Rare Occurrence of Recurrent Ovarian Cancer with Thoracic Spinal Metastasis Treated With Proton Therapy and Parp Inhibitor: A Case Report

Anne X. Gao[1,3,5], Huynh Thi Kieu Oanh[2,3,5], Garima Tripathi[3,5,8], Karen C. Wang[6], Hsin-lun Lee[7],Long-Sheng Lu[7], Jeng-Fong Chiou[7], Tungho Wu[7], Jiantai Timothy Qiu[3,4,5*]

[1]University of Texas Southwestern Medicine School, USA

[2]International Master Program in Medicine, College of Medicine, Taipei Medical University, Taiwan

[3]Department of Obstetrics and Gynaecology, School of Medicine, College of Medicine, Taipei Medical University, Taiwan

[4]Department of Obstetrics and Gynaecology, Taipei Medical University Hospital, Taiwan

[5]International Ph.D. Program in Cell Therapy and Regenerative Medicine, Taipei Medical University, Taiwan

[6]Department of Gynaecology and Obstetrics, John Hopkins Hospital, USA

[7]Department of Radiation Oncology, Taipei Medical University Hospital, Taiwan 8 8 Medical Oncology at Apollo Gleneagles Hospital, India

*Corresponding Author**

J. Timothy Qiu
Department of Obstetrics and Gynaecology, International Ph.D. Program in Cell Therapy and Regenerative Medicine, Taiwan
E-mail: 191010@h.tmu.edu.tw

Received: 12-Jun-2025, **Manuscript No.** occrs-25-165086; **Editor assigned:** 16-Jun-2025, **PreQC No**. occrs-25-165086; **Reviewed:** 24- Jun-2025, **QC No.** occrs-25-165086; **Revised:** 08-Jul-2025, **Manuscript No.** occrs-25-165086; **Published:** 21- Jul-2025, **DOI:** 10.37532/24.11.3.1-4

Abstract

Background

Spinal cord metastases from ovarian cancer are extremely rare. This study reports the case of a female patient with ovarian cancer diagnosed with spine metastasis, completely resolved with treatment. With few reported cases, this study presents a diagnostic and therapeutic approach that can guide management for similar rare presentations.

Case Report

A now 71-year-old female was diagnosed with ovarian and breast cancer with homologous recombination deficiency (HRD) positivity in 2013. She underwent surgical staging and modified radical mastectomy, archiving remission after receiving adjuvant chemotherapy and tamoxifen. In 2020 and 2022, the patient experienced chest wall metastases, necessitating surgery in both incidences, followed by chemotherapy. In October 2022, MRI confirmed a T7 compression fracture with metastatic disease. She received proton therapy and began maintenance with a PARP inhibitor, and gemcitabine selected based on circulating tumor cell (CTC) analysis using the E.V.A Select platform. Recent imaging and CA125 levels show no evidence of metastatic recurrence in the spinal cord, and the patient is receiving surveillance and management for systemic recurrence.

Conclusion

Clinicians should be vigilant in diagnosing central nervous system metastases in patients with advanced ovarian cancer. Here, the patient's personalized treatment regimen for spinal cord metastasis included proton beam therapy, which provides precise tumor targeting. CTC testing informed the selection of chemotherapy drugs and the PARP inhibitor niraparib based on the patient's positive HRD status. This case highlights the importance of regular neuroimaging for early detection and underscores the need for a personalized, multidisciplinary approach that combines distinct therapies to optimize outcomes in such rare cases.

Keywords: Ovarian Neoplasms, Spinal Cord Neoplasms, Recombinational DNA Repair, Poly (ADP-ribose) Polymerase Inhibitors, Proton Therapy, Circulating Tumor Cell.

Introduction

Ovarian cancer is the seventh most common cancer in women and the third most common gynecological cancer in the world [1, 2]. Ovarian cancer is commonly divided histopathologically into four types (serous, clear cell, endometrioid, and mucinous tumor), whereas the less common types are seromucous and Brenner types. Serous type is the most common and aggressive type of ovarian cancer [3]. In the majority of cases, the spread of ovarian cancer is to the abdominal and pelvic organs and lymph nodes [4]. Distant metastases are most commonly found in the liver (37.49%), followed by lymph nodes (29.36%), lung (28.42%), bone (3.74%), and brain (0.99%)[5]. Ovarian cancer metastasis to the spinal cord is an extremely rare finding; from highest to lowest frequency, the order is metastasis to the thoracic region, followed by the cervical spine, and then in the medullary cone [6, 7].

Currently, the scarcity of reported spinal cord metastases from ovarian cancer reveals the need for guidance on successful diagnosis and treatment of similar cases. Spinal cord metastasis from ovarian cancer shows a high mortality rate, and treatment often includes methods that have significant adverse effects such as radiotherapy and surgery, which is invasive and risky. Previous reports have focused on early detection and diagnosis, and more work is needed to explore conservative treatment methods that reduce these consequences and result in complete resolution of the metastasis. To achieve this, more targeted and personalized treatment regimens are needed, which can be developed with the help of methods such as genetic testing and CTC analysis, a growing technique. An effective treatment regimen should involve multiple distinct therapies. In this case study, the patient underwent proton beam therapy, followed by chemotherapy and PARP inhibitor.

Proton therapy has shown potential for treating metastatic gynecological cancers. Traditional methods like External beam radiation therapy (EBRT) and brachytherapy struggle with recurrent and advanced stages, often failing to deliver curative doses or causing debilitating side effects. Proton therapy's precision and ability to spare adjacent critical organs make it a promising alternative, especially for difficult-to-treat cases [8]. PARP inhibitors (PARPi) are increasingly used in cancer treatment, particularly for high-grade serous ovarian and endometrial cancer. Recommended as maintenance therapy after initial chemotherapy, especially in patients with BRCA gene mutations, PARPi shows benefits in various settings. They may enhance immunotherapy effectiveness, although further study is needed. PARPs play a crucial role in DNA repair, preventing cell death by fixing damaged DNA. The exploration of PARPi combinations with other DNA-damaging agents continues [9, 10]. Circulating tumor cells (CTCs) can be harnessed for analysis using various methods, such as the E.V.A. Select test used in this patient case. CTC analysis can reveal the most effective combination of drugs on a patient-specific basis.

This is a literature review and case study of a patient with dual malignancy in the ovary and breast whose ovarian cancer spread to the spinal region and was treated with proton therapy in combination with an oral PARP inhibitor, i.e, niraparib. Also key in her treatment has been the effort to personalize treatment with distinct strategies, most notably CTC testing.

CASE REPORT

- A now 71-year-old woman (normotensive, non-diabetic) was initially diagnosed at 60 years old with primary right-sided ovarian and left-sided breast cancer at an external facility. On October 17, 2013, she underwent surgical staging followed by modified radical mastectomy of the left breast. Histopathological findings identified the right ovarian tumor as high-grade adenocarcinoma (stage pT1cN0) with focal capsular invasion (PAX8+, BRCA wild-type, HRD+) [Table 1]. The histopathological report of left breast MRM showed invasive ductal carcinoma (stage pT1cN0) with moderate differentiation (ER/PR+, HER2neu+). Post-operatively, she received adjuvant chemotherapy for ovarian cancer and adjuvant tamoxifen for breast cancer, achieving complete remission and was advised to undergo regular surveillance following treatment.
- On December 13, 2019, she had a Video-assisted thoracoscopic surgery (VATS) wedge resection of right lung segments 6 and 2, which showed lower lung adenocarcinoma in situ and upper lung atypical adenomatous hyperplasia. In April 2020, she was diagnosed with a chest wall mass concerning recurrence, which prompted partial resection of the chest wall (xiphoid process and costal cartilages) on April 6, 2020. Histopathological analysis revealed metastatic ovarian carcinoma with positive immunohistochemical staining for PAX8 [Figure 1] and negative staining for GATA3, confirming ovarian cancer as the primary source of metastasis. After the resection, the patient underwent chemotherapy with bevacizumab, carboplatin, and paclitaxel from April 28, 2020 to January 5, 2021, followed by bevacizumab maintenance until December 2021.
- A second chest wall recurrence in June 2022 led to re-excision on June 30, 2022. The patient also complained of severe back pain and insomnia, which impeded completion of an MRI. Instead, she completed an X-ray and CT scan, which found metastasis to the spinal cord (T7-8). The patient refused an operation and instead underwent further chemotherapy with bevacizumab, cisplatin, and paclitaxel from July to September 2022. Serial levels of CA-125 were also monitored throughout the treatment [Figure 2].
- In October 2022, the patient presented to Taipei Medical University Hospital for the first time with complaints of anorexia and malaise. The patient received rehabilitation prior, enabling the completion of an MRI of the thoracic spine on October 24, 2022, which showed T7 pathological fracture with marrow edema [Figure 3]; She rejected the suggestion

