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**Zaawansowane techniki obrazowania w diagnostyce wznowy raka
jajnika: rola rezonansu magnetycznego w ocenie wszczepów
otrzewnowych i przetoki nowotworowej**

**Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu
w dyscyplinie nauki medyczne**

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Wykaz stosowanych skrótów

ADC – *Apparent Diffusion Coefficient* – rzeczywisty współczynnik dyfuzji

CR – *Complete resection* – całkowita resekcja

CT / TK – *Computed Tomography / Tomografia Komputerowa*

DCE-MRI – *Dynamic Contrast-Enhanced Magnetic Resonance Imaging* – dynamiczne obrazowanie rezonansu magnetycznego po podaniu kontrastu

DWI – *Diffusion-Weighted Imaging* – obrazowanie dyfuzyjne

EOC – *Epithelial Ovarian Cancer* – nabłonkowy rak jajnika

HGSOC – *High-Grade Serous Ovarian Cancer* – wysokozłośliwy surowiczy rak jajnika

MRI / MR – *Magnetic Resonance Imaging / Rezonans Magnetyczny*

PCI – *Peritoneal Cancer Index* – wskaźnik rozsiewu nowotworu w jamie otrzewnej

Perf. Max. En. – *Perfusion Maximum Enhancement* – maksymalne wzmocnienie kontrastowe

PFS – *Progression-Free Survival* – czas przeżycia wolnego od progresji

TTP – *Time To Peak* – czas do osiągnięcia maksymalnego wzmocnienia kontrastowego

USG – *Ultrasonografia* – badanie ultradźwiękowe

Streszczenie w języku polskim

Wstęp

Wznowa surowiczego raka jajnika stanowi poważne wyzwanie diagnostyczne ze względu na wysoką częstość występowania, zróżnicowany obraz kliniczny i radiologiczny. Rezonans magnetyczny odgrywa kluczową rolę w wykrywaniu nawrotów, w tym ich rzadkich postaci. Dwa analizowane artykuły pracy doktorskiej skupiają się na optymalizacji diagnostyki wznowy raka jajnika pod postacią przetoki nowotworowej oraz wszczepów otrzewnowych poprzez zastosowanie zaawansowanych technik obrazowania MR, co może przyczynić się do poprawy personalizacji leczenia.

Publikacja nr 1 wchodząca w skład cyklu rozprawy doktorskiej

Jankowska-Lombarska M., Grabowska-Derlatka L., and Derlatka P. "Tumor-Bowel Fistula as a Rare Form of Recurrent Ovarian Cancer—Imaging and Treatment: Preliminary Report." *Current Oncology* 30.1 (2022): 506-517.

Pierwszy artykuł stanowiący cykl jest pracą oryginalną, której celem była ocena przydatności technik obrazowania: tomografii komputerowej oraz rezonansu magnetycznego w diagnostyce rzadkiego typu wznowy raka jajnika. Nawroty miał charakter przetoki między guzem a jelitem. Dodatkowo ocenialiśmy efekty leczenia wznowy.

Do badania włączono 8 pacjentek po operacji cytoredukcyjnej, które zakończyły I linię leczenia systemowego (paclitaxel + karboplatyna) z całkowitą remisją (CR) utrzymującą się co najmniej przez 6 miesięcy. Podejrzenie wznowy wysunięto na podstawie obrazu klinicznego (objawów niedrożności przewodu pokarmowego, krwawienia z dolnego odcinka przewodu pokarmowego oraz dolegliwościach bólowych w jamie brzusznej), co najmniej dwukrotnym w stosunku do najniższej wartości wzroście stężenia CA-125 oraz nieprawidłowego wyniku przezpochwowego badania ultrasonograficznego (USG).

U wszystkich badanych wykonano tomografię komputerową (TK) przed i po podaniu środka kontrastowego oraz rezonans magnetyczny (MR) również przed i po podaniu środka kontrastowego. Badania oceniało niezależnie dwóch radiologów. U wszystkich pacjentek wykazano cechy przetoki między guzem a jelitem grubym. W tomografii komputerowej obserwowano jedynie pośrednie cechy przetoki pod postacią nacieku jelita przez guz (zatarcia tkanki tłuszczowej między guzem a ścianą jelita, przerwanie ciągłości ściany jelita lub obecność gazu w obrębie guza). W badaniu MR

uwidoczniono bezpośrednio przetoki. Wszystkie pacjentki zakwalifikowano do wtórnej operacji cytoredukcyjnej.

Śródoperacyjnie potwierdzono obecność przetok oraz wznowy raka. U 7 pacjentek po zabiegu nie pozostawiono makroskopowych ognisk choroby (operacja R0), u jednej pacjentki pozostawione resztki w postaci wszczepów w krezce jelita krętego miały średnicę 1-2 mm. Wykonano 7 zespożeń jelitowych i jedną kolostomię. U jednej pacjentki dodatkowo resekowano fragment pęcherza moczowego oraz moczowodu z naciekającym je guzem. Przebieg pooperacyjny u wszystkich pacjentek był niepowikłany.

Do kolejnego nawrotu choroby doszło u 6 pacjentek. U dwóch przez 36 i 28 miesięcy obserwacji nie odnotowano wznowy, jedna pacjentka zmarła. Mediana PFS po zakończeniu II linii leczenia wyniosła 13,4 miesiąca (8,4-22,6).

Na podstawie analizowanych badań uznano, że tomografia komputerowa nie jest wystarczającą metodą aby jednoznacznie potwierdzić obecność przetoki nowotworowej. Rezonans magnetyczny dobrze uwidacznia przetokę oraz pozwala na dokładne określenie jej lokalizacji. Resekcja jelita z jednoczasowym wykonaniem zespolenia okazała się dobrą i bezpieczną metodą leczenia w tej grupie pacjentek.

Publikacja nr 2 wchodząca w skład cyklu rozprawy doktorskiej

Jankowska-Lombarska M., Grabowska-Derlatka L., Kraj L. & Derlatka P. „Dynamic Contrast-Enhanced and Diffusion-Weighted Imaging in Magnetic Resonance in the Assessment of Peritoneal Recurrence of Ovarian Cancer in Patients with or Without BRCA Mutation” *Cancers*, 2024, 16.22: 3738.

Drugi artykuł jest pracą oryginalną, której celem była ocena porównawcza parametrów dyfuzyjnych (z wykorzystaniem map ADC- Apparent Diffusion Coefficient) oraz niektórych parametrów stosowanych w badaniu dynamicznym po podaniu środka kontrastowego (DCE) we wszczepach otrzewnowych u pacjentek z mutacją genu BRCA1/2 oraz bez mutacji ze wznową wysokozłośliwego surowiczego raka jajnika(HGSOC). W pracy uwzględniono szeroki przegląd literatury oraz dokładnie omówiono różnice w obrazie radiologicznym w obu grupach pacjentek.

Grupę badaną stanowiły badania MR u pacjentek z klinicznym podejrzeniem wznowy raka jajnika na podstawie wyników CA-125 i/lub badań TK.

Do badania włączono 43 pacjentki, z czego 18 pacjentek miało potwierdzoną mutację genu BRCA1/2, z podejrzeniem wznowy raka jajnika po I linii leczenia, u których wykonano badanie MR 1,5T aparatem bez i po podaniu środka kontrastowego. Wszystkie badane pacjentki w wieku

21-76 lat przebyły pierwotną operację cytoredukcyjną z powodu platynowrażliwego raka jajnika. Analizowane badania ocenione przez dwóch niezależnych badaczy pod kątem pomiarów ilościowych na mapie ADC oraz TTP (time to peak) i Perf. Max. En.(perfusion maximal enhancement) w badaniu dynamicznym po podaniu środka kontrastowego. W ocenie lokalizacji występowania wszczepów jamę brzuszną i miednicę podzielono na okolice wg PCI index. Każda okolica była analizowana pod kątem obecności wszczepu, następnie każdy z badaczy wybierał wszczep do pomiaru w danej okolicy o jakościowo najwyższej restrykcji dyfuzji. Te wszczepy były następnie oceniane również w parametrach perfuzyjnych. Implanty zostały również podzielone na grupy względem wielkości.

W analizie statystycznej wyników stwierdzono statystycznie istotne różnice między parametrami ADC, TTP i Perf. Max. En w obu grupach pacjentek: bez mutacji i z mutacją. Wartości TTP były statystycznie wyższe u pacjentek bez mutacji 256.3 vs 160.6, a Perf. Max. En. były wyższe u pacjentek z mutacją 233.6 vs 148.6. Nie zaobserwowano różnic między parametrami perfuzyjnymi a wielkością wszczepów.

Wartości parametru ADC były statystycznie wyższe u pacjentek z mutacją 977.3 vs 788.7. Poza tym zaobserwowano różnice między parametrem ADC a grupami wielkości wszczepów, przy czym najniższe wartości obserwowano w grupie średnich wszczepów (1-2cm).

W powyższym badaniu potwierdzono różnice w obrazie radiologicznym wszczepów otrzewnowych na mapach ADC i badaniu perfuzyjnym u pacjentek bez i z mutacją w genu BRCA1/2.

Na podstawie naszego badania uważamy, iż w przypadku podejrzenia wznowy raka jajnika dodanie do protokołu badania MR parametrów perfuzji jest cennym elementem diagnostycznym.

Podsumowanie

Przedstawione powyżej artykuły dotyczą diagnostyki z wykorzystaniem zaawansowanych technik obrazowania MRI w szczególnych postaciach nawrotu raka jajnika. W pierwszej pracy opisano kohortę ośmiu pacjentek z rzadką formą nawrotu jaką są przetoki guzowo-jelitowe, u których badanie MRI, zwłaszcza sekwencje T2-zależna i T1-zależna z kontrastem, okazały się najskuteczniejsze w identyfikacji przetok. Sekwencje dyfuzyjne nie wniosły istotnej wartości diagnostycznej, z wyjątkiem przypadków ze współistnieniem stanu zapalnego.

Druga praca analizuje korelacje pomiędzy parametrami MRI (DWI i DCE) a statusem mutacji BRCA1/2 u 43 pacjentek z nawrotem HGSOE. Stwierdzono istotne różnice między obiema grupami w sekwencjach zarówno dyfuzyjnych jak i perfuzyjnych. Wyniki te mogą mieć znaczenie kliniczne w planowaniu terapii.

Streszczenie w języku angielskim

Advanced Imaging Techniques in the Diagnosis of Ovarian Cancer Recurrence: The Role of Magnetic Resonance Imaging in the Assessment of Peritoneal Implants and Tumor-Related Fistula

Introduction

The recurrence of serous ovarian cancer is a serious diagnostic challenge due to its high frequency and heterogeneous clinical and radiological presentation. Magnetic resonance imaging plays a crucial role in detecting relapse, including their rare forms. The two analyzed articles in the doctoral dissertation focus on optimizing the diagnosis of ovarian cancer recurrence in the form of tumor-related fistulas and peritoneal implants using advanced MR imaging techniques, which may contribute to more personalized treatment.

