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Molecular Imaging and Theranostics in Ovarian Cancer: The Role of Nuclear Medicine

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Abstract: Ovarian carcinoma remains an important cause of mortality and morbidity, which tends to be diagnosed at an advanced stage due to the non-specific and generalized nature of the symptoms. In this chapter, we review the clinical significance of ovarian cancer, its current diagnosis and treatment and the evolving role of nuclear medicine in the early, non-invasive detection and further management of these patients. We also consider some of the current and future theranostic possibilities in the quest for targeted treatment with fewer systemic side effects.

Keywords: molecular imaging in ovarian carcinoma; nuclear medicine in ovarian cancer; ovarian cancer theranostics; PET/CT imaging of ovarian cancer; SPECT/CT imaging of ovarian cancer

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INTRODUCTION

Ovarian carcinoma is noted as being the most lethal gynaecological cancer (1). According to the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute, in the United States of America, Ovarian carcinoma is the 11th most common cancer in women, accounting for 2.5%, and is the 5th leading cause of cancer-related death among women (2). The American Cancer Society estimated that in 2021, it accounted for approximately 1.1% of all new cancer cases, and 2.3% of all cancer deaths (3). The relative 5-year survival rate is 49.1%, ranging from 92.6% for local disease to 27.0% for unknown extent of disease. Ovarian cancer rates are highest in the 55–64-year age group, with the median age of diagnosis being 63, and the median age of death being 70. Approximately 16% of women are diagnosed with early-stage ovarian cancer and have a much better 5-year survival rate (2, 3).

In 2014, the International Federation of Gynaecology and Obstetrics (FIGO) revised the staging to incorporate ovarian, fallopian tube, and peritoneal cancer in the same system (4). These are divided into five histological subtypes that have different identifiable risk factors, cells of origin, molecular compositions, clinical features, and treatments. The epithelial origin group accounts for approximately 90% of ovarian cancers, of which high-grade serous carcinoma (HGSC) is the most commonly diagnosed. Other rarer histologies include small-cell carcinoma, and non-epithelial ovarian cancers, including germ-cell tumours and sex cord stromal tumours (5).

RISK FACTORS

A range of genetic factors are associated with an increased risk of developing ovarian cancer. Germline BRCA1 and BRCA2 mutations are the most significant genetic risk factors for ovarian cancer and either mutation is found in up to 17% of patients. Other germline mutations in genes involved in DNA repair can increase the risk of developing ovarian cancer, including genes that are part of the Fanconi anaemia-BRCA pathway. Other inherited disorders that present with germline mutation in genes of the DNA mismatch repair system (e.g., Lynch Syndrome), can increase the risk of ovarian cancer (5). The oral contraceptive reduces the risk in individuals with a germline BRCA1 mutation, as well as in those without a genetic predisposition. Conversely, hormone replacement therapy has been shown to increase the risk of developing ovarian cancer in postmenopausal women (5). Women who have given birth have a reduced risk for ovarian cancer. Uni- or bilateral oophorectomy reduces risk in women with a genetic predisposition for ovarian cancer. Tubal ligation and hysterectomy are also associated with risk reduction (5). Obesity, other lifestyle factors such as diet and smoking, and persistent depression have been suggested, but require further investigation (5).

DIAGNOSIS

Most women are diagnosed later in life, with a median age of 63 years (2). Most women are symptomatic at presentation and have ascites and

gastrointestinal dysfunction. Other symptoms at initial presentation include abdominal bloating, abdominal and/or pelvic pain, fatigue and shortness of breath. Symptoms of ovarian cancer may initially be missed or attributed to another disease process due to their general and nonspecific nature (6). Diagnosis therefore frequently occurs when the cancer has reached an advanced stage (either stage III or IV) and the patient presents with symptom which may or may not require intervention. Importantly, these symptoms — and their late presentation — largely apply to those with HGSC. By contrast, histologies, such as clear-cell and small-cell carcinomas, can become symptomatic at an earlier stage. For example, hypercalcaemia can be the initial presentation of clear-cell or small-cell carcinomas. These tumour types are also associated with many of the same symptoms observed with more-advanced HGSC, such as abdominal distension, pelvic pressure and/or pain, as well as pressure of the ovarian mass on the bowel or urinary tract system. Most patients with clear-cell carcinoma present at an early stage and might present with symptoms related to pelvic pressure (5).

The diagnostic work-up entails physical examination (inclusive of pelvic and rectovaginal assessment) and both morphological- and molecular medical imaging. Serum carbohydrate antigen 125 (CA125) can be used in combination with other diagnostic tests for detection of ovarian cancer (5). Laparoscopic surgery with removal of the mass is recommended (7) and will also give further information on the tumour histology. Results from diagnostic testing, especially trans vaginal ultrasonography, can provide information about the ovarian mass, such as size, location, and level of mass complexity, which can help clinicians to determine the level of suspicion for cancer (8). More-advanced cancer is associated with ascites and peritoneal carcinomatosis within the abdominal cavity; to confirm a diagnosis of ovarian cancer, a tissue biopsy must be performed.