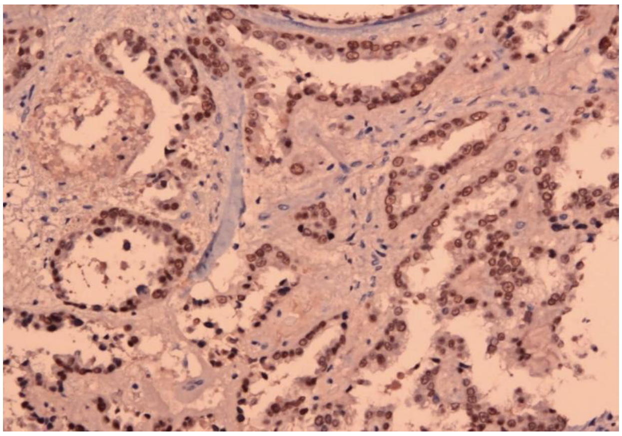

Figure 1. PAX8 expression in the chest wall lesion is strong and diffuse, which indicates that the tumor is ovarian in origin.

Table 1. Genetic analysis report showing BRCA WT and HRD positive status.

Genomic Integrity Index (GII)	BRCA 1/2 Gene	HRD STATUS	ATM GENE	TP53
Genomic Instability : 0.8	Wild Type	Positive	Pathogenic	Likely Pathogenic

of fine needle biopsy. She received proton radiotherapy to T7 oligometastasis (30 Gy/12 fx) in November 2022 [Figure 4, 5, 6, 7]. Subsequently, she started maintenance with the PARP inhibitor niraparib due to her HRD positivity (200 mg/day), which was well tolerated.

- December 2023 CT scans showed no evidence of disease recurrence, and the patient was doing well without adverse effects. Then, in January 2024, CT revealed a soft tissue mass near the sternum. A follow-up PET scan on May 15, 2024 showed a 3.2 cm malignant lesion in the left anterior

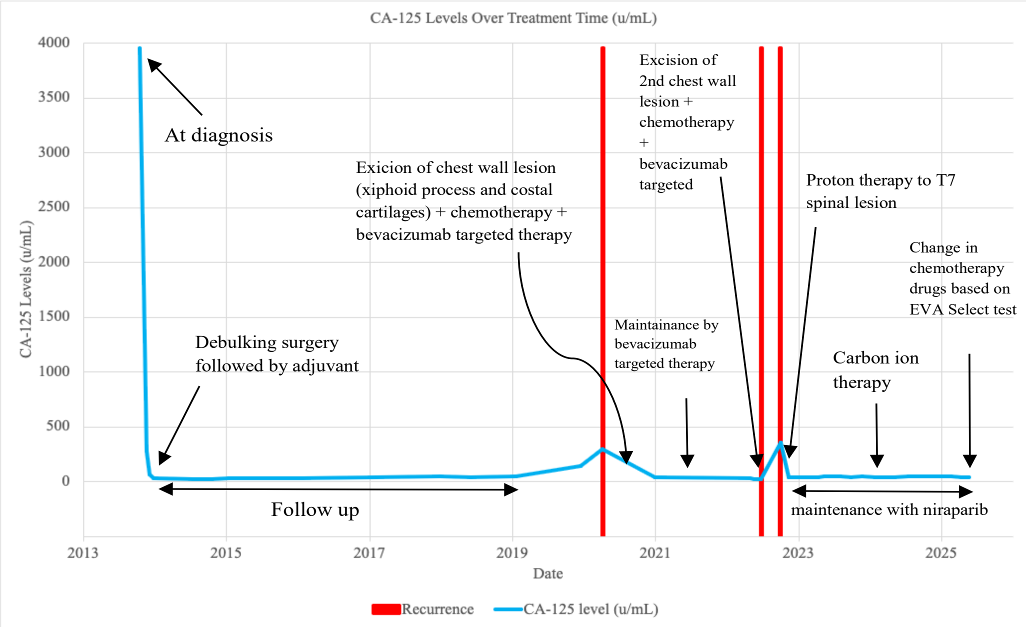

Figure 2. CA-125 monitoring.

Figure 3. MRI film showing T7 spinal metastasis (red arrow) in sagittal view.

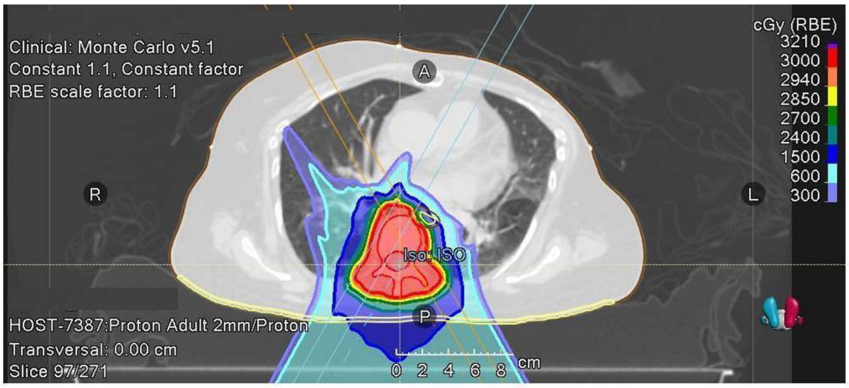

Figure 4. Treatment plan of PBT with isodose distribution in axial view (CTV:red, spinal cord:blue, heart:violet).

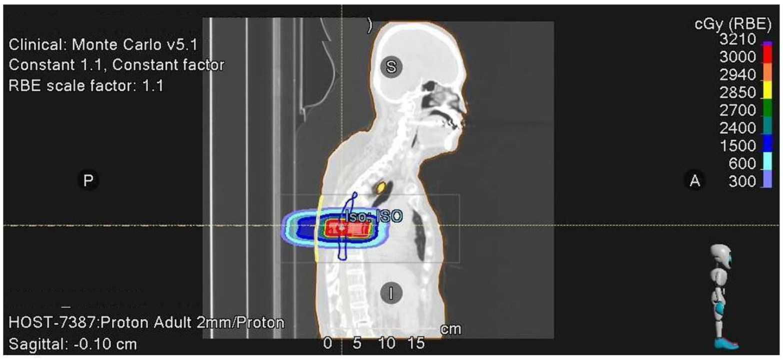

Figure 5. Treatment plan of PBT with isodose distribution in lateral view (CTV:red, spinal cord:blue, heart:violet).

