Role of 18FDG Positron emission computer tomography (PET-CT) in characterization and preoperative staging of ovarian cancer

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Abstract

Ovarian cancer is a challenging disease. It often presents at an advanced stage with frequent recurrence despite optimal management. Accurate staging and restaging are critical for improving treatment outcomes and determining the prognosis. Imaging is an indispensable component of ovarian cancer management. Hybrid imaging modalities, including positron emission tomography/computed tomography (PET/CT) is emerging as potential non-invasive imaging tools for improved management of ovarian cancer.

Keywords: ovarian cancer, Positron emission computer tomography

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Epithelial ovarian cancer is one of the most common gynecologic malignant tumors, with incidence rate ranking third after corpus carcinoma and cervical cancer. Ovarian cancer has the highest mortality rate among gynecologic malignancies due to its insidious symptoms in the early stage and its characteristics that recurrence and metastases are likely to occur after the first cytoreductive surgery and chemotherapy. Seventy percent of ovarian cancer patients will suffer from recurrence and metastasis within 5 years [1].

Histogenetically, OC are classified into three major subtypes, including epithelial, stromal, or germ cell tumors (Virarkar et al., 2021). Approximately 90% of ovarian cancers have been found to be epithelial ovarian cancer (EOC) subtypes (Forstner, 2020). Surgical resection and chemotherapy are the standard treatment options [2].

Radiation therapy planning can be defined as the process of image acquisition, volume delineation, dose-fractionation prescription, assigning of treatment fields and beam modifiers, evaluation of dose distribution, and quality assurance before final approval for treatment delivery. Radiotherapy treatment planning is complex and relies heavily on imaging and computing technologies to ensure the delivery of therapeutic doses of radiation to the tumour while minimizing the amount of radiation to the adjacent healthy tissue [3].

Positron emission tomography (PET) is an advanced functional imaging modality. It is mainly used for the diagnosis, staging, prognostication, and surveillance of numerous types of oncology care. CT or MRI-based imaging are currently the main radiological techniques used [4].

A major advantage of PET functional imaging is its ability to distinguish between neoplastic and normal tissues with more accuracy than CT or MRI, which are reliant on morphological features to make this differentiation [5].

2-deoxy-2- [18 F]-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/computed tomography (CT) is very useful for detecting recurrent ovarian cancer and for identifying the patients who are more likely to benefit from secondary cytoreductive surgery [6].

A systematic review and meta-analysis of literature data have shown that pretreatment volume-based metabolic parameters of 18 F-FDG-PET can be correlated with the clinical outcome of patients with different malignancies including ovarian cancer [7].

Integrated PET/CT is superior for the detection of ovarian cancer than anatomic imaging such as CT and MRI, with the use of a metabolic tracer and simultaneous acquisition of anatomic data to determine the exact location of lesions. Moreover, compared to anatomic imaging, PET/CT is used to survey the entire body to detect recurrence in multiple sites that are crucial for further treatment planning to avoid further relapse [8].

PET/CT is not commonly used to characterize an adnexal mass, as physiologic uptake may be seen in normal ovaries, limiting its value. However, several authors have reported on the utility of PET/CT in characterization of pelvic masses. Studies show that PET CT has 81–100% sensitivity and 93–95% specificity for diagnosing malignant ovarian tumor [9].

While the above studies report the utility of PET CT in diagnosing ovarian tumors, its cost effectiveness for this purpose remains unproven. Currently, pelvic ultrasound and MR are the most commonly used imaging modality for the diagnosis and characterization of ovarian tumors.

Different Imaging Techniques in Ovarian Cancer

Most females with ovarian cancer experience non-specific symptoms (e.g. abdominal pain or discomfort, urinary frequency, weight changes). Therefore, ovarian cancer is often diagnosed on CT while searching for a cause of non-specific symptoms or to evaluate the abdomen after worrisome ultrasound findings [10].

For the primary tumors, location, size, and invasion of nearby structures can influence treatment decisions. Presence of malignant nodes can also significantly impact the treatment strategy, especially malignant suprarenal lymph nodes, which could be a contraindication for surgery. The extent of peritoneal metastases can also be a contraindication for surgery [11].