Publication No. 1 included in the doctoral dissertation cycle

Jankowska-Lombarska M., Grabowska-Derlatka L., and Derlatka P. "Tumor-Bowel Fistula as a Rare Form of Recurrent Ovarian Cancer—Imaging and Treatment: Preliminary Report" *Current Oncology* 30.1 (2022): 506-517.

The first article of the cycle is an original work aimed at evaluating the usefulness of imaging techniques: computed tomography and magnetic resonance imaging in diagnosing a rare type of recurrence of ovarian cancer. The recurrence took the form of a fistula between the tumor and the intestine. Additionally, we evaluated the outcomes of treatment for the recurrent disease.

The study included eight patients who had undergone cytoreductive surgery, completed first-line systemic treatment (paclitaxel + carboplatin) with complete remission (CR) which lasted at least six months. The suspicion of recurrence was based on clinical presentation (symptoms of gastrointestinal obstruction, lower gastrointestinal bleeding, abdominal pain), at least twofold increase in CA-125 levels compared to the lowest value, and abnormal transvaginal ultrasound (TVS) findings.

All patients underwent CT before and after contrast administration, as well as MRI before and after contrast administration. The imaging was assessed by two independent radiologists. In all patients, features of a fistula between the tumor and the large intestine were found. In CT, only indirect signs of a fistula were observed, such as tumor infiltration of the intestine (obliteration of fatty tissue

between the tumor and intestinal wall, discontinuity of the intestinal wall, or gas within the tumor). In MRI direct visualization the fistulas was achieved. All patients were qualified for secondary cytoreductive surgery.

Intraoperatively the presence of fistulas and tumor recurrence was confirmed. In seven patients, no macroscopic residual tumor was left after surgery (R0 resection), while in one patient, residual implants in the mesentery of the ileum with diameters of 1–2 mm were left. Seven bowel anastomoses and one colostomy were performed. In one patient, a portion of the bladder and ureter infiltrated by the tumor was also resected. Postoperative recovery in all patients was uneventful.

Six patients had another recurrence. In two patients, no recurrence was observed during 36 and 28 months of follow-up and one patient died. The median progression-free survival after the second line of treatment was 13.4 months (8.4–22.6).

Based on the analyzed data, CT was found to be insufficient to definitively confirm the presence of a fistula within the tumor. MRI effectively visualized the fistula and allowed precise localization. Bowel resection with simultaneous anastomosis proved to be a good and safe treatment option for this group of patients.

Publication No. 2 included in the doctoral dissertation cycle

Jankowska-Lombarska M., Grabowska-Derlatka L., Kraj L. & Derlatka P. „Dynamic Contrast-Enhanced and Diffusion-Weighted Imaging in Magnetic Resonance in the Assessment of Peritoneal Recurrence of Ovarian Cancer in Patients with or Without BRCA Mutation” *Cancers*, 2024, 16.22: 3738.

The second article is an original study aimed at comparative evaluation of diffusion parameters (using ADC maps) and selected parameters used in dynamic contrast-enhanced imaging in peritoneal implants in patients with and without BRCA1/2 gene mutations, experiencing recurrence of high-grade serous ovarian cancer. The study includes an extensive literature review and thoroughly discusses radiological differences between the two patient groups.

The study group consisted of MR examinations in patients with clinically suspected ovarian cancer recurrence based on CA-125 results and/or CT imaging. A total of 43 patients were included, 18 of whom had confirmed BRCA1/2 gene mutations and underwent 1.5T MRI with and without contrast administration due to suspected recurrence following first-line treatment. All patients, aged 21–76 years, had undergone primary cytoreductive surgery for platinum-sensitive ovarian cancer. The MR scans were evaluated by two independent researchers for quantitative measurements in ADC maps and for TTP and Perf. Max. En. in the DCE study.

For the assessment of implant location, the abdomen and pelvis were divided into regions according

to the PCI index. Each region was analyzed for the presence of the implants. Then, each researcher selected the implant with the highest qualitative diffusion restriction for measurement in each region. These implants were then also evaluated using perfusion parameters. The implants were also categorized in the groups according to size.

Statistical analysis revealed significant differences in ADC, TTP, and Perf. Max. En. parameters between the groups with and without mutations. TTP values were statistically higher in patients without mutations (256.3 vs. 160.6), while Perf. Max. En. values were higher in patients with mutations (233.6 vs. 148.6). No differences were observed between perfusion parameters and implant size.

ADC values were statistically higher in patients with mutations (977.3 vs. 788.7). Furthermore, differences in ADC values were found across implant size groups, with the lowest values observed in the group of medium-sized implants (1–2 cm).

This study confirmed differences in the radiological appearance of peritoneal implants on ADC maps and DCE MRI between patients with and without BRCA1/2 mutations. Based on our study, we believe that adding perfusion parameters to the MRI protocol is a valuable diagnostic component in suspected ovarian cancer recurrence.

Summary

The presented articles concern diagnostics using advanced MRI imaging techniques in specific forms of recurrent ovarian cancer. The first study describes a cohort of eight patients with a rare form of recurrence—tumor-bowel fistulas—where MRI, particularly T2-weighted and contrast-enhanced T1-weighted sequences, proved most effective in detecting fistulas. Diffusion sequences provided limited diagnostic value, except in cases of coexisting inflammation.

The second study analyzes correlations between MRI parameters (DWI and DCE) and BRCA1/2 mutation status in 43 patients with recurrent HGSOE. Significant differences were found between the two groups in both diffusion and perfusion sequences. These results may have clinical significance in treatment planning.

Wstęp

Wznowa surowiczego raka jajnika stanowi istotne wyzwanie diagnostyczne i terapeutyczne zarówno dla lekarzy klinicystów, jak i radiologów, przede wszystkim ze względu na wysoką częstość występowania. Odnotowuje się ją u około 30% pacjentek, a nawet w 70% przypadków zaawansowanego raka jajnika. Dodatkowo, problem wznowy komplikuje różnorodność obrazu klinicznego. Ryzyko nawrotu choroby jest przede wszystkim związane z stopniem zaawansowania procesu nowotworowego w chwili diagnozy oraz stopniem doszczętności operacji cytoredukcyjnej.

Obraz radiologiczny wznowy raka jajnika może przybierać zróżnicowane formy, obejmując zarówno zmiany rozsiane, jak i zlokalizowane, co prowadzi do szerokiego wachlarza objawów klinicznych. W związku z tym dokładna ocena obrazowa jest kluczowa dla prawidłowej diagnozy oraz skutecznego zaplanowania leczenia, uwzględniając indywidualne cechy każdego przypadku. Jedną z rzadkich postaci zlokalizowanej wznowy jest przetoka pomiędzy guzem a jelitem, która jest trudna do zdiagnozowania, gdyż objawia się niespecyficznymi symptomami, takimi jak ból brzucha, krwawienie z dolnego odcinka przewodu pokarmowego czy niedrożność jelit.

W obrębie miednicy kobiecej przetoki mogą rozwijać się w różnych lokalizacjach, a ze względu na duże wymiary guza może dochodzić do naciekania okolicznych narządów. Obrazowanie radiologiczne za pomocą rezonansu magnetycznego, odgrywa kluczową rolę w diagnozowaniu oraz dalszym leczeniu przetok w obrębie miednicy, ze względu na najlepszą rozdzielczość tkanek miękkich. Protokół badania powinien obejmować sekwencje T1 i T2 w różnych orientacjach, również z supresją tkanki tłuszczowej, sekwencje po podaniu środka kontrastowego oraz sekwencje dyfuzyjne. W zależności od charakterystyki przetoki obraz może przybierać różne formy. Badanie rezonansu magnetycznego pozwala również na precyzyjne określenie lokalizacji przetoki, obejmowanych narządów oraz stopnia zaawansowania nawrotowego guza.

W przypadku pacjentek z rakiem jajnika zarówno w momencie rozpoznania, jak i podczas wznowy choroby, często obserwuje się rozsianą formę nowotworu, objawiającą się rozsiewem wewnątrznaczyniowym. Wiele badań koncentruje się na ocenie obrazu pierwotnych guzów jajnika w rezonansie magnetycznym, ze szczególnym uwzględnieniem ich morfologii. Dzięki zastosowaniu szerokiego wachlarza sekwencji obrazowania w rezonansie magnetycznym, możliwe jest uzyskanie istotnych informacji na temat charakterystyki nowotworu. Parametry perfuzyjne pozwalają na ocenę unaczynienia a przez to pośrednio angiogenezy guza, natomiast wartości ADC, uzyskane z obrazowania dyfuzyjnego, są odwrotnie skorelowane z komórkowością nowotworu. Niemniej jednak, istnieje niewielka liczba prac dotyczących oceny wszczepów otrzewnowych we wznowie

raka jajnika, a także brak badań porównujących obrazy radiologiczne u pacjentek z mutacją i bez mutacji genów BRCA1/2.

Mutacje w genach BRCA1 i BRCA2 występują u co najmniej 21% pacjentek z wysokozłośliwym rakiem surowiczym jajnika. Zgodnie z literaturą, u tych pacjentek obserwuje się podobną częstość nawrotów choroby w porównaniu do pacjentek bez mutacji. Badania wykazują, że guzy przerzutowe raka jajnika są lepiej unaczynione niż guzy pierwotne, co stanowi istotną informację w kontekście leczenia.

Cykl obu artykułów pracy doktorskiej stanowi spójną całość koncentrując się na ocenie obrazowania rezonansu magnetycznego w diagnostyce wznowy raka jajnika, z uwzględnieniem różnych aspektów radiologicznych. Pierwszy artykuł bada przydatność technik obrazowania, takich jak tomografia komputerowa oraz rezonans magnetyczny, w diagnostyce rzadkiej formy wznowy raka jajnika, jaką jest przetoka między guzem a jelitem. Analizowane są tu techniki obrazowania, które umożliwiają wykrycie oraz ocenę tej patologii ze szczególnym uwzględnieniem roli MR w bezpośrednim wykazywaniu przetok. Drugi artykuł, z kolei, ma na celu porównanie parametrów dyfuzyjnych oraz perfuzyjnych w ocenie wszczepów otrzewnowych u pacjentek z mutacją BRCA1/2 oraz bez mutacji, ze szczegółową analizą obrazu radiologicznego pod względem różnic między obiema grupami pacjentek. Wspólnym celem obu prac jest optymalizacja procesu diagnostycznego i ocena, jak różne techniki obrazowania mogą wpłynąć na dokładność wykrywania wznowy raka jajnika. W kontekście rozwoju terapii i dostosowania leczenia do specyfiki pacjentki, wnioski płynące z tych badań stanowią istotny krok ku lepszemu zrozumieniu obrazu choroby oraz mogą stanowić podstawę do dalszych badań i usprawnienia diagnostyki w praktyce klinicznej.

Założenia i cele pracy

- Ocena wartości technik obrazowania: tomografii komputerowej i rezonansu magnetycznego, w diagnostyce rzadkiej postaci wznowy raka jajnika – przetoki nowotworowo-jelitowej.
- Ocena porównawcza wybranych parametrów sekwencji DWI i DCE w badaniach rezonansu magnetycznego u pacjentek z nawrotem otrzewnowym raka jajnika o wysokim stopniu złośliwości w grupach z mutacją BRCA i bez mutacji BRCA.