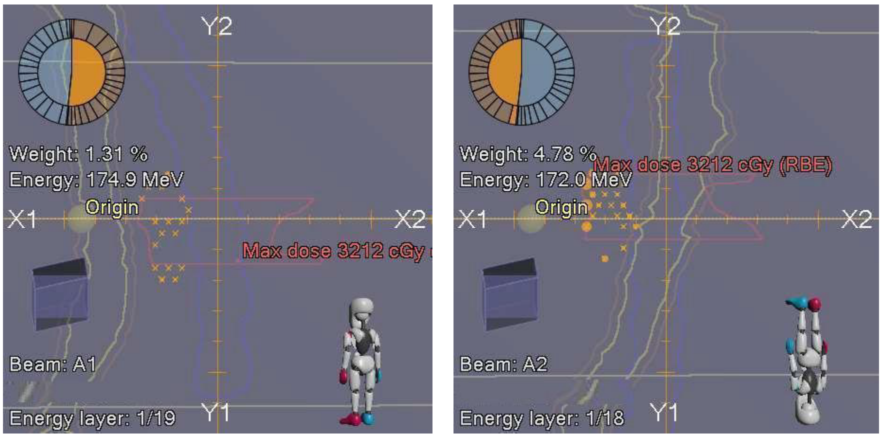

Figure 6. The image displays proton beam therapy planning, showing dose distributions from two different beam angles (A1 and A2). The left side (Beam A1) delivers 174.9 MeV energy with 1.31% weight, while the right side (Beam A2) delivers 172.0 MeV with 4.78% weight. Both aim to deliver a maximum dose of 3212 cGy (relative biological effectiveness) to a specific target region, represented by the outlined area.

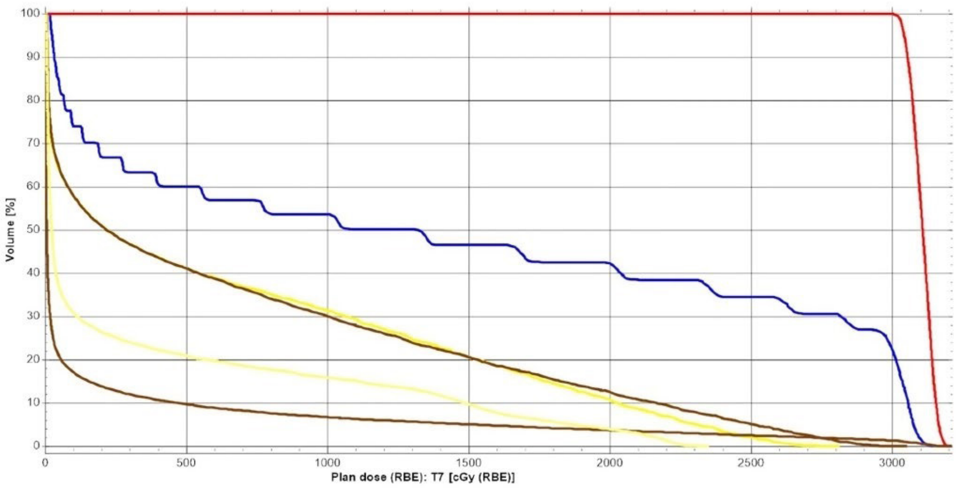

Figure 7A. Dose volume histogram of PBT for the patient.

chest wall [Figure 8], a possible ovarian recurrence. As a result, she received carbon ion radiotherapy (12 fx) from May to June 2024 at the Taipei Veterans General Hospital.

- Because of rising CA125 levels during the monitoring period after carbon ion radiotherapy [Figure 7A & 7B], a bone scan and CT were conducted in February 2025, showing no disease. However, on March 3, 2025, CT detected a suspicious lesion near the xiphoid process. On March 11, 2025, a mediastinal biopsy showed hyalinization and no cancer [Figure 9]. However, CTC analysis showed presence of tumor cells; thus, the EVA Select test was performed [Table 2 & Table 3]. The test indicated resistance to carboplatin and paclitaxel, so the patient was treated with gemcitabine (800 mg/m²) and bevacizumab (100 mg) starting April 12, 2025. The dose of gemcitabine was later reduced to 300 mg/m² because of fatigue on May 13, 2025. On May 20, 2025, the patient switched from chemotherapy to immunotherapy with nivolumab (20 mg) and continued her niraparib (200 mg/day) treatment from November 2022. She is currently under monitoring.

Region of Interest (ROI)	Color Name	Color box
Spinal Cord	Blue	
Esophagus	Yellow	
Esophagus- PRV	Brown	
Clinical Target Volume	Red	
Skin	Light Yellow	

Figure 7B. Color code for Dose volume histogram of PBT for the patient.

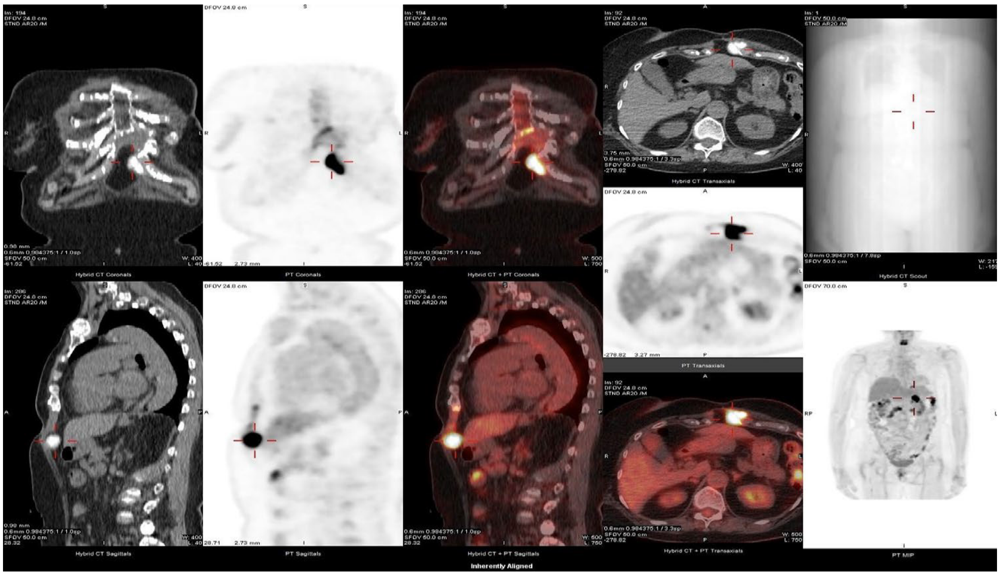

Figure 8. PET scan showing malignant lesion on left anterior chest wall, May 2024.

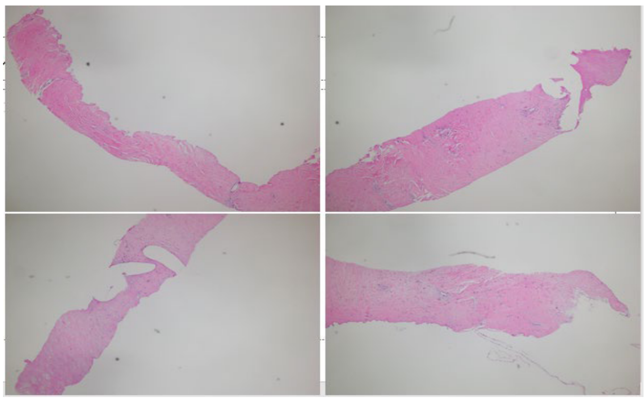

Figure 9. CT-guided biopsy of the mediastinum, showing hyalinization, March 2025.

Table 2. Results of patient-specific drug sensitivity testing via E.V.A. Select, indicating resistance to carboplatin and gemcitabine.

Drug name	Drug category	Mechanism of Action	Tumor Inhibition Strength
Carboplatin	Chemotherapy	Inhibits DNA synthesis	**Low**
Doxorubin	Chemotherapy	Inhibits nucleic acid synthesis	**High**
Gemcitabine	Chemotherapy	Inhibits DNA synthesis	**High**
Paclitaxel	Chemotherapy	Inhibits microtubule division	**Low**
Topotecan	Chemotherapy	Inhibits DNA synthesis	**Low**
Dasatinib	Targeted therapy	Inhibits TKI (Tyrosine Kinase Inhibitor)	**Moderate**
Lapatinib	Targeted therapy	Inhibits 4- anilinoquinazoline enzymes (EGFR, HER2)	**Low**
Olaparib	Targeted therapy	Inhibits PARP	**Moderate**
Megestrol	Hormonal therapy	Anti-hormone agent	**Low**
Tamoxifen	Hormonal therapy	Estrogen receptor inhibitor	**Low**

Table 3. Clinical goal vs Fulfilled Dose volume histogram of PBT for the patient.