The ESMO-ESGO guidelines describe essential features that may contraindicate CRS. These are summarized in table 5; involvement of small bowels, stomach, pelvic wall, and ureter, e.g. could result in a suboptimal CRS. The T.R.U.S.T. trial investigators set criteria that contraindicate primary CRS, which are also helpful as a reference for radiologists (**Table**) [12].

For radiologists, a structured report can help to effectively communicate these important imaging findings, as shown by **(Chandramohan et al., [13]** This structured report incorporates findings relevant to estimating the FIGO stage and operability.

Table 1: T.R.U.S.T. criteria indicating a contraindication for primary CRS and triage to neoadjuvant chemotherapy [14]

Lymph node enlargement above the renal hilum (larger than 10 mm short axis)
– Tumor involvement of the stomach or duodenum
– Tumor involvement of the pancreas
– Tumor involvement of the celiac trunk, hepatic artery, gastric artery
– Extensive tumor involvement of the mesentery and/or small bowel

CRS, cytoreductive surgery.

Table 2: ESGO 2017 recommendations for contraindications for CRS [14]

- Diffuse deep infiltration of the root of small bowel mesentery
– Diffuse carcinomatosis of the small bowel involving such large parts that resection would lead to a short bowel syndrome (remaining bowel < 1.5 m)

– Diffuse involvement/deep infiltration of:
– Stomach/duodenum
– Head or middle part of the pancreas
– Involvement of coeliac trunk, hepatic arteries, left gastric artery
– Central or multisegmental parenchymal liver metastases
– Multiple parenchymal lung metastases (preferably histologically proven)
– Non-resectable lymph nodes
– Brain metastases

CRS, cytoreductive surgery.

Although CT is most commonly used to stage ovarian cancer patients, MRI and positron emission tomography (PET)-CT are increasingly used in specialized centers to stage advanced cases. These functional imaging modalities may provide additional information to determine whether a complete CRS is possible and guide further treatment [14].

- **PET-CT**
  - **Principles of ^{18}F-FDG-PET**

The basic principle of PET is that cyclotron-generated positron-emitting radiopharmaceuticals are administered to a patient intravenously. The isotopes decay to emit a neutron, a positron (positively charged electrons sometimes called a β^+ particle) and a neutrino. The positrons annihilate with electrons to produce two 511-keV photons directed approximately 180° apart. The external detectors on the PET scanner detect these photons [3].

Radiopharmaceuticals (tracers) are biologically important materials such as glucose or oxygen, which have been labelled with radionuclides such as ^{11}Carbon, ^{13}Nitrogen, ^{15}Oxygen and ^{18}Fluoride. There are many types of tracers used in PET scans (and more under investigation) depending on the organ of interest; however, ^{18}F-labelled fluoro-2-deoxyglucose (^{18}F-FDG) is the most common tracer widely used [3].

The tracer ^{18}F-FDG tracer is a glucose analogue which enters the cells via glucose transporters. It is taken up more avidly by tumours than healthy tissues due to the increased rate of glucose metabolism in tumours, and it becomes trapped inside tumour cells due to the fluorine substitution in the glucose molecule. Other tracers that depict other tumour characteristics apart from glucose metabolism include ^{18}F-Fluoro-L-dihydroxyphenylamine (^{18}F-fluoro-L-DOPA), Somatostatin-based radiotracers, ^{11}C-Choline, ^{18}F-16 β-Fluoro-5α-dihydrotestosterone (FDHT), ^{18}F-3-Fluoro-3-deoxy-thymidine (^{18}F-FLT), ^{11}C-Acetate, ^{18}F-Fluoride, and ^{11}C-Methionine [3].

  - **Initial diagnosis-differentiation between malignant and benign ovarian tumors and prognosis**

The role of [^{18}F]FDG-PET/CT for differentiating between malignant and benign ovarian tumors remains controversial, and false-negative and false-positive cases have been reported. Concerning the prognostic value of [^{18}F]FDG-PET/CT, there have been reports that a high (>13.15) pretreatment SUVmax of the primary tumor in patients with ovarian cancer was associated with a poor prognosis. The SUVmax of the primary tumor had a statistically significant association with stage ($p = 0.010$) and histology ($p = 0.001$) [15].