Article

Tumor-Bowel Fistula as a Rare Form of Recurrent Ovarian Cancer—Imaging and Treatment: Preliminary Report

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Abstract: Background. The aim of this pilot study was to evaluate the value of imaging techniques, including computed tomography (CT) and magnetic resonance imaging (MRI), in the diagnosis of a tumor-bowel fistula as a rare form of epithelial ovarian cancer (EOC) relapse. We also performed an initial assessment of the effectiveness of the treatment of this form of relapse. Methods. The study group consisted of eight patients with suspected platinum-sensitive recurrence in the form of a tumor/bowel fistula. All patients finished their first line of chemotherapy and subsequently showed complete remission for 6 months or more. To qualify patients for further treatment, CT and MRI were performed, which suggested the presence of a fistula between the recurrent tumor and intestine. DESKTOP study criteria were used to qualify patients for secondary cytoreduction. Second-line chemotherapy was given after secondary debulking. Results. In all patients, fistulas formed between the tumor and large bowel. On CT, the fistulas were indirectly visible. In all cases, the fistula was visible on MR images, which showed hypointensity on the T2 and T1 post-contrast sequences but did not show restricted diffusion on the diffusion-weighted imaging (DWI) sequence. Patients who were qualified for the study underwent secondary debulking with bowel resection. In all eight cases, the fistula between the tumor and surrounding organs was confirmed. During surgery, seven intestinal anastomoses and one colostomy were performed. No residual macroscopic tumor remained in seven cases (resection R0–87.5%). The progression-free survival (PFS) was 8.4–22.6 months (median 13.4). In the group with cytoreduction R0, the median PFS was 15.5 months (12–22). Conclusion. In patients with suspected EOC recurrence with clinically suspected fistula, CT scan is not sufficient. In CT, the presence of a fistula is suspected based on indirect symptoms. MRI, as a method with much greater tissue resolution, confirms the diagnosis. In addition, MRI can identify the point of the tumor/bowel junction. This is especially true with a large infiltration covering several intestinal parts. Bowel resection with simultaneous anastomosis is a good and safe solution for these patients. However, appropriate qualification for the procedure is necessary, which will allow for surgery without residual macroscopic disease (R0 surgery). Due to the small number of cases, our results cannot be generalized. We treat them as a hypothesis that can be verified in a larger study.

Keywords: recurrent ovarian cancer; tumor-bowel fistula; computed tomography (CT); magnetic resonance imaging (MRI); surgical treatment



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1. Introduction

Epithelial ovarian cancer (EOC) is the fifth most common cancer in women and is also the fourth leading cause of death from cancer because of the lack of discernible symptoms and effective screening tools [1,2]. Tumor prognosis depends on the use of optimal cytoreductive surgery and adjuvant platinum-based chemotherapy [3,4]. Current maintenance treatment with bevacizumab or a polyadenosine diphosphate-ribose polymerase

(PARP) inhibitor has been associated with longer progression-free survival (PFS) [5,6]. The standard of care for relapsed cancer has mainly been systemic treatment. However, a few trials, especially the DESKTOP I-III series, have shown a significant overall survival benefit with cytoreductive surgery followed by chemotherapy in patients with recurrent platinum-sensitive ovarian cancer compared with patients who received chemotherapy alone [7–9].

The risk of recurrence in ovarian cancer depends on the stage of the disease at the time of diagnosis and post-operative residual tumor; however, overall, 70% of patients with advanced disease will experience recurrence [10]. Relapsing ovarian cancer can manifest as localized or widespread recurrence. Fistula formation is frequently associated with relapsed ovarian cancer [11].

A fistula is an abnormal connection between two epithelial surfaces, such as hollow organs, skin, and vessels. In the female pelvis, fistulas can develop in various locations; however, the most common sites are the enterovaginal, colonovaginal, rectovaginal, and vesicovaginal sites. In malignancy, their formation is a rare complication of radiation therapy and surgery and a rare symptom of primary or recurrent tumors, such as ovarian, cervical, and rectal cancer. Spontaneous rectovaginal fistula has also been reported in women with primary and recurrent ovarian cancer undergoing bevacizumab therapy [12]. Rarely due to a large size, a tumor can infiltrate local tissues such as the intestine, bladder, and vagina and form a fistula between the mass of the tumor and adjacent organs. Radiological imaging by magnetic resonance and computed tomography are key in the diagnosis and further treatment of pelvic fistulas [13].

Usually, the first imaging technique used for suspected ovarian cancer is transvaginal ultrasound, as it is accessible. It is also often used to monitor patients after surgeries, chemotherapy, and radiation. To confirm or reject the suspicion of ovarian cancer, other imaging techniques need to be used, such as magnetic resonance and computed tomography. Magnetic resonance is the most important technique for imaging of the female pelvis, as it provides the best possible soft tissue resolution [14]; thus, it is useful for determining local spread of the tumor and post-treatment, radiation, and surgical complications. Computed tomography is usually used as a first method to monitor progression or regression of malignant disease after surgery, radiotherapy, or chemotherapy [15].

The aim of this pilot study was to evaluate the value of imaging techniques, including computed tomography and magnetic resonance imaging, in the diagnosis of a rare form of ovarian cancer recurrence, tumor-bowel fistula. We also performed an initial assessment of the effectiveness of the treatment of this form of relapse.

2. Methods

A single-center study was conducted at the Medical University of Warsaw in the 2nd Department of Clinical Radiology and the 2nd Department Obstetrics and Gynecology. From 2016 to 2021, the study included 8 patients aged 37–78 years with recurrent ovarian cancer and suspected platinum-sensitive recurrence due to their clinical symptoms (e.g., bowel obstructions, rectal bleeding, and abdominal pain), transvaginal ultrasound results, and elevated CA 125 values. All patients completed their first line of chemotherapy and subsequently showed complete remission for 6 months or more. To qualify patients for further treatment, computed tomography and magnetic resonance imaging were performed, which suggested the presence of a fistula between the recurrent tumor and intestine or urinary bladder in all the patients. The clinical data of the patient population are summarized in Table 1.

Table 1. Patient characteristics.

Clinical Data	Number (Median)
Number of patients	8
Age	37–78 (59)
FIGO stage	
II	1
III	6
IV	1
Histopathology of EOC	
high-grade serous	5
low-grade serous	1
carcinosarcoma	1
clear cell carcinoma	1
Primary surgical treatment	
optimal debulking surgery	4
suboptimal surgery	4
Adjuvant therapy	
paclitaxel + carboplatin	8
bevacizumab *	4
Treatment response (after first-line chemotherapy)	
CR	8
PR	0
SD	0
PD	0
PFS (months)	6–27 (17)
Diagnosis of recurrence/clinical symptoms	
CT/MRI	8
bowel obstruction	1
rectal bleeding/bloody diarrhea	2
abdominal pain	3
weight loss	3

EOC—epithelial ovarian cancer; CR—complete remission; PR—partial remission; SD—stable disease; PD—progression disease; PFS—progression-free survival; CT—computed tomography; MRI—magnetic resonance imaging.

* According to the results of the ICON study, patients at high risk of relapse received maintenance treatment with bevacizumab at a dose of 7.5 mg/kg every three weeks for a total of 18 courses or until progression [5].

2.1. Imaging Technique

2.1.1. CT Protocol

All patients underwent computed tomography in the supine position. All patients were examined in a GE computed tomography 64-row scanner with the following scanning parameters: the axial slice thickness of the images was 1.25–2.5 mm, the electric current was 509 mA, and the electrical potential was 120 kV. Some of the parameters are shown in Table 2. Two radiologists experienced in pelvic CT evaluated images of the fistula and its type. The protocol included a precontrast phase and arterial and venous phases. Postcontrast phases were obtained after administering 70–90 mL of the intravenous low-osmolality iodinated contrast with a constant injection velocity 4 mL/s.

Table 2. Technical parameters of computed tomography.

Current	120 kV
Voltage	250 mA
Slice Thickness	1.25–2.5 mm
FOV	33.7 × 39.9 cm
Rotation time	0.7 s
Pitch	0.984:1

2.1.2. MRI Protocol

All patients underwent MR imaging using a 1.5 T clinical whole-body MR system (MAGNETOM Avanto; Siemens AG, Erlangen, Germany).

The MRI protocol for the abdomen and pelvis included turbo spin-echo (TSE), T2-weighted images (T2w), fat-suppressed T2-weighted and T1-weighted images (fsT2w and fsT1w), diffusion-weighted echo planar imaging (DW-EPI), and pre- and post-contrast dynamic T1-weighted gradient echo (3D T1 GRE) sequences. Some of the MRI parameters are shown in Table 3.

Table 3. Some of the parameters of the 1.5T Magnetic Resonance (Magnetom Avanto, Siemens AG, Erlangen) used in the study.

Parameter	T2 TSE	T2 Tirm	VIBE T1 GRE 3D	T2 TSE Fat-Sat	DWI EPI b = 5,050,010,001,500 mm ² /s	T1 TSE Fat-Sat	T2 TSE BLADE (Fat-Sat) SPAIR	T1 GRE (In- and Out-Phase)
FOV [mm]	360	360	360	360	360	360	360	360
Orientation	axial, sagittal, coronal	axial	axial	axial	Axial	axial, coronal, sagittal	axial, coronal	axial
Repetition time [ms]	3190	6100	3.05	4250	4240	666	2300	125
Echo time [ms]	116	39	1.13	114	73	10	116	1:2.22 2:4.92
Flip angle [deg.]	137	150	10	137	90	90	150	70
Breath hold	no	no	no	no	No	no	yes	no
Matrix	256 × 236	320 × 320	188 × 216	256 × 256	128 × 84	256 × 168	256 × 256	512 × 384
Slice thickness [mm]	3	4	3	3	6	3	4	6
Number of signal averages	1	1	1	1	4	1	1	1

TSE—turbo spin-echo; TIRM—turbo inversion recovery magnitude; VIBE—volumetric interpolated breath-hold examination; GRE—gradient echo sequence; EPI—echo planar imaging; DWI—diffusion-weighted imaging; BLADE—in MRI system for Siemens name for periodically rotated overlapping parallel lines with enhanced reconstruction (PROPELLER).

Two radiologists experienced in pelvic MRI evaluated images of the fistula and its type. In all patients, gadobutrol (Gadovist, Bayer Schering, Berlin, Germany) was administered as a bolus dose of 0.1 mmol/kg, which was immediately followed by a bolus dose of 20 mL of physiological saline (NaCl 0.9%). Interobserver agreement was assessed using the kappa coefficient.

2.2. Treatment Protocol

DESKTOP study criteria were used to qualify patients for secondary cytoreduction. Among the criteria, a good general condition according to the Eastern Cooperative Oncology Group (ECOG)-0, residual disease after primary surgery-0 mm, and ascites <500 mL were included [7]. Surgery treatment was performed by a team of experienced gynecologic oncologists. Considering the possibility of extensive surgery consisting in resection of the intestine, pre-operative and post-operative parenteral nutrition was used in each patient.

Second-line chemotherapy was given after secondary cytoreduction surgery according to the following regimen: two patients received liposomal doxorubicin (30 mg/m²) with carboplatin (AUC 5), and six patients received paclitaxel (175 mg/m²) with carboplatin (AUC 6) every three weeks. Two patients with BRCA1 mutation were given olaparib 2 × 300 mg (days 1–28) as maintenance treatment.