ROI(Region of Interest)	Clinical Goal	Value	Fulfilled	% Outside Grid
Whole Lung	At most 1700 cGy average dose	244 cGy	Yes	20%
Whole Lung	At most 35.00% volume at 2000 cGy	2.61%	Yes	20%
Whole Lung	At most 50.00% volume at 500 cGy	15.21%	Yes	20%
Spinal Cord	At most 4500 cGy dose at 0.03 cm³ volume	3127 cGy	Yes	46%
Esophagus	At most 3400 cGy average dose	679 cGy	Yes	49%
Esophagus	At most 17.00% volume at 6000 cGy	0.00%	Yes	49%
Esophagus	At most 6300 cGy dose at 0.03 cm³ volume	2659 cGy	Yes	49%
Heart	At most 50.00% volume at 3000 cGy	0.04%	Yes	16%
Heart	At most 35.00% volume at 4000 cGy	0.00%	Yes	16%
Heart	At most 25.00% volume at 5000 cGy	0.00%	Yes	16%
Heart	At most 2000 cGy average dose	78 cGy	Yes	16%
Heart	At most 7000 cGy dose at 0.03 cm³ volume	3088 cGy	Yes	16%
CTV (LCS) - T7 - 250*12	At least 100.00% volume at 3000 cGy	99.98%	No	0%
CTV (LCS) - T7 - 250*12	At most 3210 cGy dose at 0.03 cm³ volume	3204 cGy	Yes	73%
Skin 3mm	At most 2500 cGy dose at 0.03 cm³ volume	2331 cGy	Yes	0%

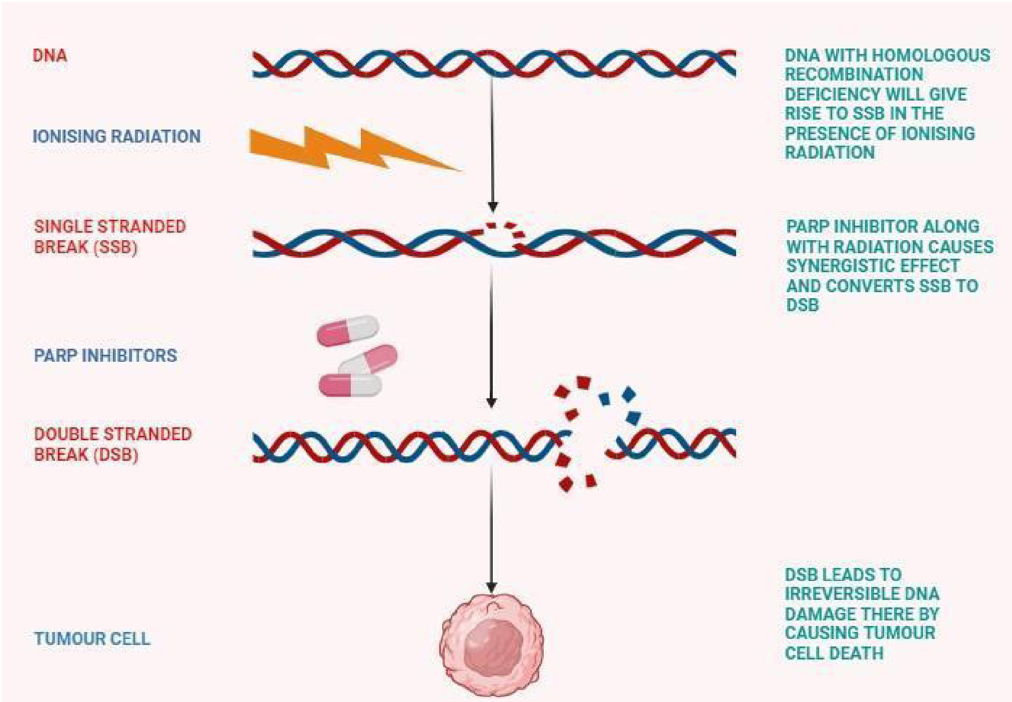

Figure 10. The image illustrates the process where ionizing radiation induces single-stranded breaks (SSB) in DNA with homologous recombination deficiency. When combined with PARP inhibitors, these SSBs convert to double-stranded breaks (DSB), resulting in irreversible DNA damage and subsequent tumor cell death.

Discussion

Current Understanding of Spinal Metastases in Ovarian Cancer

Primary ovarian cancer metastasis to the intramedullary spinal region is exceedingly rare finding with a prevalence of 2.1% of all intramedullary spinal cord metastasis [11]. Neoplasms that most commonly metastasize to the intramedullary spinal cord are lung (40%–60%), followed by breast cancer (14%)[12]. Patients develop various symptoms depending on the level of cord involvement- primarily pain, sensory loss, motor weakness, and abnormal autonomic function. Patients with such presentations have very poor and variable prognosis with expected survival of 10 months to 3 years, depending on the onset of symptoms and the time of diagnosis and treatment received by the patient [7].

Because there are limited information available and intramedullary spinal cord metastases occurrences stemming from ovarian cancers are rare, there remains uncertainty in establishing precise diagnostic approaches and treatment protocols. Typically, post-treatment monitoring for ovarian carcinoma includes regular contrast CT scans of the abdomen and chest, as these areas are prone to solid tumor metastasis through peritoneal spread. Monitoring serum CA-125 levels is also common practice, despite previous studies showing potential for misleading results.

The mechanism by which ovarian cancer spreads to distant parts of the body remains poorly understood. The most common widely accepted theory is that cancer cells from affected lymph nodes in advanced-stage disease travel through lymphatic channels to reach the internal jugular vein. From there, they can spread to distant organs through the bloodstream during disease progression. Factors that strongly predict the likelihood of distant metastasis include the presence of TP53 gene mutation that leads to its inactivity, as well as the advanced stage of the primary tumor [13].

To date, only seven cases of isolated intramedullary metastasis of ovarian cancer, without concurrent cranial or extramedullary metastasis, have been reported. Of these cases, four involved the cervical spine, one involved the conus medullaris and cauda equina, and two involved the thoracic spine. Six of the primary ovarian carcinomas were high grade (≥ Grade III, FIGO), and one was Grade IB. All primary cancers were effectively treated with surgical resection and systemic chemotherapy. Six patients were followed regularly with normal CA-125 levels and were considered disease-free until neurological symptoms appeared. On average, spinal disease was diagnosed 24 months after the initial ovarian cancer diagnosis. Five patients underwent surgical resection for intramedullary spinal cord metastasis (IMSCM) with additional therapies, while two patients received radiation therapy as their initial treatment. Sadly, two patients died 5 and 10 months after their diagnosis [14-16].

Proton Beam Therapy (PBT): Advancing Precision in Radiation Therapy

In the recent era, radiation therapy (RT) has advanced significantly due to improved imaging, powerful computational systems, and innovative delivery methods. Traditional two-dimensional RT, which relies on basic X-ray imaging, is a common approach utilized by 50% of cancer patients [17]. Over the years, more advanced RT technologies have been introduced, such as three-dimensional RT using CT imaging. This advancement led to intensity-modulated radiation therapy (IMRT), which precisely shapes radiation doses to tumors while minimizing exposure to adjacent critical organs. Volumetric modulated arc therapy (VMAT) further enhances dose conformity and reduces treatment time. Additionally, image-guided radiotherapy (IGRT) uses pre-treatment imaging to correct organ movement and patient positioning errors. These innovations have enabled stereotactic body radiotherapy (SBRT) to effectively target small, isolated tumors throughout the body [18].