  - **Initial staging**

In ovarian cancer [^{18}F]FDG-PET/CT has an effective role in staging patients with advanced disease, providing useful information about extrapelvic sites, such as supraclavicular and paraaortic nodular involvement, peritoneum and omentum implants, and bone and muscle metastases. A meta-analysis, including data from

882 patients with ovarian cancer, showed that [^{18}F]FDG-PET or [^{18}F]FDG-PET/CT was a more accurate modality for detecting metastatic lymph nodes [16].

Approximately 70% of metastatic lymph nodes and 97% of negative lymph nodes could be correctly diagnosed by [^{18}F]FDG-PET or [^{18}F]FDG-PET/CT. Though significantly better than those of CT and MR imaging, the sensitivity of [^{18}F]FDG-PET or [^{18}F]FDG-PET/CT was moderate. A possible explanation is that this method can only detect lesions with sufficient malignant cells to change the glucose metabolism and that FDG uptake may not be increased in low-grade tumors [16].

The main effect of [^{18}F]FDG-PET/CT seems to be the detection of metastases outside the pelvis as it may detect distant metastasis in the liver, pleura, mediastinum, and supraclavicular lymph nodes that had been missed on CT imaging. It has been shown that [F]FDG-PET/CT may increase the pretreatment staging accuracy to 69–87% compared with 53–55% with CT alone. [^{18}F]FDG-PET/CT is particularly useful in distinguishing patients with stages IIIC–IV cancer from those with stages I–IIIB. For this classification, the specificity, sensitivity, and accuracy of [^{18}F]FDG-PET/CT was 91%, 100%, and 98%, respectively, in comparison with 64%, 97%, and 88% for CT [17].

Although fusion PET/CT shows higher staging accuracy, mostly by identifying extraabdominopelvic disease, it has not been widely adopted, as evidence that this capability alters treatment is lacking [18].

- **Radiotherapy planning**

The utility of PET/CT in ovarian cancer is still being investigated. A pilot study by [19] showed that ^{18}F-DCFPyL-PET had higher specificity than CT in detecting advanced high-grade ovarian serous carcinoma tumour sites. It detects fewer disease sites than CT, especially in the upper abdomen and the gastrointestinal tract, likely limiting its clinical utility. In ovarian cancer, published studies reported the utility of PET/CT in improving the detection of metastatic lymph nodes and recurrent disease.

In 2012, [16] published a meta-analysis carried out to compare the diagnostic performances of computed tomography (CT), magnetic resonance (MR) imaging, and positron emission tomography (PET or PET/CT) for detection of metastatic lymph nodes in patients with ovarian cancer. A total of 18 studies, with 882 patients, were included in the study, which showed that FDG-PET was more accurate than CT or MR imaging in the detection of lymph node metastases.

In a 2013 meta-analysis of 29 studies involving 1651 patients Limei et al. reported a pooled sensitivity and specificity of 89% and 90%, respectively, and concluded that PET/CT is a useful tool for predicting the diagnosis and restaging of suspected recurrent ovarian carcinoma. While PET/CT is not routinely used in clinical practice in the treatment of ovarian cancer, the 2022 NCCN guidelines endorses the use of PET/CT for post treatment surveillance and treatment planning for recurrent disease [20].

- **Restaging after treatment**

Several studies have demonstrated that [^{18}F]FDG-PET/CT-derived parameters , including SUV and percentage change, have the potential to predict response to therapy in patients with ovarian cancer **(Figure) [21].**

When an arbitrary SUV of 3.8 was taken as the cutoff for differentiating between responders and nonresponders after therapy, [^{18}F]FDG-PET/CT showed a sensitivity of 90% and specificity of 63.6%. When an arbitrary percentage change of 65% was taken as the cutoff, the sensitivity was 90% and specificity 81.8% [22].