3. Results

3.1. Imaging Findings

The median diameter of the relapsed tumor was 89 mm (range 36–130 mm). In all cases, fistulas formed between the tumor and large bowel. In three cases, fistulas formed between the rectum, including two between the sigmoid colon, one sigmoid and descending colon, one between the cecum and ascending colon, and one between the sigmoid colon and left ureter. On CT, in all cases, the fistulas were not directly visible, with only indirect signs of the fistula observed, such as infiltration of the intestine by the tumor, which we observed as vanishing of the fatty tissue between the tumor and the description of the intestinal wall, disruption of the intestinal wall, or the presence of gas in the tumor. In five patients, we observed thickening of the intestinal wall associated with a fistula (Figures 1–3).



Figure 1. Images from 58-year-old patient with carcinosarcoma of the ovary and recurrence in the rare form of giant cell carcinoma. The fistula between tumor and rectum (arrow), CT post-contrast image in venous phase obtained in the axial plane, shows pelvic tumor and adjacent intestine, fatty tissue between the tumor and intestine vanished as indirect sign of the fistula.

To confirm the suspected fistula, the patients were referred for MRI. In all cases, the fistula was visible on the MR images, showing hypointensity on the T2 and T1 post-contrast sequences but no restricted diffusion on the DWI sequence. The fistula in one of the patients was hyperintense on T2 images and hypointense on T1-weighted images and showed restricted diffusion on DWI.

Interobserver agreement was 75% for CT and 87.5% for MRI, corresponding to a high level of agreement (Figures 4 and 5).



Figure 2. Images of a 54-year-old patient with an ovarian cancer recurrence in the form of the fistula between the tumor and rectum. CT obtained in the coronal (A), sagittal (B), and axial plane (C) shows large pelvic tumor with adjacent rectum.



Figure 3. Images of a 57-year-old patient with high-grade serous ovarian cancer recurrence. Computed tomography shows large cystic-solid pelvic tumor with fluid/gas level and adjacent rectum as indirect sign of fistula.

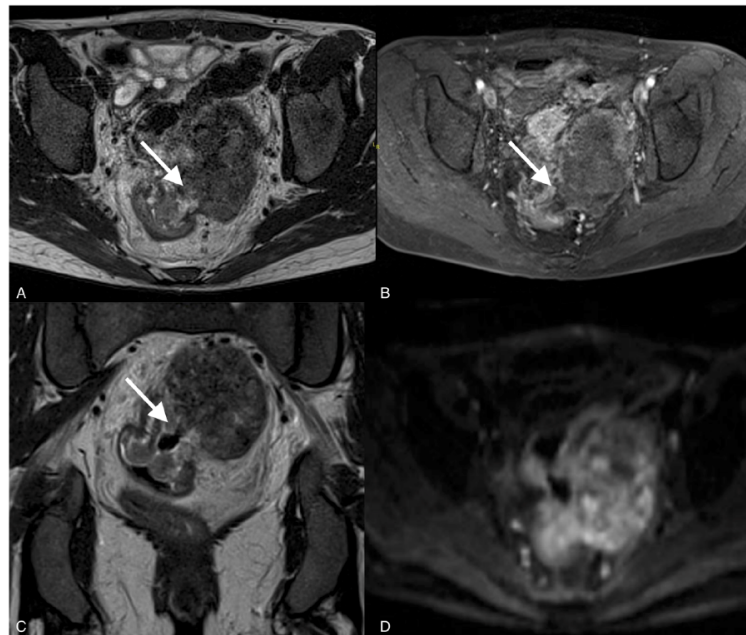


Figure 4. Images of a 37-year-old woman with a recurrent tumor of high-grade serous ovarian cancer with fistula between tumor and sigmoid colon. MRI T2-weighted images obtained in axial plane (A), coronal plane (B), and T1 post-contrast (C) show a large solid/cystic tumor and the fistula (arrows) between tumor and sigmoid colon. DWI (b1200) shows restricted diffusion in the tumor but not in the fistula (D).

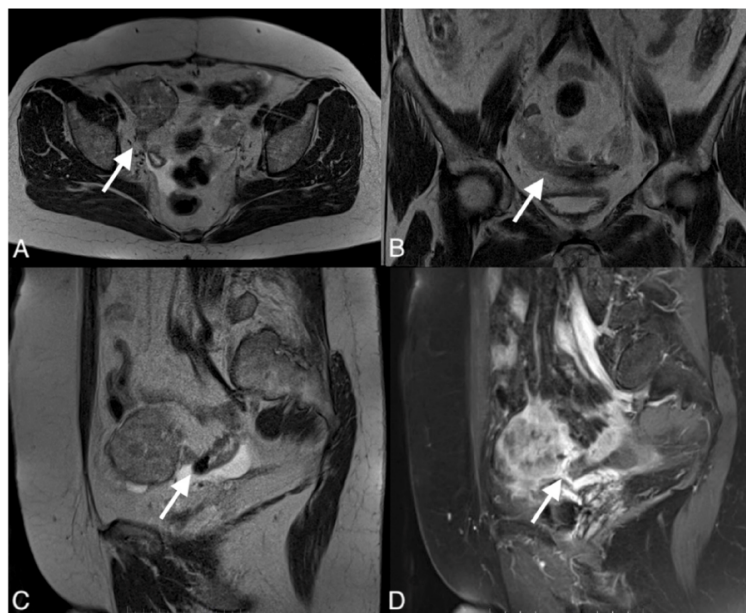


Figure 5. Images of a 67-year-old woman with a recurrent high grade serous ovarian cancer. MRI T1-weighted post-contrast image obtained in the axial plane (A), coronal plane (B), sagittal plane (C), and T1-weighted image post-contrast (D) show large pelvic tumor and fistula (arrows) between the tumor and sigmoid colon.

3.2. Surgical Findings

Patients who were qualified for the study underwent secondary cytoreductive surgery. In all eight cases, the fistulas between the tumor and surrounding organs were confirmed as a concomitant sign of cancer relapse. No residual macroscopic tumor remained in seven cases (resection R0-87.5%). In one patient, 1–2 mm implants were left in the mesentery of the ileum (resection R1). During surgery, seven intestinal anastomoses, one colostomy in the descending colon, and one case of tumor resection with fragments of bladder and ureter with implantation of the ureter to the bladder were performed. The types of fistulas, their locations, and the type of surgery are described in Table 4.

Table 4. The types and localization of the fistulas and the type and outcome of the surgical procedure.

Patient's Number	Localization	Surgical Procedure	Anastomosis	Surgical Outcome
1	sigmoid	anterior resection	end to end	R-0
2	sigmoid and descending colon	left hemicolectomy	end to end	R-0
3	rectum	anterior resection	end to end	R-0
4	rectum	Hartman's operation	colostomy	R-1 (1–2 mm peritoneal implants in the mesentery)
5	cecum and ascending colon	right hemicolectomy	side to side	R-0
6	sigmoid and left ureter	anterior resection and resection of part of the ureter with implantation into the urinary bladder	end to end	R-0
7	rectum	anterior resection	end to end	R-0
8	sigmoid	anterior resection	end to end	R-0

Right hemicolectomy was performed over a linear cutter stapler (GIA), anterior rectal resection with a linear stapler, and anastomosis with a trans-rectal circular end-to-end anastomosis (EEA) device. Overall morbidity was 25% (two of eight patients), including fever greater than 38 degrees for three days in two patients and suppuration of the wound in one patient (this patient also had fever over 38 degrees). No bowel-specific morbidity was noted, such as an anastomotic leak, ileus greater than one week, and pelvic abscess.

3.3. Oncological Outcomes

Six of our patients experienced another relapse. Two patients who received olaparib as a maintenance treatment were observed for 36 and 28 months after the end of second-line chemotherapy, with no cancer recurrence. One of the patients died. The progression-free survival (PFS) after the end of second-line chemotherapy was 8.4–22.6 months (median 13.4 months). In the group with cytoreduction R0, the median PFS was 15.5 months (12–22 months). The mean survival time after receiving second-line chemotherapy was 56.2 months.

4. Discussion

The present study on eight patients showed the imaging and treatment data of a tumor/bowel fistula as a rare form of relapsed ovarian cancer. Patients were qualified for surgery using the AGO score criteria, with R0 resection in seven of eight cases. The median PFS was 13 months, and the mean survival time after receiving second-line chemotherapy was 56 months.

According to the literature, a fistula between the intestine and the tumor is a rare sign of relapsed ovarian cancer and is very difficult to diagnose, as it manifests with nonspecific symptoms. A fistula between a tumor and the intestine can be diagnosed only with the use of imaging methods such as CT and MRI. According to our study, the primary method of diagnosing and confirming a suspected pelvic fistula is MRI, which has also been demonstrated in other studies. MRI allows not only recognition of a fistula between the vagina, bladder, and rectum but also assessment of regional anatomy and relationships with other organs [16,17]. Additionally, gynecological societies recommend MR for patients for whom CT is contraindicated or when findings are inconclusive [18]. Other methods such as CT are also useful, which is usually the first method used to evaluate progression or regression of the disease and causes of the acute abdomen; however, it has limitations when diagnosing the fistula [16].

Fluid-containing fistulas appear as a high signal on T2-weighted images and STIR, while gas-containing fistulas have a low signal in all sequences and demonstrate contrast enhancement. Old, healed fistulas typically demonstrate low T1 and T2 signals without contrast enhancement, reflecting fibrosis [19]. Our study showed that fistulas were hypointense on T2 sequences and hypointense on T1 sequences, and the best sequences to diagnose fistulas on MRI were T2 sequences and late arterial phase post-contrast T1 sequences, which suggest no active inflammatory processes or necrosis.

The study showed that the DWI sequence was not superior to the other sequences in diagnosing fistulas on MRI, except for one of the patients in whom an acute inflammatory process was involved. Recent studies have shown that diffusion-weighted images are useful for diagnosing fistulas in the pelvis and determining whether they involve acute inflammation. However, DWI alone was not superior to T2 and T1 sequences with contrast [20]. DWI can show restricted diffusion in the tumor, which has an important role in the detection, characterization, and definition of local tumor spread [17].

On computed tomography, we observed only indirect imaging signs of fistulas, such as infiltration of the intestine by the tumor, which we observed as vanishing of the fatty tissue between the tumor and the intestine, disruption of the intestinal wall, and gas in the tumor. Computed tomography's limitation is evident when evaluating local tumor spread due to its lower soft tissue resolution. In other studies, CT was very useful for diagnosis, revealing indirect signs of fistulas, such as obvious thickening of the tumor wall and an air-fluid level within the tumor, suggesting that the ovarian tumor might have communication with the digestive tract; however, they also did not observe fistulas directly [11].

In the literature, only a few case studies have described fistulation associated with ovarian cancer.

The observed patients were older than 50 years and showed symptoms similar to those in our study: abdominal pain and bloody diarrhea [11]. The organs involved in the fistula were the bladder, small intestine, and large intestine; however, in our study, we observed patients with a fistula between the tumor and large intestines [21].