RT, which is less invasive than surgery, has been used in cases of recurrent gynecological cancers, and studies have demonstrated its positive outcomes in such cases. For instance, Smart et al. conducted a retrospective study of 40 patients with localized recurrent ovarian cancer, many first-time or platinum-sensitive recurrences. After treatment with salvage RT (including 2D-RT, 3D Conformal Radiation Therapy (3D-CRT), and SBRT) for localized recurrent ovarian cancer, analysis revealed three-year disease-free and overall survival rates of 18% and 80%, respectively [19]. An additional study by Bae et al. showed that salvage radiotherapy (IMRT, 3D-CRT, SRT, or PBR) in 79 patients with recurrent ovarian cancer resulted in local control, with one- and two-year local control (LC) rates of 86.7% and 80.7%, respectively [20].

However, a frequently cited concern is that traditional RT leads to adverse side effects, a result of limited precision and harm to surrounding healthy tissue. Furthermore, after passing through the tumor, the exit dose of radiation can reach healthy tissue behind the tumor. This places sensitive organs, such as the brain and spinal cord, at considerable risk [17]. Smart et al. observed acute toxicities affecting the bowel, rectum, and bladder in 28%, 8%, and 8% of cases. Late toxicities were also reported, notably grade 3 bowel obstruction in up to 5% of cases [19]. Chundury et al. found that IMRT in a study of 33 patients with recurrent ovarian cancer led to acute and late gastrointestinal toxicities in 6% and 36% of patients, respectively. Acute and late haematological toxicities also occurred in 15% and 42% of patients, respectively, as well [21].

Another ground-breaking development is the use of heavy charged particles like protons, neutrons, and various heavy ions (such as helium, carbon, and neon) in radiation therapy. A retrospective, bi-institutional, single-arm study evaluated the effectiveness and safety of carbon ion radiation therapy (CIRT) in oligo metastatic, persistent, or recurrent ovarian cancer. The primary endpoints were 1-year and 2-year actuarial local control rates and objective response rate (ORR) on a per lesion basis, with toxicity as a secondary endpoint. Using Kaplan-Meier and Log-rank tests, 26 patients with 36 lesions received a median dose of 52.8 Gy. Within 12 months, 47% achieved complete response and 50% partial response, resulting in a 97% ORR. Higher doses per fraction and total doses correlated with complete responses. One-year and two-year local control rates were 92% and 83%, respectively, with no grade > 3 toxicities observed [22].

Proton beam therapy (PBT) stands out among these for its effectiveness in treating various cancers. PBT works by guiding protons through the body with minimal radiation exposure as they travel, releasing their maximum energy at a precise point called the Bragg peak, where they stop. This leads to a sharp decline in radiation beyond that spot, protecting nearby healthy tissues far better than traditional X-ray therapy. Compared to conventional radiotherapy, PBT optimizes the dose distribution of radiation by focusing a lower entrance dose on the tumor, which limits scattered or exit radiation outside of the tumor and significantly reduces adverse side effects [17, 23]. Despite its higher cost, the choice of proton therapy should be carefully considered for its unique benefits. Overall, these advancements in RT highlight significant strides in treatment precision and effectiveness, while also reducing side effects [21].

In adults, PBT targets cancers like prostate, uveal melanoma, and lung cancer. For patients with ovarian cancer and other gynaecological cancers in particular, PBT can reduce radiation exposure to gastrointestinal and genitourinary organs in the pelvic area while retaining pelvic control. Additionally, evidence suggests that PBT is especially advantageous for metastasis to the para-aortic lymph nodes and selected re-irradiation cases where limiting the exit dose of radiation is crucial [23]. Previous studies on gynaecologic neoplasms showed PBT's effectiveness in sparing organs and bone marrow [24]. The APROVE study, a prospective one-arm phase-2 trial, investigated the safety and tolerability of postoperative proton beam therapy in women with cervical or endometrial cancer. The study's primary focus was on safety and treatment tolerability, including toxicity rates and progression-free survival (PFS). Twenty-five patients were administered a dose of 45-50.4 Gy using intensity-modulated proton beam therapy (IMPT). No patients experienced grade 3 or higher gastrointestinal or genitourinary toxicity, achieving a 100% tolerability rate. With a median follow-up of 25.1 months, the mean PFS was estimated at 39.9 months [25].

The literature also reports a successful case of a 48-year-old woman with recurrent ovarian carcinoma treated with PBT. After surgery and initial chemotherapy, a recurrent tumor in the sigmoid colon necessitated a colectomy and diverting colostomy. With ineffective second-line chemotherapy, PBT was chosen, and at 1 year follow up post PBT- there was no evidence of tumor, the patient remained disease-free for over 8 years and only experienced a low grade fever during treatment [26].

A newly published study by Endo et al. is an important development that demonstrates the effect of proton on recurrent ovarian cancer specifically. 13 patients with recurrent ovarian cancer were treated with proton beam therapy, with ten exhibiting platinum resistance. Results included one- and two-year local control rates of 91.5% and 71.3%, respectively, as well as median progression-free and overall survival of 9.4 and 30.1 months. Treatment yielded not only effective local control of recurrence but also no serious toxicities, only mild skin reactions. Gastrointestinal toxicities, observed with conventional radiotherapies, were not reported [27]. Present evidence suggests that PBT may offer an effective, safer, and less invasive option for treating recurrent ovarian carcinoma [26]. In our report, PBT allowed high-dose palliative RT with minimal damage to healthy organs.

PARP Inhibitors: Treatment and Maintenance of Ovarian Tumors

PARP inhibitors constitute an effective maintenance therapy for ovarian cancers with homologous recombination deficiency (HRD), which can be caused by mutations in BRCA 1/2 or other related genes. HRD impairs the ability of cells to repair DNA damage, specifically double-stranded breaks (DSBs), via the homologous recombination (HRR) pathway [28]. Cells affected by HRD must rely on more error-prone methods of DSB repair, such as nonhomologous end joining (NHEJ), which joins the ends of DNA without a template and can lead to the loss of genetic material. As a result, HRD compromises DNA stability and cell function, which can lead to the accumulation of mutations and the development of cancer [29].

The poly ADP-ribose polymerase (PARP) family of 17 proteins is involved in multiple cellular processes, including DNA repair. Within the PARP family, PARP1 is the most widely recognized protein and is involved in repairing single-stranded breaks (SSBs) [30]. In HRD-positive ovarian tumors, PARP inhibitors induce synthetic lethality to produce an enhanced therapeutic effect. By inhibiting PARP, cancer cells lose their ability to repair SSBs, which accumulate and may develop into DSBs during DNA replication. Since the HRR pathway is defective in HRD-positive ovarian tumors, DSBs remain either unrepaired or repaired through error-prone NHEJ activity. The resulting DNA damage eventually overwhelms the cell, leading to apoptosis [31]. HRD-positivity is a common feature among ovarian cancers, occurring in approximately 50% of high-grade serous ovarian carcinomas (HGSOCs) [31].

As such, HRD testing is clinically significant in ovarian cancer because it can predict benefit from PARPis and guide treatment decisions. Assessing HRD status involves examining the presence of causal genes, such as BRCA and other genes involved in homologous recombination repair (HRR), as well as analyzing the genomic scar. However, ovarian cancers can have HRD even in the absence of BRCA 1/2 mutations; therefore testing is still recommended irrespective of BRCA 1/2 status. For instance, our patient was wild type for BRCA 1/2 but still HRD positive. Following National Comprehensive Cancer Network (NCCN) recommendations, ovarian cancer patients should be tested for BRCA1/2 mutations first. If positive, they may benefit more from PARP inhibitors. If negative, HRD testing is the next step. A positive HRD result can also help guide the use of PARP therapy [32]. There are now several tests available for determining HRD status, each with its own specific criteria and methodologies [33].