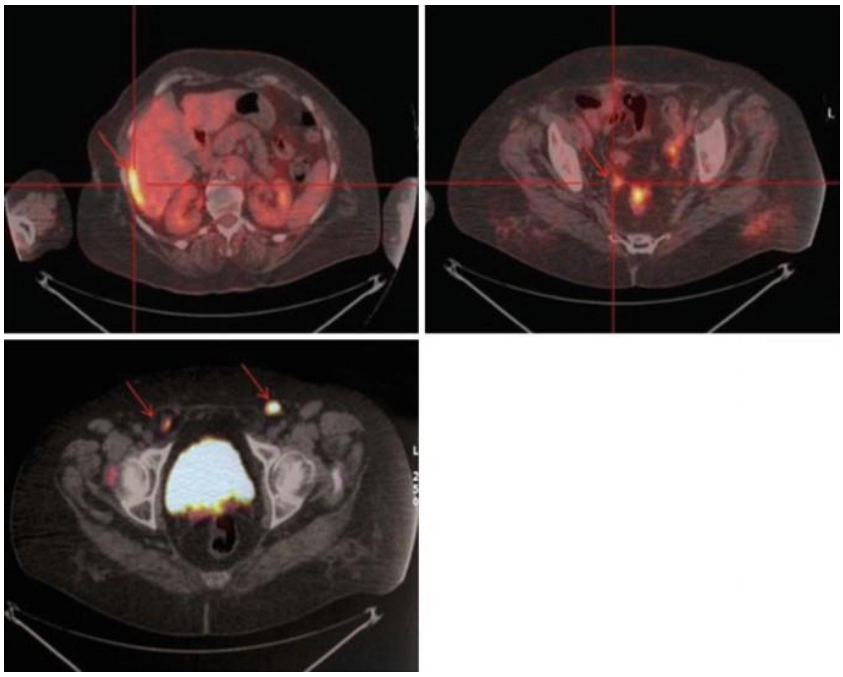

Figure 1: 78-year-old woman post-treatment for ovarian carcinoma, presenting with rising tumor serum markers and negative findings on recent CT imaging. [^{18}F]FDG-PET/CT revealed increased [^{18}F]FDG uptake in the peritoneum and in bilateral inguinal lymph nodes **[15].**

- **Tumor recurrence**

Potential advantages of the use of integrated [^{18}F]FDG-PET/CT for evaluation of recurrent ovarian cancer include increased lesion detection with the use of a metabolic tracer, simultaneous acquisition of anatomic reference points to determine the exact location of lesions, and, in most cases, differentiation of disease processes from physiologic processes [23].

Moreover, [^{18}F]FDG-PET/CT may survey the entire body in one examination. These superior qualities may help identify which patients are eligible for secondary surgical cytoreduction. There have been many reports discussing the usefulness of [^{18}F]FDG-PET/CT for detecting ovarian cancer recurrence. When the gold standard was clinical follow-up including radiological imaging, the diagnostic accuracy of [^{18}F]FDG-PET/CT was very high with 73–100% sensitivity, 71–100% specificity, and 83–100% accuracy in patient-based analysis [16].

However, when the gold standard was histopathology by surgery, the diagnostic accuracy of [^{18}F]FDG-PET/CT tended to be poorer, and it was reported that the sensitivity, specificity, and accuracy of patient-based analysis were 53–83%, 40–86%, and 63–82%, respectively. The discrepancies in these values between the clinical follow-up and the surgical histopathology as a gold standard may partly depend on the resolution of the [^{18}F]FDG-PET/CT systems used and partly on the size of microscopically small lesions. The spatial resolution of PET is approximately 6–10 mm; therefore, its sensitivity for depicting lesions smaller than 1 cm is lower than that for larger lesions **(Figure and Figure) [15].**