Proposed mechanisms of fistula formation include torsion of the tumor with resultant ischemia and pressure necrosis, infection with adhesion to and eventual rupture into an adjacent organ, and malignant transformation with direct invasion [22].

The lack of bowel-specific morbidity in our group confirms the thesis that such operations can be safely performed by teams of experienced gynecologic oncologists. This finding is confirmed by other studies comparing operations performed by gynecologic oncologists and intestinal surgeons. However, the data are only for primary cytoreduction [23,24].

In our study, the mean PFS for all patients was 13.4 months, but for the subpopulation with complete secondary cytoreduction surgery (R0), it was 15.5 months. Despite a high percentage of complete cytoreduction 87.5, the PFS in our study was shorter than that in the DESKTOP I-III study (18.4 months), the CALIPSO study (18.2 months), the GOG 213 study (18.9 months), and the SOC-1 study (17.4 months). In the last two trials, the median PFS rates for patients with complete secondary cytoreduction resection (R0) were 22.4 months and 19.2 months, respectively [25,26]. Therefore, we can hypothesize that ovarian cancer relapse associated with a fistula between the bowel and tumor accounts for the poor prognosis. Of course, this is only a hypothesis.

The limitation of the present study is the sample size, which was small because a rare form of ovarian cancer recurrence was examined. Furthermore, this was a single-center study.

5. Conclusions

In patients with suspected EOC recurrence with clinically suspected fistula, CT scan is not sufficient. In CT, the presence of a fistula is suspected, based on indirect symptoms. MRI, as a method with much greater tissue resolution, confirms the diagnosis. In addition, MRI can identify the point of the tumor/bowel junction. This is especially true with a large infiltration, covering several intestinal parts.

Bowel resection with a simultaneous anastomosis is a good and safe solution for these patients. However, appropriate qualification for the procedure is necessary, allowing for surgery without residual macroscopic disease (R0 surgery).

Due to the small number of cases, our results cannot be generalized. We treat them as hypothetical and encourage other researchers to verify them in a larger study.

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Article

Dynamic Contrast-Enhanced and Diffusion-Weighted Imaging in Magnetic Resonance in the Assessment of Peritoneal Recurrence of Ovarian Cancer in Patients with or Without BRCA Mutation

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Simple Summary: Recurrence in patients with ovarian cancer is common and causes difficulties for oncologists, radiologists and gynecologists. The mutation rate of the BRCA gene in high-grade serous ovarian cancer is greater than 21%. Patients suspected of having local recurrence and intraperitoneal spread are examined via magnetic resonance, owing to its excellent soft tissue resolution. The aim of this study was to determine the differences in diffusion-weighted imaging and dynamic contrast enhancement parameters in patients with peritoneal HGSOc recurrence with or without BRCA mutations. In this study, we revealed statistically significant differences in the DWI and DCE MRI parameters between patients with BRCA mutations and BRCA wild type. Additionally, we showed the difference between the parameters on MRI and the size of the peritoneal metastases. Adding DCE perfusion to the MRI protocol for detecting ovarian cancer recurrence in patients with BRCA mutations could be a valuable tool.

Abstract: Background: The aim of this study was to determine the differences in diffusion-weighted imaging (DWI) and dynamic contrast enhancement (DCE) parameters between patients with peritoneal high-grade serous ovarian cancer (HGSOc) recurrence with BRCA mutations (BRCAmut) or BRCA wild type (BRCAwt). Materials and Methods: We retrospectively analyzed the abdominal and pelvic magnetic resonance (MR) images of 43 patients suspected of having recurrent HGSOc, of whom 18 had BRCA1/2 gene mutations. Patients underwent MRI examination via a 1.5 T MRI scanner, and the analyzed parameters were as follows: apparent diffusion coefficient (ADC), time to peak (TTP) and perfusion maximum enhancement (Perf. Max. En.). Results: The mean ADC in patients with BRCAwt was lower than that in patients with BRCAmut: 788.7 (SD: 139.5) vs. 977.3 (SD: 103), p -value = 0.00002. The average TTP value for patients with BRCAwt was greater than that for patients with mutations: 256.3 (SD: 50) vs. 160.6 (SD: 35.5), p -value < 0.01. The Perf. Max. En. value was lower in the BRCAwt group: 148.6 (SD: 12.3) vs. 233.6 (SD: 29.2), p -value < 0.01. Conclusion: Our study revealed a statistically significant correlation between DWI and DCE parameters in examinations of peritoneal metastasis in patients with BRCA1/2 mutations. Adding DCE perfusion to the MRI protocol for ovarian cancer recurrence in patients with BRCAmut may be a valuable tool.

Keywords: ovarian cancer; recurrence; MRI; BRCA 1 or BRCA2 mutations; DCE; DWI

1. Introduction

Epithelial ovarian cancer (EOC) is associated with high morbidity and mortality because it is usually detected at an advanced stage [1,2]. The leading type of malignant tumor of the ovary is high-grade serous ovarian cancer (HGSOC) [3].

Approximately 15% of unselected cases of EOC, tubal, or peritoneal carcinoma are caused by germline mutations in the BRCA1 and BRCA2 genes. According to current large-scale studies of patients with HGSOC, the mutation rate in this type of cancer is estimated to be greater than 21%. Germline mutations in more recently identified ovarian cancer predisposition genes, such as RAD51C, RAD51D and BRIP1, are also observed in approximately 3% of patients [4].

Tumor prognosis depends on the use of optimal cytoreductive surgery and adjuvant platinum-based chemotherapy [5,6]. Current maintenance treatment with bevacizumab or polyadenosine diphosphate-ribose polymerase (PARP) inhibitors is associated with longer progression-free survival (PFS) [7–11].

A similar recurrence rate has been reported between BRCAwt and BRCAmut groups (35.3% vs. 29.2%) [12]. The basic method of treating recurrent ovarian cancer is chemotherapy. Secondary cytoreductive surgery is currently an option for second-line treatment in selected patients [13]. The choice of chemotherapy program depends primarily on the time of disease recurrence, the drugs used in the first line of treatment, and the molecular state of the tumor [14]. In addition, maintenance therapy with antiangiogenic therapy and PARP inhibitors has emerged as the standard of care. Novel combinations, including immunotherapy and antiangiogenic agents, have also been developed [15,16].

The role of imaging in the treatment of ovarian cancer recurrence is crucial. All clinically available methods, such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) CT, are used, and each method has advantages and limitations. The main indications for MRI are suspicion of local recurrence in the pelvis and intraperitoneal spread [17,18]. Owing to its excellent high resolution of soft tissues, MRI allows for the distinction between post-treatment changes and tumor recurrence [18]. We know that intraperitoneal lesions, like primary tumors, differ in terms of MRI diffusion and perfusion parameters depending on the type of EOC, e.g., HGSOC vs. low-grade serous ovarian cancer (LGSOC) [19]. To date, there are no studies on the diffusion and perfusion parameters in recurrent ovarian cancer. However, there are reports that secondary and recurrent tumors are better vascularized [20]. Assessment of diffusion-weighted imaging (DWI) parameters, especially dynamic contrast enhancement (DCEs), in recurrent tumors may be helpful in selecting therapies for recurrent ovarian cancer that combine PARP inhibitors and antiangiogenic agents [20–22].

The aim of this study was to determine the differences in the DWI and DCE parameters in patients with peritoneal HGSOC recurrence in the BRCAmut and BRCAwt groups.

2. Materials and Methods

2.1. Study Protocol

This retrospective analysis of the abdominal and pelvic MR images of 43 patients aged 21–76 years was conducted in the Second Department of Radiology at the Medical University of Warsaw. The patients who were examined were suspected of having ovarian cancer recurrence after first-line treatment, and 18 of these patients had BRCA1/BRCA2 mutations. Relapse was suspected due to an elevated Ca-125 (above twice the nadir value) and computed tomography findings. The study group included only patients with platinum-sensitive HGSOC [23,24].

2.2. Imaging Protocol

All of the patients underwent MRI on a 1.5 Tesla MR scanner (MAGNETOM Avanto, Siemens AG, Erlangen, Germany). The imaging protocol included the following: T1 in and out phase, T1 pre- and postcontrast (dynamic contrast-enhanced; DCE), T2 turbo spin echo (TSE), fat-suppressed T2, T2 weighed sequence, turbo inversion recovery magnitude

(TIRM), and diffusion-weighted imaging (DWI). For the DCE sequences, patients were administered a bolus dose (0.1 mmol/kg) of gadobutrol (Gadovist, Bayer AG, Leverkusen, Germany) followed by a bolus dose of 20 mL of 0.9% saline solution. Motion correction was applied automatically. Several parameters are shown in Table 1. DWI was performed using the b values of 0, 50, 400 and 1200 mm²/s. Apparent diffusion coefficient (ADC) maps were produced automatically via computer software.

Table 1. Selected parameters used in the study protocol.

Sequence	TE	TR	Flip Angle	Slice Thickness (mm)	FOV (mm)	Orientation	NEX	Breath Hold
T1 in and out phase	1–2.22, 2–4.92	125	70	6	300 × 225	axial	1	no
T2 TIRM	89	4840	150	3	219 × 199	axial	2	no
T2 TSE	116	4250	137	3	299 × 286	axial, coronal and sagittal	1	no
T2 fat sat Tra	123	2110	150	3	300 × 300	axial	1	no
DWI	76	3200	90	6	289 × 234	axial	2	no
Vibe T1 GRE	1.1	3.1	10	3	288 × 156	axial, sagittal and coronal	1	no

Two radiologists with experience in abdominal and pelvic MRI (one with more than 15 years of experience in oncological imaging and one with a European diploma in radiology) independently analyzed the images. First, the abdomen was divided into the following areas according to the PCI index: the right hypochondrium, epigastrium, left hypochondrium, left flank, left iliac fossa, pelvis, right iliac fossa, central, right flank, proximal jejunum and ileum and distal jejunum and ileum. Each area was analyzed according to the presence of peritoneal metastases and their size, which were further subdivided into groups: small (<1 cm), medium (1–2 cm) and large (>2 cm). Then, the metastasis with the qualitatively highest diffusion restriction was selected to quantitatively measure the ADC values. Small ROIs (5 mm) were placed into the areas with the solid part of the metastasis on the DWI scans, which were acquired with a b value of 1500 mm²/s, and the cystic parts and artifacts were avoided. Then, according to the DWI selection, the ROIs were placed on the ADC maps (Figures 1 and 2). The measurements on the ADC maps were saved. Three measurements were made by each radiologist independently.

For the DCE T1 images, first, precontrast images were acquired, and then each phase was subsequently acquired after contrast was administered. The perfusion maps and charts were produced automatically via AV Server 4.2 software. The areas of metastases were analyzed as described above. For the peritoneal metastases selected for measuring the ADC values, small ROIs were placed on the T1 postcontrast images and recreated on the DCE parametric maps (Figures 3 and 4). Again, three measurements were made by each radiologist independently. Parameters such as the time to peak (TTP) and perfusion maximum enhancement (Perf. Max. En.) were measured, and all the values were saved.