Aside from their primary mechanism of interfering with DNA repair, growing evidence suggests that PARPis can also modulate the tumor microenvironment (TME). Specifically, PARPis show the ability to convert tumors from “cold” to “hot.” Cold tumors are characterized by an immunosuppressive TME, including a low presence of tumor-infiltrating lymphocytes (TILs) and reduced (Programmed cell death protein 1) PD-1 expression. Hot tumors are the opposite, characterized by an immunosupportive environment, including an increased presence of TILs and heightened PD-1 expression [34] .

PD-1, an immune checkpoint, suppresses T-cell activation and the immune response when bound to PD-L1 on cancer cells. Tumor-associated macrophages (TAMs) also express PD-1, which decreases their ability to perform phagocytosis. Since PD-1/PD-L1 inhibits immune response through these methods, using antibodies to block this interaction is a promising immunotherapy that leverages T-cells and TAMs to restore immune function and slow tumor growth [35]. Ovarian tumors are typically considered cold tumor, limiting the ability to leverage the immune system for treatment [36]. Consequently, by changing the TME of ovarian tumors from “cold” to “hot,” PARP inhibitors make them more responsive to treatment with immune checkpoint inhibitors.

Clinical trials support using PARPis (olaparib, niraparib, rucaparib) for second-line or later maintenance therapy in platinum-sensitive relapsed ovarian cancer. They are generally well tolerated with manageable adverse events and no negative impact on quality of life, although differences exist between them. Real-world data and upcoming trials on novel combinations like PARPis with immune checkpoint inhibitors are anticipated to help establish the optimal sequencing of therapies [37].

Niraparib: Selected PARP Inhibitor for Treatment

Niraparib is a PARP inhibitor with demonstrated efficacy for maintenance after the treatment of newly diagnosed and recurrent ovarian cancer. Even though niraparib is more effective for BRCA 1/2 and HRD-positive ovarian tumors, it can be prescribed regardless of BRCA 1/2 and HRD status. In contrast, olaparib, the most widely used PARPi, is only indicated if patients are BRCA positive. According to some studies, niraparib is more toxic than other PARPis, with greater risks for adverse hematological events such as neutropenia, thrombocytopenia, and anemia. Therefore, it is important to personalize the dose of niraparib according to the patient’s physical condition [38].

Niraparib monotherapy was approved based on the QUADRA study, a phase II trial evaluating its efficacy and safety in ovarian cancer patients treated with three or more chemotherapy regimens. The primary goal was to assess the ORR (Objective Response Rate) in patients with HR-deficient tumors sensitive to their last platinum-based therapy. Out of 463 patients, 47 were in the primary efficacy group, achieving a 28% ORR. This led to FDA approval for advanced ovarian cancer patients with HR-deficiency positive status after three prior chemotherapy regimens, marking the first approval of a PARP inhibitor as monotherapy for heavily pretreated ovarian cancer, regardless of BRCA mutation status [39].

The PRIMA trial tested niraparib maintenance after frontline treatment in a phase III, randomized, double-blind study with 733 newly diagnosed advanced ovarian cancer patients. After responding to platinum-based chemotherapy, patients received either niraparib or a placebo. Tumor samples identified HR-deficiency through BRCA mutation or a myChoice score of ≥42. In HR-deficient patients, median PFS was 21.9 months with niraparib versus 10.4 months without (HR, 0.43; $P<0.001$). In the overall population, median PFS was 13.8 months with niraparib versus 8.2 months with placebo (HR, 0.62; $P<0.001$).

Notably, the niraparib group did experience a higher frequency of adverse effects, especially myelosuppression and related events, including nausea and fatigue. These results confirmed niraparib's efficacy in not only recurrent ovarian cancer but also newly diagnosed ovarian cancer. Additionally, niraparib is effective regardless of HR-deficiency status [40].

Combined Radiation and PARP Inhibitor Treatment

The FDA also approved PARP inhibitors for BRCA-mutated ovarian, breast, and prostate cancers. They enhance radiation sensitivity and are effective as stand-alone or combination therapies. Radiation therapy reduces resistance to PARPis by causing DNA double-strand breaks (DSBs), which increase cancer cell sensitivity to PARPis. PARPis inhibit single-strand break (SSB) repair, causing DSBs and enhancing sensitivity to radiation. Radiation also affects the tumor microenvironment, boosting PARP inhibitors' effects, inducing DNA damage, cell death, and immune activation [41] [Figure 10].

Despite the widespread use of Poly-ADP ribose polymerase inhibitors, their combination with radiotherapy (RT) for newly diagnosed or recurrent tumors remains uncertain. There was review of twelve studies done in literature suggesting that combining PARPis with RT is feasible, though efficacy and safety profiles vary. These studies encompassed seven single-arm dose-escalation phase I trials, two phase II trials, one parallel-arm phase I study, and two phase I/II studies conducted from 2015 to 2021.The diseases under trial included brain metastases, rectal cancer, peritoneal carcinomatosis, breast cancer, head and neck cancers, pancreatic cancer, diffuse intrinsic pontine glioma, non-small cell lung cancer (NSCLC), and glioblastoma. Acute toxicity ≥ grade 3 ranged from 25% to over 96%, with both haematological and non-haematological adverse events observed. The studies used various RT schedules with photon beams, aiming for definitive, neoadjuvant, adjuvant, or radical treatment, and assessed outcomes like loco regional control, disease-free survival, and overall survival [42]. Key findings highlight that tumor cells with defects in DNA repair mechanisms, like BRCA mutations, are more sensitive to PARPis and RT, leading to synthetic lethality. However, the optimal administration sequence and comprehensive toxicity profiles are still not well-established, necessitating further research [42].The SOPRANO trial which is under process evaluates the effectiveness of SBRT and continued PARP inhibitor therapy in patients with oligo metastatic or oligo progressive ovarian, fallopian tube, or primary peritoneal carcinoma. It compares SBRT followed by niraparib versus SBRT alone, focusing on treatment feasibility and patient outcome [43].

Our patient in this case report had surgery and chemotherapy after diagnosis, followed by 8 years disease-free. Recurrences were treated with surgery and proton therapy. Niraparib maintenance led to no toxicity, and she remains disease-free to this day.

CTC Analysis as a Strategy for Personalized Cancer Treatment

Developing a treatment regimen for cancer patients is most effective when personalized to the tumor's molecular and genetic profile. Recently, evidence suggests that circulating tumor cells (CTCs) can serve as a valuable tool for understanding the composition of tumors and informing care. CTCs originate from the main tumor and break off to enter the bloodstream, enabling the tracking of metastasis in solid tumors like ovarian cancer. The study and analysis of CTCs can reveal tumor characteristics that guide the development of personalized treatments. Studies have shown that analyzing gene expression in CTCs has the potential to predict diagnosis, prognosis, and response to specific treatments in cancer patients [44]. Additionally, CTC analysis can help identify drug resistance early and monitor ongoing dynamics to determine the most effective therapy at different stages of tumor development, indicating a switch in treatments if necessary [45]. What enhances the clinical utility of CTC evaluation is that its prognostic value remains significant regardless of traditional clinical factors like tumor grade, patient age, race, or platinum response. Consequently, continued research on CTCs can provide valuable insight into further applications of CTC analysis in personalizing treatments [46].

In ovarian cancer, metastasis can occur through transcoelomic, lymphatic, and haematogenous spread. The transcoelomic route is most common, but the lymphatic and haematogenous routes have been demonstrated by the detection of CTCs in the blood. The analysis of these CTCs, particularly invasive CTCs (iCTCs), is more accurate in predicting disease progression or recurrence than CA125 (79.5% vs. 67.6%). A possible explanation could be that during disease progression, iCTC levels change before the presentation of clinical symptoms or a change in CA125 levels. Therefore, CTC analysis could become a reliable strategy in shaping a personalized treatment regimen for ovarian cancer [46].