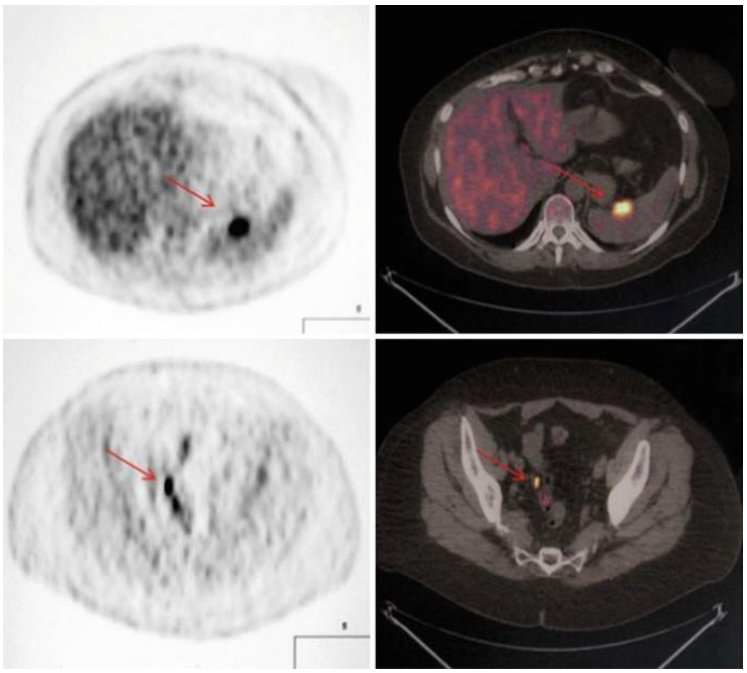

Figure 2: 52-year-old woman with a history of bilateral ovarian carcinoma presenting with slight but persistent elevation of tumor marker serum levels and negative findings on MRI imaging. [^{18}F]FDG-PET/CT revealed two [^{18}F]FDG avid lesions in the peritoneum **[15]**

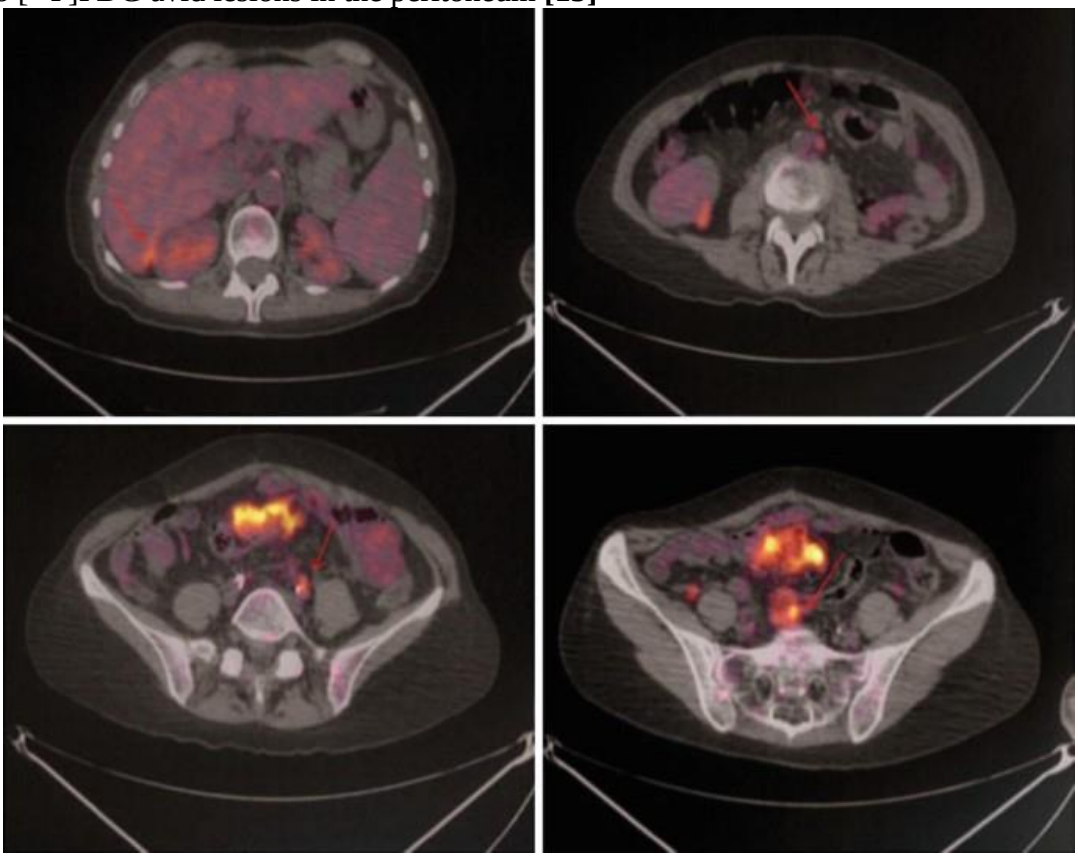

Figure 3: 66-year-old woman, status post-treatment for ovarian carcinoma, presenting with progressively elevated CA-125 antigen and negative conventional imaging evaluation. [^{18}F]FDG-PET/CT revealed several foci of increased [^{18}F]FDG uptake in the peritoneum. Abnormal metabolic activity was also present in a small left paraaortic and a small left common iliac lymph node **[15]**