2.3. Statistical Analysis

IBM SPSS Statistics (version 28.0.1.0 (142)) was used to analyze the distribution of the variables, perform some of the statistical tests, and calculate some of the statistics. PQStat (version: 1.8.6.102.) was used for the same purpose: to analyze the data and to prepare the visualizations included in this article. Power BI (version: 2.123.684.0) was used to create the chart showing the percentage distribution of the peritoneal metastasis size between the patients with and without BRCA mutations. The Shapiro-Wilk test was used to determine whether a variable was normally distributed. All numerical values characterized by a normal distribution are presented as the means and standard deviations, whereas the qualitative variables are presented as raw numbers and percentages. The *p*-values were determined via three different tests, and a *p*-value less than 0.05 indicated a statistically significant difference. For interval scale variables that met the condition of a

normal distribution and for those that were independent, the t test for independent groups was used, which is specifically designed for such conditions. For normally distributed quantitative variables, one-way ANOVA for independent groups was used. For nominal and independent variables, the chi-square test or Fisher's exact test was used. For variables characterized by a normal distribution, the post hoc Fisher's LSD test was performed to determine statistically significant differences between groups. For interval variables, ICC was used to determine the interobserver agreement between the two reviewers.

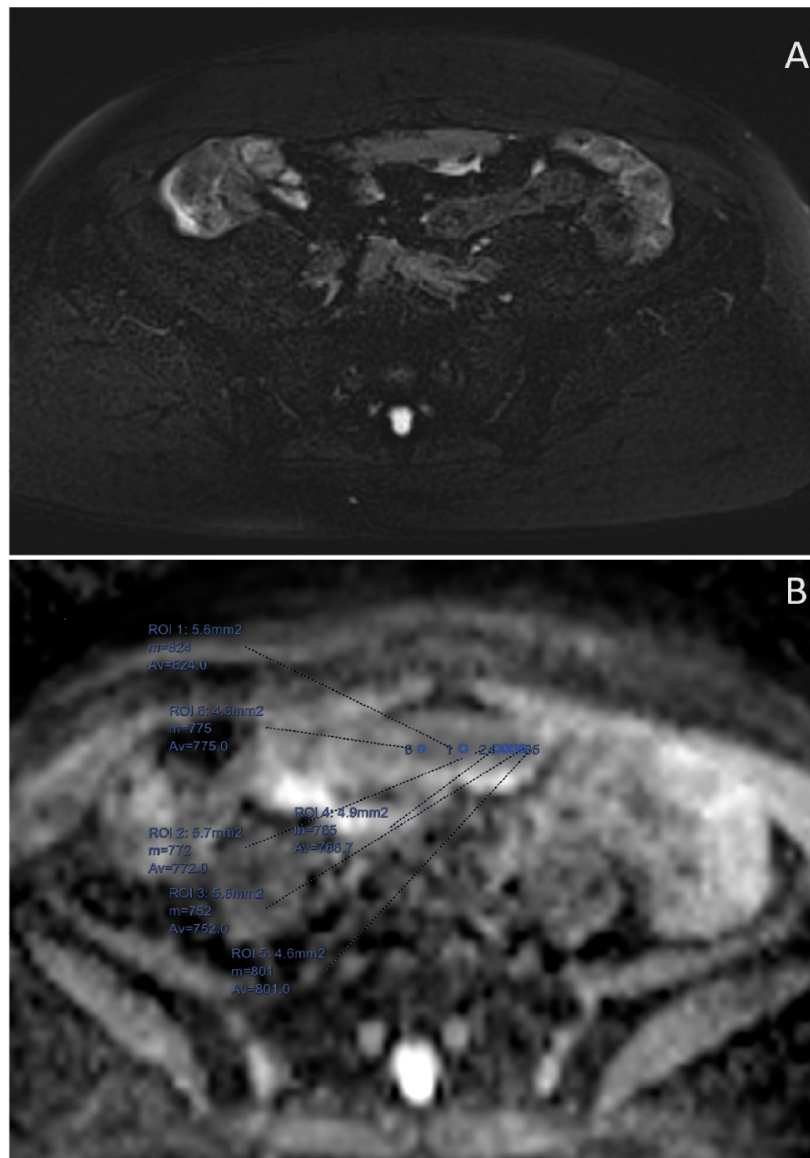


Figure 1. MRI of a 65-year-old patient with HGSOc recurrence BRCAwt. (A) Midline large peritoneal metastases on the STIR sequence. (Short tau inversion recovery) (B) ADC map image of the same peritoneal implant with small ROIs placed in the areas that qualitatively have the lowest signal.

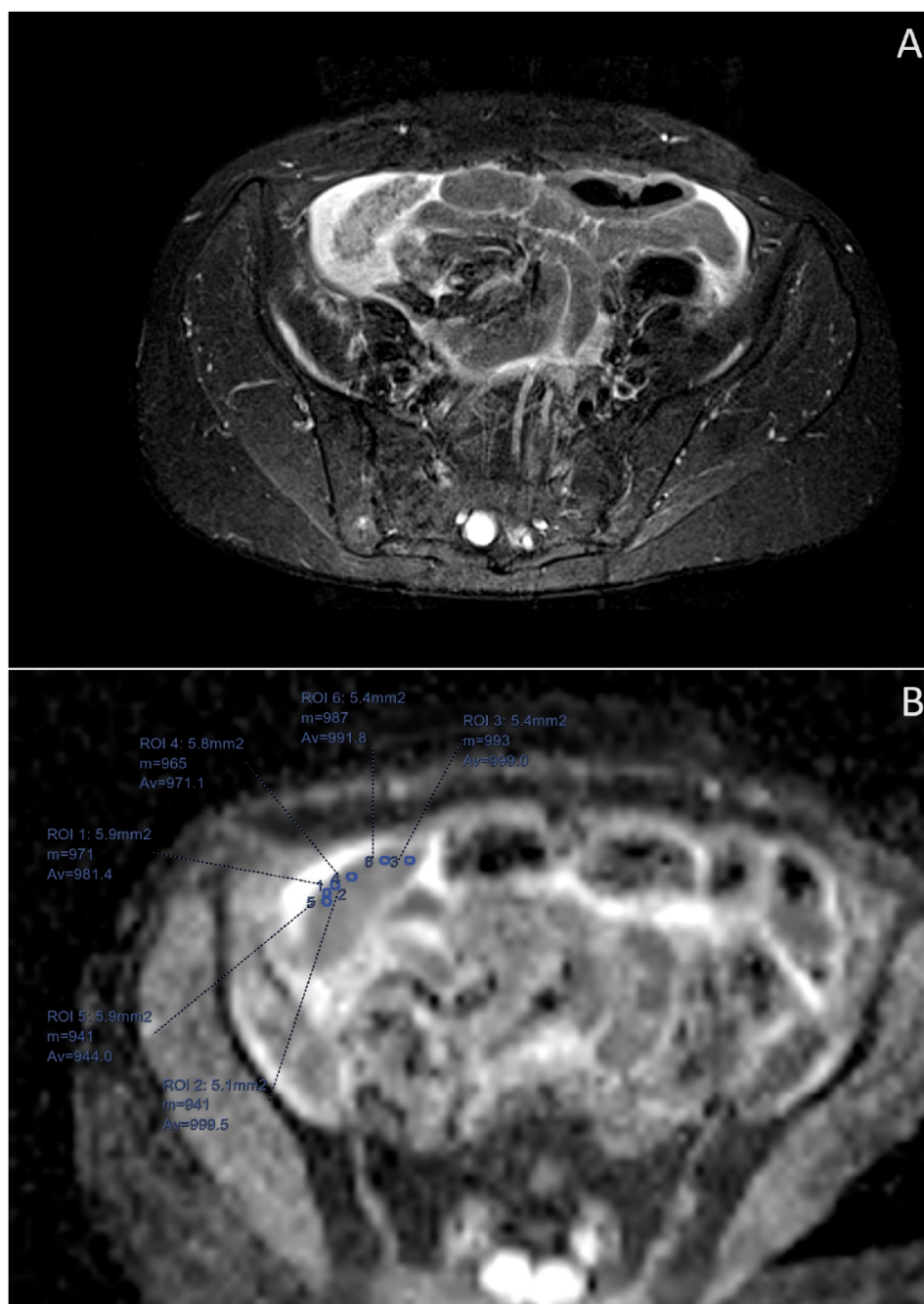


Figure 2. Images of the same 46-year-old patient with HGSOV recurrence BRCAmut. (A) Large peritoneal metastases in the right iliac fossa on the STIR sequence. (B) ADC map. Magnified image of the same peritoneal implant with small ROIs placed in the areas that qualitatively have the lowest signal.

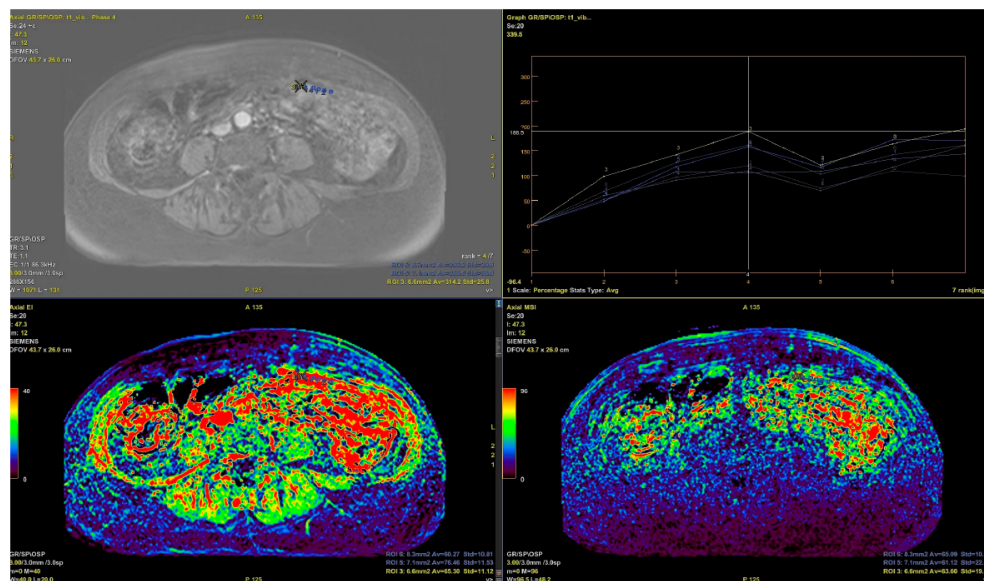


Figure 3. Images from the 65-year-old patient with HGSOc recurrence BRCawt, contrast enhancement maps and curves.