A major challenge in using CTCs as a tool to study tumors is that they can become difficult to detect. Detection is complicated by the rarity of CTCs, with just 1-10 CTCs per mL of blood. Additionally, the most frequently used marker of CTCs is epithelial cell adhesion molecule (EpCAM), which has limitations, even in EpCAM-positive tumors like ovarian cancer. In EpCAM-positive tumors, EpCAM expression is still low during epithelial-to-mesenchymal transition (EMT), causing CTCs to evade detection [46]. Currently, Cell Search is the only FDA-approved system for CTC detection and detects EpCAM-positive cells. However, CTCs may evade detection if EpCAM expression is reduced or absent. Other techniques, such as CanPatol and CTC-chip, may detect a wider range of CTCs and offer unique advantages. To develop a better understanding of CTCs and their application, future work can focus on developing more accurate CTC technologies and combining different technologies with complementary benefits [44].

Advancing CTC Utility: Creating Tumor Avatars to Personalize Therapy with E.V.A. Select

In response to the need for personalized cancer treatment, a recently developed technique has shown the potential to address certain shortcomings of CTC technologies. Instead of testing detected CTCs directly, this technique leverages the informative nature of CTCs by using CTCs to generate cancer avatars, or organoid cultures. These CTC-derived organoids are then studied to provide insight into the qualities of the tumor, which inform prognosis and treatment [47].

The E.V.A. Select system, founded in Taiwan, is a personalized cancer testing service that engineers cancer avatars by isolating CTCs from a simple blood sample and expanding them to form organoid cultures representative of tumor conditions. Then, these avatars are used to conduct anti-cancer drug testing of chemotherapy, hormone therapy, and targeted therapy. Screening is conducted for hundreds of drug combinations and can incorporate genetic testing to generate a fully customized chemical drug list for the patient. E.V.A. Select is especially advantageous because it only requires a blood sample, making it convenient and less invasive, especially for patients who are elderly or cannot tolerate tissue biopsy. Additionally, blood samples reflect greater tumor diversity than local tissue samples, meaning that they offer a broader view of tumor metastasis [48].

E.V.A. Select has been demonstrated to successfully predict drug response and inform treatment for a select few cancers. For instance, studies applying E.V.A. Select toward thymic malignancies and pediatric glioma concluded that drug sensitivity tests on CTC-derived organoids were significantly correlated with clinical response. However, certain areas remain unstudied, such as the ability of E.V.A. Select to assess the tumor microenvironment, including angiogenesis or immune-related therapies. Additionally, there is a lack of published work surrounding the use of E.V.A. Select in most types of cancer, including in ovarian cancer, the subject of this case study. Therefore, E.V.A. Select is a promising tool for personalized cancer treatment, as well as other technologies that create and study CTC-derived tumor avatars. Further exploration can reveal areas of analysis for CTC-derived tumor avatars and improve their ability to achieve personalized treatment plans and monitor tumors over time [47].

CONCLUSION AND FUTURE PROSPECTIVE

Drawing from our insights, we recommend that clinicians remain exceptionally attentive when diagnosing central nervous system metastases in patients with advanced ovarian carcinoma. We propose regular neuroimaging, as well as neuraxis MRI screenings during follow-up upon the presence of suspicious neurological findings, regardless of CA-125 levels. Treatment plans should be tailored to each patient, incorporating a combination of surgical procedures, oral steroids, chemotherapy, and localized radiotherapy. The decision to proceed with surgical resection depends significantly on factors such as disease progression, expected survival rates, and performance metrics.

Personalized oncology, integrating biomarkers and genetic profiling, has revolutionized gynecologic cancer treatment by predicting responses to therapies like radiotherapy (RT) and immunotherapy. A breakthrough in gynecologic cancer treatment involves understanding the DNA damage response (DDR) mechanism. DDR defects indicate immune checkpoint inhibitor (ICI) response and underscore the role of RT-induced DNA damage in eliciting immune responses to inhibit tumor growth. Beyond genetic testing, new strategies based on CTCs have the potential to change approaches to personalized treatment. CTCs can be leveraged in various ways for analysis, for instance, through the generation of CTC-derived tumor avatars by systems such as E.V.A. Select. CTCs offer valuable insight into tumor development and can be used to determine drug resistance and tailor treatments, including chemotherapy and maintenance drugs.

In this case, E.V.A. Select was able to customize a drug list for the patient, which informed the use of PARP inhibitors for maintenance and changes in chemotherapy drugs based on drug resistance. Maintenance therapy with PARP inhibitors is crucial for preventing recurrences and extending disease-free intervals in homologous recombination-deficient or BRCA-mutated cancers. In this study, the patient was treated with the PARPi Niraparib based on BRCA Wild-type and positive HRD status. Profiling the TME for immunogenicity helps optimize outcomes with combined radiotherapy and immunotherapy strategies. Ovarian cancer is typically characterized by cold tumors, with an immunosuppressive TME. Treatment with PARPis converts cold tumors to immunologically active hot tumors that can enhance the effect of immunotherapy in ovarian cancer.

Proton therapy represents a significant advancement in treating recurrent gynecologic cancers, offering precise tumor targeting while minimizing damage to surrounding organs. Combining proton therapy with PARP inhibitors leverages the precision of proton therapy and the DNA repair inhibition of PARP inhibitors, offering a promising strategy for treating gynecologic cancers and potentially improving patient outcomes and quality of life. Understanding the tumor microenvironment (TME) has refined patient selection and treatment planning. Pre-clinical and clinical trials have demonstrated the safety and efficacy of these approaches, although more data from randomized clinical trials are needed.

References

1. Gaona-Luviano, P., Medina-Gaona, L. A., & Magaña-Pérez, K. (2020). Epidemiology of ovarian cancer. *Chin Clin Oncol or CCO*, *9*(4), 47-47.
2. Huang, J., Chan, W. C., et al (2022). Worldwide burden, risk factors, and temporal trends of ovarian cancer: a global study. *Cancers*, *14*(9), 2230.
3. Zamwar, U. M., Anjankar, A. P., & Anjankar, A. (2022). Aetiology, epidemiology, histopathology, classification, detailed evaluation, and treatment of ovarian cancer. *Cureus*, *14*(10).
4. Kłębczyk, A. W., Wolszczak, Z., Urbaniak-Wąsik, S., & Podlewski, S. (2021). Metastasis of ovarian cancer to the spinal cord—case study. *OCP*, *17*(2), 81-84.
5. Deng, K., Yang, C., Tan, Q., et al (2018). Sites of distant metastases and overall survival in ovarian cancer: a study of 1481 patients. *Gynecol Oncol*, *150*(3), 460-465.
6. Miranpuri, A. S., Rajpal, S., Salamat, M. S., & Kuo, J. S. (2011). Upper cervical intramedullary spinal metastasis of ovarian carcinoma: a case report and review of the literature. *J. Med. Case Rep*, *5*(1), 311.
7. Safadi, S., Rendon, P., Rutledge, T., & Mayasy, S. (2016). Ovarian carcinoma with isolated spinal cord metastasis. *J. Investig. Med. High Impact Case Rep*, *4*(3), 2324709616657644.
8. Pollock, A. E., Risher, H., Berger, M., et al (2023). Clinical outcomes of intensity modulated proton therapy reirradiation for gynecologic malignancies. *Adv Radiat Oncol*, *8*(4), 101191.
9. Drew, Y. (2015). The development of PARP inhibitors in ovarian cancer: from bench to bedside. *Br J Cancer*, *113*(1), S3-S9.
10. Luo, X., & Kraus, W. L. (2012). On PAR with PARP: cellular stress signaling through poly (ADP-ribose) and PARP-1. *Genes Dev*, *26*(5), 417-432..
11. Soylemez, B., Ozum, U., & Egilmez, R. (2020). Cervical Spinal Intramedullary Metastasis of Ovarian Adenocarcinoma: A Case Report. *AJCRS [Internet]*, *5*..
12. Samartzis, D., Gillis, C. C., Shih, P., et al (2015). Intramedullary spinal cord tumors: part I—epidemiology, pathophysiology, and diagnosis. *GSJ*, *5*(5), 425-435.
13. Mitra, A. K., Chiang, C. Y., Tiwari, P., et al. (2015). Microenvironment-induced downregulation of miR-193b drives ovarian cancer metastasis. Oncogene, 34(48), 5923-5932.
14. Bakshi, A., Biswas, G., Deshmukh, C., et al. (2006). Successful complete regression of isolated intramedullary spinal cord metastases from epithelial ovarian carcinoma with chemotherapy and radiotherapy. *Indian J. Cancer*, *43*(3), 136-138.
15. Cormio, G., Di Vagno, G., Di Fazio, F., et al. (2001). Intramedullary spinal cord metastasis from ovarian carcinoma. *Gynecol Oncol*, *81*(3), 506-508.
16. Huang, J., & Lei, D. (2017). Intramedullary spinal cord metastasis from ovarian cancer in a 50-year-old female. *World Neurosurg*, *106*(1049), e3-1049.
17. Hughes, J. R., & Parsons, J. L. (2020). FLASH radiotherapy: current knowledge and future insights using proton-beam therapy. *Int. J. Mol. Sci*, *21*(18), 6492.