Several studies and a meta-analysis have compared techniques for detection of recurrence and demonstrated that [^{18}F]FDG-PET/CT was better (sensitivity 91% and specificity 88%) than CT (sensitivity 79%, specificity

84%) or MRI (sensitivity 75%, specificity 78%). In addition, [^{18}F]FDG-PET/CT had the highest positive predictive value (89–98%) for recurrence of ovarian cancer when compared with other modalities [24] [25].

A major indication for [^{18}F]FDG-PET/CT is the evaluation of ovarian cancer recurrence after first-line therapy in patients in which CA-125 levels are rising and conventional imaging studies show negative or equivocal findings. Investigators have reported that [^{18}F]FDG-PET or PET/CT has a sensitivity of 96% for localizing recurrent disease in patients with rising CA-125 levels and that PET evidence of recurrent ovarian cancer preceded CT findings by 6 months, allowing earlier reintroduction of therapy. In accordance with the results of recent studies, [^{18}F]FDG-PET/CT has a higher predictive value than the CA125 serum marker in the detection of disease recurrence [26].

Concerning the detection of peritoneal implants, a study reported that the sensitivity and specificity of [^{18}F]FDG-PET/CT were 97.5% and 100%, whereas those of MRI were 95% and 85.7%, respectively. For the small-to-medium-sized (0.5–2 cm) peritoneal implants, diagnostic accuracy values of [^{18}F]FDG-PET/CT were significantly better than those of MRI ($p < 0.05$) [27].

As reported in the literature, the change in management of patients with ovarian cancer recurrence who have undergone [^{18}F]FDG-PET/CT ranges between 25% and 58% [15].

- **Computed tomography (CT)**

On CT imaging, ovarian cancer typically presents as thick-walled cysts with septations. The CT report should address the location, size, and invasion of nearby structures. For the nodal status, each lymph node's size, shape, and border should be evaluated. For evaluating the abdominal nodal status lymph nodes, a short axis cut-off of 1 cm is often used to detect a malignant lymph node. However, CT has a disappointing diagnostic performance for detecting malignant abdominal lymph nodes with a sensitivity of 41% and specificity of 89% [28].

This means that the decision to perform an infrarenal lymphadenectomy should not be solely based on CT imaging but also on pre-operative findings. Interestingly, for malignant cardiophrenic lymph nodes, size criteria seem to be more useful; a short-axis diameter of >7 mm had a positive predictive value of 86% [28].

The presence of malignant abdominal lymph nodes is not the only feature that is being underestimated with CT. CT also structurally underestimates the presence of peritoneal metastases. In a recent meta-analysis, CT had a pooled sensitivity, specificity, and diagnostic odds ratio for the detection of PM for region-based studies of 68% (CI, 46–84%), 88% (CI, 81–93%), and 15.9 (CI, 4.4–58.0), respectively. Especially, the involvement of gastrointestinal organs and the mesentery can be difficult to recognize on CT [29].

The presence of ascites can further impede an accurate overview of PM on CT images. However, CT seems to be relatively accurate in predicting diaphragm and omental involvement. Due to these shortcomings of CT, CT cannot accurately predict a (sub)optimal cytoreduction. Axtell et al demonstrated that CT has a sensitivity of 79% and specificity of 75% for predicting an optimal cytoreduction. Other studies showed similar disappointing results for the performance of CT for predicting surgical outcome [14].

The PCI is structurally underestimated on CT images, and therefore it is not recommended to report the PCI in the CT report. CT results should be used cautiously when deciding between primary CRS and neoadjuvant chemotherapy. However, interpreting the literature on CT in ovarian cancer is challenging because the diagnostic performance of CT features varies significantly between studies, probably reflecting variations in surgical/radiological practice, experience, and technique [14].

In current clinical practice, determining response to chemotherapy is done by subjective measures on CT images because Response Evaluation Criteria in Solid Tumors v. 1.1 (RECIST 1.1) is of limited prognostic value for ovarian cancer as it is not associated with PFS nor overall survival. Therefore, RECIST is often supplemented by serum cancer antigen 125 (CA125) response. It should be noted that neither response assessment methods should determine eligibility for interval CRS as 73% of patients with RECIST stable disease and 49% of patients with no CA125 response received complete or optimal interval CRS [30].