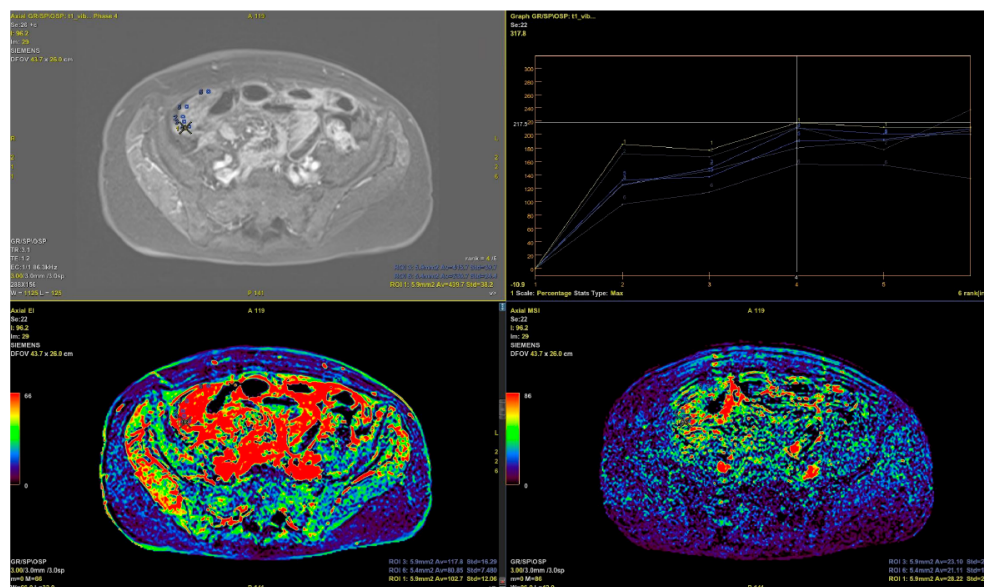


Figure 4. MRI of a 46-year-old patient with HGSOc recurrence with a BRCAmut. Contrast enhancement maps and curves.

3. Results

3.1. Statistical Analysis of the Selected Parameters

3.1.1. Categorizing Patients According to BRCA Mutation Status

There were 43 women in the patient cohort with an average age of approximately 56 years.

All patients underwent surgery. Twenty-five patients with FIGO stage III underwent primary cytoreductive surgery, including 19 who completed surgery with no residual macroscopic disease (R0 surgery). Six had residual disease < 10 mm (R1).

Eleven patients started treatment with neoadjuvant chemotherapy followed by interval debulking surgery. Ten patients had no residual disease (R0), and one had >10 mm residual disease (R2). The clinicopathological characteristics of the study group are shown in Table 2.

Table 2. Clinicopathological characteristics of the 43 patients included in this study.

Variable	BRCAmut (n = 18)	BRCAwT (n = 25) Including 5 HRD Positive	p-Value
Age (avg ± sd)	56.4 ± 9	56.6 ± 12.3	0.9 ^t
FIGO stage			0.98 ^F
I	2	3	
II	1	1	
III	14	19	
IV	1	2	
First-line chemotherapy			0.22 ^F
PCL + CBDCA	18	23	
CBDCA mono	0	2	
Maintenance treatment			0.25 ^F
Bevacizumab	0	5	
PARP inhibitors	14 (olaparib)	15 (niraparib)	
BEV & PARPi	1	1	
other	3	4	
Treatment response			0.47 ^F
Complete response	17	22	
Partial response	1	3	

The values are expressed as raw numbers and percentages. Test of significance: *p*-value: *t*—*t* test for independent groups; *F*—chi-square or Fisher’s exact test. Abbreviations: HRD—homologous recombination deficiency; PCL—paclitaxel; CBDCA—carboplatin; mono—monotherapy; PARP—polyadenosine diphosphate-ribose polymerase; BEV—bevacizumab; PARPi—polyadenosine diphosphate-ribose polymerase inhibitors.

The analyzed parameters were the ADC, TTP and Perf. Max. En. and the size of the peritoneal implants. The patients were categorized according to the absence (*N* = 25, 58%) or presence (*N* = 18, 42%) of BRCA mutations. The obtained results are shown in Table 3.

Table 3. Statistical analysis of the parameters (ADC, TTP and Perf. Max. En.) and age of the two groups (patients with or without (*w/o*) BRCA mutations).

Characteristic	BRCAwT (N = 25)	BRCAmut (N = 18)	All Patients (N = 43)	p-Value
ADC	788.7 ± 139.5	977.3 ± 103	867.7 ± 155.8	<0.001 ^t
TTP	256.3 ± 50	160 ± 35.5	216.2 ± 65	<0.01 ^t
Perf. Max. En.	148.6 ± 22.4	233.6 ± 29.2	184.2 ± 49.3	<0.01 ^t
Size of the implants ^a				0.01 ^F
<1 cm, n (%)	6 (24%)	12 (67%)	18 (41%)	
>1 cm, <2 cm n (%)	14 (56%)	3 (17%)	17 (40%)	
>2 cm, n (%)	5 (20%)	3 (17%)	8 (19%)	

The values are expressed as the arithmetic mean with the standard deviation. ^a The values are expressed as raw numbers and percentages. Test of significance: *p*-value: *t*—*t* test for independent groups; *F*—chi-square or Fisher’s exact test.

The ADC levels were significantly different between the two groups of patients. The mean ADC in the without (*w/o*) mutation group of patients was 788.7 (*SD*: 139.5), whereas for the with mutation group, this value was 977.3 (*SD*: 103; $p = 0.00002$). Regarding the TTP and Perf. Max. En. parameters, statistically significant differences were also observed between the two groups; for both parameters, the p -value was <0.01 . The average TTP for patients without mutations was 256.3 (*SD*: 50), whereas for patients with mutations, the average TTP was 160.6 (*SD*: 35.5). For the Perf. Max. En. parameter, a lower average value of 148.6 (*SD*: 12.3) was observed in the group without mutations, whereas for patients with mutations, this value was 233.6 (*SD*: 29.2).

On average, patients with BRCA mutations were characterized by greater ADC and Perf. Max. En. values, whereas the TTP value was lower in patients with BRCA mutations than in patients without BRCA mutations (p -value < 0.05).

3.1.2. Patient Categorization According to the Size of the Peritoneal Metastasis

In addition to categorizing patients according to the presence of BRCA mutations, patients were also categorized on the basis of the size of the peritoneal metastasis.

For further analysis, the patients were assigned to group one (peritoneal metastasis < 1 cm, $N = 18$, 42%), group two (peritoneal metastasis between 1 and 2 cm, $N = 17$, 40%), or group three (peritoneal metastasis > 2 cm, $N = 8$, 18%). The results are shown in Table 4.

Table 4. Statistical analysis of the parameters (ADC, TTP and Perf. Max. En.) in the three groups of patients stratified according to the size of the peritoneal metastasis.

Characteristic	Size of the Peritoneal Metastasis			All Patients ($N = 43$)	p -Value
	<1 cm ($N = 18$)	>1 cm, <2 cm ($N = 17$)	>2 cm ($N = 8$)		
ADC	956.6 ± 108.7	760.5 ± 108	895.3 ± 203	867.7 ± 155.8	0.0003
Pairwise comparison	B	A	B		
TTP	203 ± 67.2	234.4 ± 57.5	207.6 ± 73.8	216.2 ± 65	0.3
Perf. Max. En.	196.3 ± 50.9	167.5 ± 48.2	192.5 ± 43	184.2 ± 49.3	0.2

The values are expressed as the arithmetic mean with the standard deviation. Test of significance: p -value: one-way ANOVA for independent groups. Pairwise comparisons (post hoc Fisher's LSD); same letters = insignificant difference; different letters = significant difference. Abbreviations—see Table 3.

Statistically significant differences were noted for the ADC parameter among the three groups. There were significant differences in the mean ADC between patients in group two (mean ADC = 760.5, *SD*: 108) and the combined group comprising patients in group one (mean ADC = 965.6, *SD*: 108.7) and those in group three (mean ADC = 895.3, *SD*: 203; $p = 0.0003$). There were no statistically significant differences in the mean ADC between the patients in group one and those in group three; i.e., patients in group one and group three were not significantly different from each other in terms of the mean ADC.

3.2. Interobserver Agreement

The intraclass correlation coefficient (ICC) was used to examine the interobserver agreement for the ADC and TTP quantitative parameters. The ICCs revealed excellent, statistically significant interobserver agreement between the two observers for both parameters.

The interobserver concordance oscillated at the level of excellent concordance, and the ICC was >0.9 (Table 5).

Table 5. Intraclass correlation coefficients of the ADC and TTP parameters as determined by the two observers.

Parameter	ICC	95% CI	p-Value
ADC	0.98	0.96–0.99	<0.01
TTP	0.95	0.91–0.97	<0.01

ICC: intraclass correlation coefficient; CI: confidence interval.

4. Discussion

Our study involving 43 patients revealed a relationship between the DWI and DCE MRI parameters and BRCA1/2 mutation status in molecular studies of recurrent HGSOE patients. The mean ADC in patients with BRCAwt was lower than that in patients with BRCAmut: 788.7 vs. 977.3, p -value = 0.00002. The average TTP value for patients with BRCAwt was greater than that for patients with mutations: 256.3 vs. 160.6, p -value < 0.01. The Perf. Max. En. value was lower in the BRCAwt group: 148.6 (SD: 12.3) vs. 233.6 (SD: 29.2), p -value < 0.01.

Similar protocols of studies using ADC and selected perfusion parameters in 1.5 T and 3.0 T MRI have been described in previous publications [25–27].

The ADC values, which are derived from DWI and are inversely correlated with tumor cellularity, were greater in the BRCAmut group than in the BRCAwt group ($p < 0.00002$). The decrease in restricted diffusion, which was statistically significant in the tumors of patients with BRCAmut, was more fluid. Higher ADC values in peritoneal metastases before treatment may be linked to a poorer response to chemotherapy and a poorer prognosis [28].

DCE parameters allow for the evaluation of tumor vascularization/angiogenesis. Our study of recurrent tumors revealed significantly greater TTP values (longer time to peak) in the BRCAwt group than in the BRCAmut group ($p < 0.01$). The Perf. Max. En. parameter showed an inverse correlation, and the values were significantly greater in the BRCAmut group. This leads to the conclusion that peritoneal metastases in tumors with BRCA 1/2 mutations are more vascularized.

We also examined the correlation between the size of the peritoneal metastases and the DWI and DCE parameters. The results revealed that the highest diffusion restriction, in the form of the lowest ADC values, was observed in the medium-sized metastases (1–2 cm). Metastases that were <1 cm or >2 cm did not differ significantly in terms of the ADC values; however, their values were greater. There was no correlation between the TTP or the Perf. Max. En. parameters and the size of the peritoneal implants.

Finally, we determined the correlations between the presence of the BRCA1/2 mutations, the size of the recurrent implants and the DWI or DCE parameters. Our results revealed that the TTP and Perf. Max. En. parameters are dependent only on the presence or absence of BRCA mutations and not on tumor size. For the ADC values, the correlation was more complex and may require further study.

DCE parameters are widely used to characterize tumors on MRI or to evaluate the response to treatment [29]. Low perfusion values (Ktrans and kep) are inversely correlated with the risk of tumor recurrence in patients with HGSOE [30]. The TTP is the time at which the contrast agent reaches its maximal concentration, and maximal enhancement is the peak contrast concentration, which is why tumors with high vascularization will have low TTP values [31] and high perfusion maximum enhancement values on DCE [32].

Studies have shown that higher ADC values are associated with high VEGF protein expression in metastatic endothelial cells and that lower TTP values are associated with more aggressive tumors [33]. Additionally, lower TTP values were associated with shorter recurrence-free survival [34].

