brain metastases, a rare site of anatomic spread, were also well represented in this cohort (36%, 38 courses) and responded favorably to palliative intracranial radiation therapy (Table 3). Exploratory analyses demonstrated an association between HGS histology and improved clinical response in all patients, BED >39 Gy and improved clinical response in BMs, and STN sites with improved clinical response in non-CNS sites. Our analysis is unique in its (1) large sample size compared with prior reports with significant number of BMs, (2) high proportion of patients treated with modern RT techniques, (3) inclusion of patients treated with novel systemic agents (ie, PARP inhibitors, bevacizumab, and immunotherapy), and (4) dedicated toxicity analysis of RT with concurrent or prior bevacizumab, an area of increasing clinical significance in MPR-EOC with a dearth of robust data.

Our high clinical response rates (79% ORR within 1 month) are similar to other reports, including literature from prior decades demonstrating durable pain relief and bleeding control from locally directed palliative RT in 80% of OC patients.[20-22] More recently, Bansal and colleagues also found pain control rates of 88.2% and vaginal bleeding control rates of 100% in 23 heavily pretreated women who received palliative pelvic RT.[23]

Investigators from Brigham and Women's Hospital also recently published rates and predictors of response to palliative RT for recurrent OC from 2003 to 2014[24] and demonstrated high rates of response for pain and bleeding (87% and 93%, respectively).

Identified predictors of response, including HGS histology and STN sites of disease are also compatible with prior investigations. In the above Brigham and Women's Hospital study, patients treated at nonbony sites had higher response rates than those with bony sites of disease (96% vs 75%, respectively). Furthermore, patients with clear cell histology had the lowest response rates (60%), compared with others like serous histology (82%).

The sizable nature of our cohort allowed for a temporal analysis of index lesion response rates. Patients in both CNS and non-CNS cohorts tended to have clinical responses early on, with some benefitting from sustained response at last follow-up. Lesions with clinical CR often occurred within the first month. Furthermore, no patients who progressed in the index lesion within the first month of follow-up went on to have any response, suggesting that initial response is of paramount importance. Patients who had progressive symptoms after 3 months had variable initial responses, suggesting progressive disease is still expected no matter what the initial response may be.

Regarding dose response, higher BED was associated with clinical response in brain metastases. This is a result of ablative SRS technology that radiobiologically induces high rates of cell kill compared with those of conventional palliative techniques or doses. Advanced stereotactic techniques permit the delivery of otherwise unsafe high dose-per-fraction regimens due to their sharp dose gradients that allow for normal tissue sparing. In non-CNS locations, however, regimens with BED >39 Gy (ie, greater than 30 Gy in 10 fractions) were no different than lower BED regimens, suggesting dose escalation may not increase the efficacy of palliative RT. Use of higher BED regimens in such (predominantly abdominopelvic) locations is typically limited by larger fields due to tumor size and organ motion. Dose-limiting toxicities from nearby organs at risk such as the stomach, bowel, kidneys, and bladder also constrain prescriptions.

Notably, 47% of all courses were delivered with advanced radiation therapy techniques (SRS, SBRT, IMRT/volumetric-modulated arc therapy, proton therapy). This is in keeping with the increasing number of patients referred for ablative or definitive therapy to oligometastatic or oligoprogressive disease or previously irradiated lesions requiring retreatment. In such scenarios, advanced techniques allow practitioners to deliver higher dose per fraction while sparing normal organs and tissue of radiation, or even reirradiation, toxicity. In fact, recently published reports have evaluated the roles of advanced RT in OC. For example, definitive involved-field RT using IMRT has demonstrated promising rates of local control (LC) and disease-free survival with low toxicity.[25,26] Two recent retrospective studies also explored SBRT in oligometastatic OC. Lazzari et al reported the treatment of 82 patients with a median dose of 24 Gy in 3 fractions and demonstrated the safety of SBRT along with an increase in systemic therapy-free survival with reasonable LC[27] (more than one-third of patients were disease-free at 1 year). Similarly, Macchia et al reported SBRT in MPR-EOC was well tolerated and afforded higher LC in patients receiving a total dose >25 Gy.[28]

Forty-three percent of patients received targeted therapy immediately before RT in this cohort. This is in keeping with the litany of recent publications studying the use of novel systemic agents (PARP inhibitors,[29-31] bevacizumab,[32] nivolumab[33]) in the setting of MPR-EOC. The response rates described thus reflect the potential outcomes of palliative RT in conjunction with advanced systemic therapies, a scenario that will be increasingly encountered by practitioners. Furthermore, given the sizeable population that received prior or concurrent bevacizumab, a dedicated subgroup analysis was conducted and demonstrated low acute and late grade 3 or higher (G3 +) toxicities (8.7% and 4.3%, respectively) with RT. Although G3 + toxicities occurred in patients treated to CNS and mediastinal locations, it is unclear if this was in relation to prior bevacizumab or reflected the increased risk toxicity with prior RT (Gamma Knife in the CNS patient treated with craniospinal irradiation) or unfavorable tumor location (in the mediastinal patient experiencing esophagitis after receiving 59.4 Gy). No acute or late G3 + toxicity was seen in patients treated to the abdomen or pelvis (the most common treatment location), suggesting that this may be a reasonable treatment option in symptomatic patients.

Limitations

The study is limited primarily by its retrospective nature which lends itself to both selection and sample bias. For example, patient performance status and prior lines of therapy (including prior radiation) may effect physician choice of RT technique, dose, and fractionation. Furthermore, lesions necessitating reirradiation demonstrate inherent radioresistance and may negatively affect response rates. Moreover, although the study population is sizeable, it is heterogenous with respect to treatment sites and prior lines of therapy. As such appropriate interpretation required subdivision of data (ie, CNS vs non-CNS, symptomatic vs asymptomatic indication), which led to more descriptive findings. Finally, the variety of systemic therapies used negatively affect our ability

to make conclusions regarding the efficacy of RT with respect to individual agents.

Future directions

As the role for palliative radiation therapy expands in the context of the oligometastatic paradigm, nuanced decision-making must be taken to deliver the most efficacious treatment although promoting cost-effective care. As such, prospective evaluation is warranted to determine the optimal dose, timing, and fractionation of RT as it relates to systemic agents and surgery. The high response rates demonstrated in this cohort may warrant prospective investigation of RT as a standard component therapy in MPR-EOC, either before systemic agents as a cytoreductive strategy or after as consolidation therapy.

Conclusions

We performed a large retrospective cohort analysis of women with MPR-EOC receiving palliative RT in the era of modern technology and systemic agents. Our large population of patients with BMs adds relevant data to the limited body of existing literature and can be used as a practical reference when counseling women. Patients demonstrated favorable clinical and radiographic response rates within 1 month, with >60% experiencing durable clinical responses beyond 3 months. HGS histology was associated with improved clinical response in all patients. BED >39 Gy was associated with improved response in brain metastases. Bony sites were associated with worse response compared with STN sites in non-CNS locations. Acute and late grade 3 or higher toxicities were low with prior bevacizumab, and none of these occurred in patients treated to abdominopelvic locations.

Although MPR-EOC is associated with limited prognosis, our data demonstrate that responses to palliative RT can be durable and meaningful. As such, without a conclusive effect on survival, it would be reasonable to consider treatment of such disease after taking into consideration patient symptom severity, goals of care, prognosis, performance status, and extracranial disease burden for BM.

Supplementary Materials

Supplementary material for this article can be found at https://doi.org/10.1016/j.adro.2020.11.009.

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