- **Magnetic resonance imaging (MRI)**

The characteristics of ovarian cancer on MR imaging are partly similar to CT; cystic lesions with septa and solid components. A septal or wall thickness of >3 mm, nodularity, papillary projections of >4 cm, and necrosis are features linked to ovarian cancer. Additional features of malignancy include involvement of

pelvic organs or sidewall; peritoneal disease; ascites; and lymphadenopathy. A recent meta-analysis showed that MRI had a sensitivity of 91% and specificity of 85% for the diagnosis of ovarian cancer. This means that MRI outperforms CT and PET-CT for detecting ovarian cancer. MRI dynamic contrast-enhanced and diffusion-weighted MRI may therefore be used as a second-line tool after ultrasonography to further differentiate between benign, malignant, and borderline masses [31].
However, like all imaging modalities, identifying abdominal malignant lymph nodes remains a problem for MRI with a sensitivity and specificity of 77 and 91%, respectively [32].
One of the advantages of MRI is the use of functional imaging techniques like diffusion-weighted (DWI) sequences to depict small peritoneal metastases **[33].**

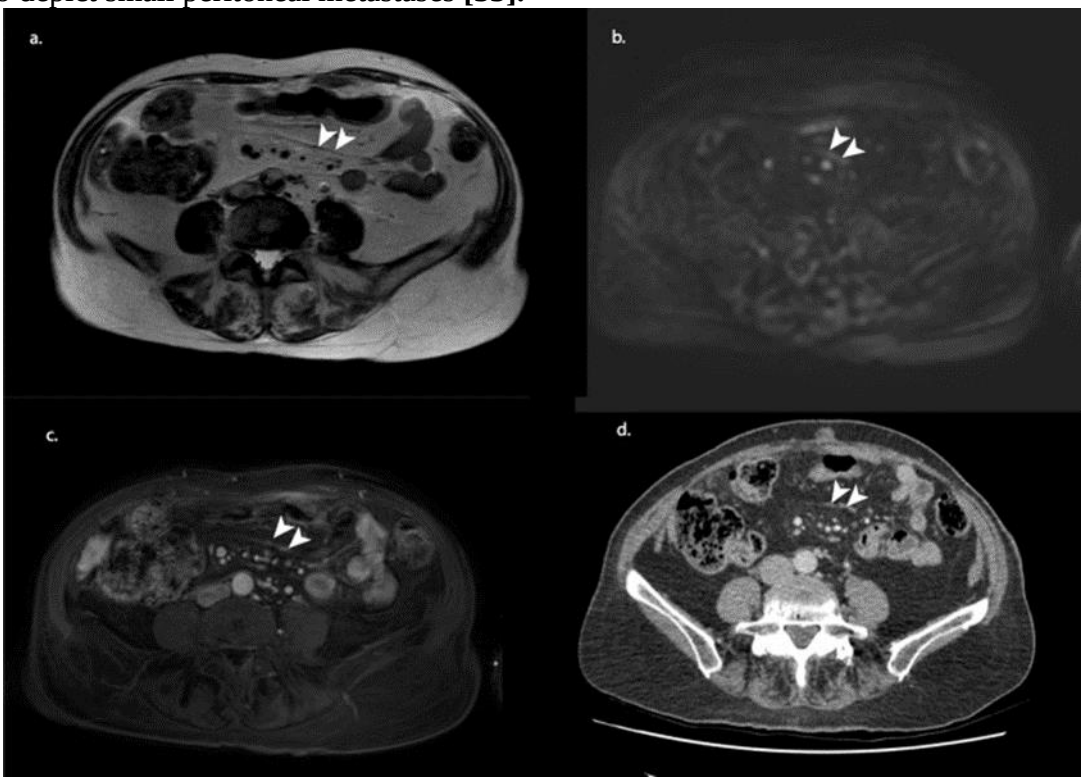

Figure 1: MRI staging example of an 80-year-old female after three courses of neoadjuvant chemotherapy. T2 weighted (a) shows a suspicious dark thickening of the mesenteries (arrowheads), which showed diffusion restriction and contract enhancement on b1000 diffusion-weighted (b) and gadolinium-enhanced T1 weighted (c) imaging. At CRS, millimetric depositions were found on the mesenteric surface. A CT of 3 weeks earlier showed a similar pattern (arrowheads); however, with CT alone, no confident distinction can be made between ascites, fibrosis or PM. Therefore, the involvement of the mesenteries was not mentioned in the original CT report. CRS, cytoreductive surgery **[14].**
Several studies demonstrate that DWI-MRI is reliable to depict and quantify peritoneal metastases using the PCI. If the ongoing large multicenter studies (MISSION and MROC) confirm these promising results than this could lead to a paradigm shift in the diagnostic work-up of ovarian cancer patient [14].