VEGF acts as a proangiogenic agent. In other tumors, such as gastric cancer, a positive predictive value has been demonstrated between DCE parameters and VEGF receptor expression [35], whereas studies examining the correlation between DCE parameters and VEGF in ovarian cancer have shown an inverse correlation [36]. One possible explanation

is that the blood flow is already increased in ovarian cancer and that high VEGF expression is no longer needed [36]. There are few studies examining peritoneal metastases on MRI in patients with EOC; however, one of the studies compared primary tumors and metastasis and demonstrated that ovarian cancer metastases show increased expression of proangiogenic proteins compared with primary tumors [37].

DWI parameters are also correlated with VEGF expression. A negative correlation between the ADC value and VEGF expression was observed in primary EOC tumors [38]. Lindgren and coauthors reported a positive correlation in one of the first articles examining the correlation between ADC values and VEGF expression in ovarian cancer. The difference in the results may be because, in one study, the ADC values were obtained only from the primary tumor, whereas in the second study, they were obtained from the primary and secondary tumors (metastases). Lindgren also reported that VEGF expression is greater in metastases than in primary tumors [19]. An inverse correlation between the ADC value and VEGF expression was also found in prostate cancer [39] and breast cancer [40].

In our study, we observed the lowest ADC values in the group with peritoneal metastases between 1 cm and 2 cm, and the difference was statistically significant compared with both the <1 cm group and the >2 cm group. The highest ADC values were found in the group with the smallest metastases (<1 cm). We suspect that the difference in our study is due to the partial volume effect, which occurs when there is more than one type of tissue in the voxel.

Unfortunately, studies examining the ADC values and the size of the peritoneal deposits are limited. A possible indirect reference here may be studies of DWI in lymph nodes less than 1 cm showing significant differences in the ADC between metastatic and normal nodes. The authors suggested that such a small size of the node excludes the presence of necrosis [41]. Some authors have suggested that the partial volume effect does not significantly influence the measurements, even in lymph nodes of approximately 6 mm [42]; however, other studies have suggested that to avoid the partial volume effect, the mass size should be at least twice as large as the slice thickness of the DWI sequence [43]. In our MRI protocol, the slice thickness on DWI was 6 mm; however, when peritoneal deposits were observed on the slice images, we also examined them because of the limited population group. Moreover, placing the ROI in a small lesion is problematic, and taking the size and ROI shape into account while measuring the ADC value is crucial [44,45]. The values obtained from placing a small ROI in the darkest area of the ADC map rather than in the entire lesion show better sensitivity, specificity and positive predictive value [46]. Our results revealed that there was a significant correlation only between the group with 1–2 cm peritoneal deposits in the corresponding BRCAwt and BRCAmut groups, possibly because in these groups, the ROIs were small, the lesions were homogenous, and we could avoid areas of micronecrosis.

A recent MRI study of EOC primary tumors in BRCAwt and BRCAmut patients revealed no differences in the ADC and DCE parameters [37], unlike our findings. This difference may be because we examined peritoneal metastases instead of primary tumors, and as mentioned above, some authors have proven that secondary tumors are better vascularized. Furthermore, the study revealed that BRCA1mut patients had more enhanced tumors than the BRCA2mut group did; thus, the study group also differed, as we did not examine the differences in the MRI characteristics of the patients with each mutation type.

The use of diffusion parameters and ADC maps is a recognized method for the diagnosis of cancer recurrence. In our study, we showed that in the case of ovarian cancer recurrence, ADC values have certain limitations related to the size of the metastases, whereas perfusion parameters (TTP and max enh) do not depend on the size of the metastases and, in our opinion, have greater diagnostic value in tumors that are richly vascularized. To reliably compare the ADC values, authors should select peritoneal metastases not only with the qualitatively greatest diffusion restriction but also with similar sizes (e.g., <2 cm). These findings may be used to qualify patients for further treatment with a combination of PARP inhibitors and antiangiogenic agents [21,22].

In the future, machine learning may be helpful in differentiating these lesions, as it provides excellent accuracy that surpasses conventional analysis and may improve the assessment of ovarian cancer recurrence in the peritoneum [47].

One limitation of our study was that it was a single-center study with a small sample size, which is why we also combined patients with BRCA1 and BRCA2 mutations. Therefore, maintenance therapy differed between the two groups, which could have affected the results. Although we controlled for ROI placement, chose a small ROI, and achieved very good interobserver agreement, we could not avoid the partial volume effect in the smallest peritoneal metastases. Additionally, we examined recurrent tumors, which is why further studies are needed to determine whether there is a similar correlation in newly diagnosed patients.

5. Conclusions

To conclude, adding DCE perfusion to the MRI protocol for detecting ovarian cancer recurrence in patients with BRCA mutations could be a valuable tool regardless of the size of the metastases.

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Wnioski

- U pacjentek z podejrzeniem nawrotu EOC oraz klinicznym podejrzeniem przetoki badanie TK nie jest wystarczające do postawienia rozpoznania, ponieważ w tomografii komputerowej obecność przetoki może być podejrzewana na podstawie pośrednich objawów takich jak: gaz w guzie, zatarcie tkanki tłuszczowej między guzem a jelitem. Rezonans magnetyczny jako metoda o znacznie wyższej rozdzielczości tkanek miękkich, pozwala na potwierdzenie diagnozy. Dodatkowo MRI umożliwia identyfikację miejsca połączenia guza z jelitem. Ma to szczególne znaczenie w przypadku dużych nacieków obejmujących kilka odcinków jelita.
- W wybranych parametrach sekwencji dyfuzyjnej oraz perfuzyjnej rezonansu magnetycznego wykazano statystycznie istotną różnicę między grupami pacjentek z i bez mutacji BRCA1/2. U pacjentek z mutacją BRCA wykazano wyższe wartości ADC, co sugeruje, że guzy te są mniej komórkowe niż u pacjentek bez mutacji. Wyższe maksymalne wzmocnienie kontrastowe oraz niższe wartości TTP mogą świadczyć o tym, że guzy te są lepiej unaczynione. Wartości ADC były najniższe we wszczepach o małych wymiarach wielkości 1-2cm, wartości perfuzyjne we wszczepach nie zależały od wielkości zmian. Dodanie sekwencji perfuzyjnych do badania MR pacjentek ze wznową raka surowiczego jajnika może być wartościowe niezależnie od wielkości

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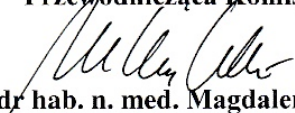
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OŚWIADCZENIE

Niniejszym oświadczam, że Komisja Bioetyczna przy Warszawskim Uniwersytecie Medycznym w dniu 16 maja 2022r. przyjęła do wiadomości informację na temat badania pt. „Przetoka guz-jelito jako rzadka forma wznowy raka jajnika-obrazowanie i leczenie („Tumor-bowel fistula as a rare form of a recurrent ovarian cancer-imaging and treatment.”). Przedstawione badanie nie stanowi eksperymentu medycznego w rozumieniu art. 21 ust. 1 ustawy z dnia 5 grudnia 1996 r. o zawodach lekarza i lekarza dentysty (Dz.U.z 2018 r. poz. 617) i nie wymaga uzyskania opinii Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym, o której mowa w art. 29 ust.1 ww. ustawy.

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OŚWIADCZENIE

Niniejszym oświadczam, że Komisja Bioetyczna przy Warszawskim Uniwersytecie Medycznym w dniu 11 marca 2024 r. przyjęła do wiadomości informację na temat badania pt. "Rozsiew wewnątrztrzewny u pacjentek ze wznową raka jajnika z i bez mutacji BRCA: zastosowanie parametrów DWI i DCE w rezonansie magnetycznym."

Przedstawione badanie nie stanowi eksperymentu medycznego w rozumieniu art. 21 ust.1 ustawy z dnia 5 grudnia 1996 r. o zawodach lekarza i lekarza dentysty (Dz.U z 2018 r poz. 617) i nie wymaga uzyskania opinii Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym, o której mowa w art. 29 ust.1 ww. ustawy.

Przewodnicząca Komisji Bioetycznej

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Oświadczenia wszystkich współautorów publikacji określające indywidualny wkład każdego z nich w ich powstanie

Warszawa, 26.05.2025

dr hab. n. med. Laretta Grabowska-Derlatka

OŚWIADCZENIE

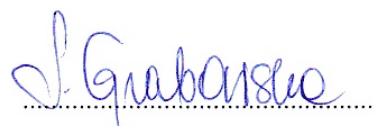
Jako współautor pracy "Dynamic Contrast-Enhanced and Diffusion-Weighted Imaging in Magnetic Resonance in the Assessment of Peritoneal Recurrence of Ovarian Cancer in Patients with or Without BRCA Mutation." *Cancers* 16.22 (2024): 3738 oraz „Tumor-Bowel Fistula as a Rare Form of Recurrent Ovarian Cancer—Imaging and Treatment: Preliminary Report." *Current Oncology* 30.1 (2022): 506-517 oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:

udział w przygotowaniu koncepcji badania, nadzór merytoryczny nad prowadzeniem badania, opracowanie metodologii, nadzór nad interpretacją otrzymanych wyników, pisanie artykułów stanowiących cykl publikacji.

Wkład Melanii Jankowskiej- Lombarskiej w powstawanie publikacji obejmował:

udział w przygotowaniu koncepcji badania, opracowanie metodologii, wykonanie badania, interpretacja wyników, pisanie artykułów stanowiących cykl publikacji.

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Melanii Jankowskiej-Lombarskiej


(podpis oświadczającego)

Warszawa, 26.05.2025

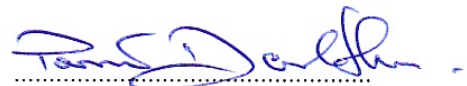
dr hab. n. med. Paweł Derlatka

OŚWIADCZENIE

Jako współautor pracy "Dynamic Contrast-Enhanced and Diffusion-Weighted Imaging in Magnetic Resonance in the Assessment of Peritoneal Recurrence of Ovarian Cancer in Patients with or Without BRCA Mutation." *Cancers* 16.22 (2024): 3738 oraz „Tumor-Bowel Fistula as a Rare Form of Recurrent Ovarian Cancer—Imaging and Treatment: Preliminary Report." *Current Oncology* 30.1 (2022): 506-517 oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
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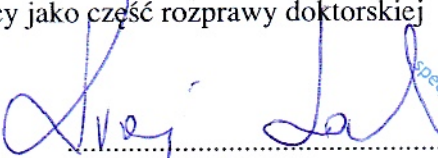
dr n. med. Leszek Kraj

OŚWIADCZENIE

Jako współautor pracy "Dynamic Contrast-Enhanced and Diffusion-Weighted Imaging in Magnetic Resonance in the Assessment of Peritoneal Recurrence of Ovarian Cancer in Patients with or Without BRCA Mutation." *Cancers* 16.22 (2024): 3738 oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi:
wsparcie merytoryczne w prowadzenie badania

Wkład Melanii Jankowskiej- Lombarskiej w powstawanie publikacji obejmował:
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(podpis oświadczającego)

dr n. med. Le-
lek. Le-
specjalista onkolog klin.
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