18. Boon, I. S., Au Yong, T. P., & Boon, C. S. (2018). Assessing the role of artificial intelligence (AI) in clinical oncology: utility of machine learning in radiotherapy target volume delineation. *Medicines*, *5*(4), 131.
19. Smart, A., Chen, Y. H., Cheng, T., (2019). Salvage radiation therapy for localized recurrent ovarian cancer. *IJGC.* , *29*(5), 916-921.
20. Bae, B. K., Cho, W. K., Lee, J. W., et al. (2023). Role of salvage radiotherapy for recurrent ovarian cancer. *IJGC.* , *33*(1), 66-73.
21. Chundury, A., Apicelli, A., DeWees, T., et al. (2016). Intensity modulated radiation therapy for recurrent ovarian cancer refractory to chemotherapy. *Gynecol Oncol*, *141*(1), 134-139.
22. Barcellini, A., Murata, K., Fontana, G., et al. (2024). The first real-world study on the role of carbon ion radiotherapy for oligo-metastatic, persistent, or recurrent (MPR) ovarian/fallopian tube cancer. *ctRO*, *47*, 100781.
23. Taunk, N. (2022). The role of proton therapy in gynecological radiation oncology. *IJCR*, *32*(3), 414-420.
24. Verma, V., Simone, C. B., Wahl, A. O., et al. (2016). Proton radiotherapy for gynecologic neoplasms. *Acta oncologica*, *55*(11), 1257-1265.
25. Arians, N., Lindel, K., Krisam, J., et al. (2023). Treatment tolerability and toxicity of postoperative proton beam therapy for gynecologic malignancies: results of the prospective phase 2 APROVE trial. *Int J Radiat Oncol Biol Phys*, *116*(4), 825-836..
26. Kino, T., Ando, N., Ogawara, Y., & Shigeta, H. (2019). Proton beam therapy for recurrent ovarian carcinoma: A case report. *J. Obstet. Gynaecol. Res, 45*(9), 1952-1956..
27. Endo, Y., Takagawa, Y., Yoshimoto, Y., et al. (2025). Proton beam therapy achieves excellent local control for recurrent epithelial ovarian cancer: a single-center retrospective study. *J. Ovarian Res*, *18*(1), 110..
28. Mangogna, A., Munari, G., Pepe, F., et al. (2023). Homologous recombination deficiency in ovarian cancer: from the biological rationale to current diagnostic approaches. *J. Pers. Med.*, *13*(2), 284.
29. Lord, C. J., & Ashworth, A. (2017). PARP inhibitors: Synthetic lethality in the clinic. *Science*, *355*(6330), 1152-1158.
30. Rose, M., Burgess, J. T., O'Byrne, K., et al. (2020). PARP inhibitors: clinical relevance, mechanisms of action and tumor resistance. *Front. Cell Dev. Biol*, *8*, 564601..
31. Zhang, K., Qiu, Y., Feng, S., et al. (2025). Development of model for identifying homologous recombination deficiency (HRD) status of ovarian cancer with deep learning on whole slide images. *J. Transl. Med 23*(1), 267..
32. Liu, J., Berchuck, A., Backes, F. J., et al. (2024). NCCN Guidelines® Insights: ovarian cancer/fallopian tube cancer/ primary peritoneal cancer, version 3.2024: featured updates to the NCCN guidelines. *JNCCN*, *22*(8), 512-519.
33. Stewart, M. D., Merino Vega, D., Arend, R. C., et al. (2022). Homologous recombination deficiency: concepts, definitions, and assays. *The Oncologist*, *27*(3), 167-174..
34. Ollauri-Ibáñez, C., Ayuso-Íñigo, B., & Pericacho, M. (2021). Hot and cold tumors: is endoglin (CD105) a potential target for vessel normalization?. *Cancers*, *13*(7), 1552.
35. Jiang, Y., Chen, M., Nie, H., & Yuan, Y. (2019). PD-1 and PD-L1 in cancer immunotherapy: clinical implications and future considerations. *Human vaccines & immunotherapeutics*, *15*(5), 1111-1122..
36. Garlisi, B., Lauks, S., Aitken, C., et al. (2024). The complex tumor microenvironment in ovarian cancer: therapeutic challenges and opportunities. *Current oncology*, *31*(7), 3826-3844..
37. O'Malley, D. M., Krivak, T. C., Kabil, N., et al. (2023). PARP inhibitors in ovarian cancer: a review. *Targeted Oncology*, *18*(4), 471-503..
38. Valabrega, G., Scotto, G., Tuninetti, V., Pani, A., & Scaglione, F. (2021). Differences in PARP inhibitors for the treatment of ovarian cancer: mechanisms of action, pharmacology, safety, and efficacy. *Int. J. Mol. Sci*, *22*(8), 4203.
39. Moore, K. N., Secord, A. A., Geller, M. A., et al. (2019). Niraparib monotherapy for late-line treatment of ovarian cancer (QUADRA): a multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol*, *20*(5), 636-648..
40. González-Martín, A., Pothuri, B., Vergote, I., et al (2019). Niraparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med*, *381*(25), 2391-2402..
41. Monjazeb, A. M., Schalper, K. A., Villarroel-Espindola, F., et al. (2020, April). Effects of radiation on the tumor microenvironment. Semin Radiat Oncol (Vol. 30, No. 2, pp. 145-157). WB Saunders..
42. Barcellini, A., Loap, P., Murata, K., et al. (2021). PARP inhibitors in combination with radiotherapy: to do or not to do?. *Cancers*, *13*(21), 5380.
43. Nguyen, N. P., Chirila, M. E., Page, B. R., et al. (2024). Immunotherapy and stereotactic body radiotherapy for older patients. *Multimodality Therapy for Older Cancer Patients*, 60.
44. Lin, D., Shen, L., Luo, M., Zhang, et al. (2021). Circulating tumor cells: biology and clinical significance. *STTT*, *6*(1), 404..
45. Coumans, F., van Dalum, G., & Terstappen, L. W. (2018). CTC technologies and tools. *CYTOM Part A*, *93*(12), 1197-1201.
46. Szczerba, A., Śliwa, A., Pieta, P. P., & Jankowska, A. (2022). The role of circulating tumor cells in ovarian cancer dissemination. *Cancers*, *14*(24), 6030..
47. Wu, Y. H., Chao, H. S., Chiang, C. L., et al. (2023). Personalized cancer avatars for patients with thymic malignancies: a pilot study with circulating tumor cell derived organoids. *Thoracic Cancer*, *14*(25), 2591-2600.