MRI could become the standard imaging tool for advanced ovarian cancer to select those patients in which a completer CRS is possible. In order to detect all small peritoneal metastases on DWI images. it is essential to avoid the high signal in normal bowels and feces. Therefore, the use of pineapple juice prior to the examination is strongly advocated. Patients need to drink at least 1 liter pineapple juice 1 h prior to the examination to make sure that its manganese content results in a low signal on DWI images within the bowels. In this way, peritoneal metastases are more easily detected on DWI images. In addition to subjective evaluation of DW-MRI, a more quantitative approach using quantitative Kurtosis variables and apparent diffusion coefficient values could help in discriminating benign and malignant ovarian lesions [34].
No concrete quantitative MR criteria are widely adopted in the daily clinic. Another advantage of MRI is that ascites does not hamper with visibility of nodular peritoneal metastases unlike CT. This might explain the

promising results of MRI in staging the peritoneal disease. In the same meta-analysis which compared CT, PET-CT, and MRI for detecting peritoneal metastases, MRI had the highest pooled regionwise sensitivity and specificity of 92 and 84%, respectively [29].

The additional value of MRI was also demonstrated in a study by **[35]** which showed that MRI was superior to CT for primary tumor characterization and staging and the prediction of whether the extent of peritoneal metastases made a suboptimal resection feasible. In this study, MRI had a sensitivity of 94%, a specificity of 97.7%, and overall accuracy of 95% for predicting a suboptimal resection.

Three other prospective cohort studies showed similar results; MRI was accurate in predicting surgical outcome, reporting area under the curves (AUCs) of 0.88–0.95 **(**Error! Reference source not found.**)**. Two multicenter studies are currently ongoing to define the role of MRI in females with advanced ovarian cancer [14].

If these studies confirm the promising results, then a paradigm shift is imminent; females with advanced ovarian cancer could be individually stratified to their appropriate treatment according to their clinical and MR risk factors [14].

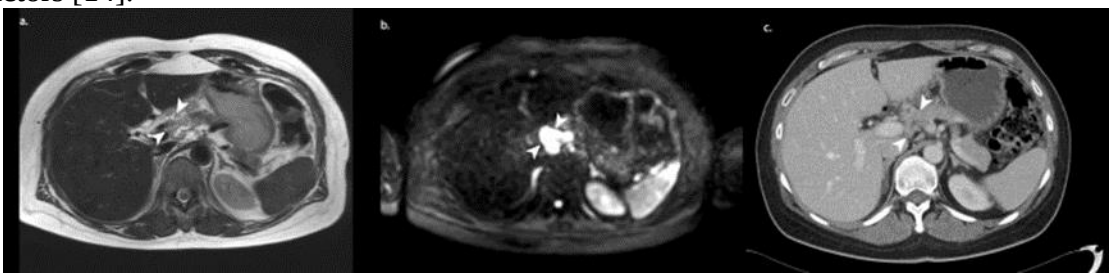

Figure 5: MRI staging example of a 56-year-old female after three courses of neoadjuvant chemotherapy. On diffusion-weighted imaging (b), a conspicuous lesion (arrowheads) is found in the area of the hepatic hilum. On T2 weighted imaging, the lesion can be distinguished as malignant. With CT (2 weeks earlier) alone, this large lesion largely "fades" into its surroundings, making it difficult to spot and was therefore not mentioned in the original CT report. This extensive disease in the liver hilum, among others, rendered the patient inoperable **[14].**

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