The following factors point to the presence of a malignancy and are useful in the clinical assessment of masses: Age of the patient (young for germ cell, older for epithelial malignancies); bilaterality; Tumor fixation clinically; Ascites; Ultrasonographically complex, especially if solid areas; CT finding of metastatic nodules; Elevated tumor markers. (4)

Pathological evaluation and tumour staging of ovarian cancer is based on surgical assessment of the cancer at initial diagnosis, including removal of lymph nodes, tissue biopsy and abdominal fluid, and uses the FIGO staging system (4, 5). With regards to surgical staging, it has been shown superior and more beneficial to patient outcomes when performed by a gynaecological oncologist rather than a non-oncological (general) surgeon (9–11).

SCREENING AND PREVENTION

There are currently no documented effective screening methods that reduce the mortality. Creation of a successful screening strategy is challenging because this is not a common disease and includes a range of histological subtypes, each with different biological and clinical properties (5). Studies using CA125, pelvic ultrasound and pelvic examination do not demonstrate adequate sensitivity and specificity in the general and high-risk populations (12–15). Risk-reducing bilateral salpingo-oophrectomy is noted as being the most effective prophylactic

treatment for BRCA carriers. Other measures include avoiding long-term (greater than five years) postmenopausal hormone therapy and maintaining a healthy lifestyle (16).

TREATMENT

The primary aim of treatment is to maximize cancer control and to palliate disease symptoms for as long as possible. The extent of surgery and choice of chemotherapy regimen is therefore determined by the stage of ovarian cancer and various patient factors.

Surgery

Surgery constitutes the primary treatment for ovarian cancer. It is used for staging and cytoreduction (debulking), however, if the disease is confined to the ovaries, it is a potentially curative procedure. Fertility-sparing surgery in an option in premenopausal women with early-stage ovarian cancers with a low potential for malignancy, invasive epithelial ovarian cancers, germ cell tumours, or sex cord-stomal tumours (1). Systematic pelvic and para-aortic lymph node dissection is also necessary in patients with high-risk early-stage ovarian cancer or in patients with stage II and stage IIIA disease, as nodal metastases signify a higher stage of disease, poorer prognosis, and the need for different treatment strategies (5). Defining the best surgical approach and determining the appropriateness of surgery before the administration of chemotherapy versus neo-adjuvant chemotherapy (NACT) are crucial. If NACT is to be administered, a biopsy is needed to confirm pathology consistent with an ovarian, tubal, or peritoneal primary cancer, before chemotherapy can be commenced (5).

Chemotherapy

Recommendations for the use of adjuvant chemotherapy using platinum-based chemotherapy for patients with early-stage ovarian cancer depend on the cancer stage, grade and histology. Many patients with grade I, stage I cancer are not treated with chemotherapy post-surgery, but those with higher grades (grade II or above) and/or specific histologies (such as HGSC and clear-cell carcinoma) undergo adjuvant systemic platinum-based chemotherapy. Combination regimens of platinum-based agents, taxanes, anti-angiogenic agents, and other drugs are being utilised and undergoing trials for improved patient outcomes (5, 17). There are differing schools of thought regarding neo-adjuvant chemotherapy (NACT), with some believing that it has no advantage over adjuvant therapy (1, 5). For those who implement such regimens, NACT is then followed by interval (that is, between rounds of chemotherapy) surgical cytoreduction and additional chemotherapy. NACT is a possible treatment alternative to upfront surgical cytoreduction for ovarian cancer, especially for patients who are too ill for initial surgery or if the cancer burden is too extensive to allow macroscopic complete resection (5, 17). The aims of maintenance therapy are to prolong a clinically meaningful survival end point, such as progression-free survival (PFS), and to also

preserve the quality of life of the patient. The use of maintenance therapy following platinum-based chemotherapy has been investigated and reviewed. However, owing to the risk of developing adverse effects, currently, the standard of care following completion of platinum-based chemotherapy is observation alone (5, 17).

RECURRENT DISEASE

More than 80% of patients with advanced-stage ovarian cancer will experience recurrence of their primary cancer, with a median time to recurrence of approximately 16 months (4). Recurrent ovarian cancer is generally incurable, but rare exceptions to this exist, such as patients with isolated metastatic cancer in whom the disease can be fully resected after secondary cytoreductive surgery or treatment with localized radiotherapy. Many patients with recurrent ovarian cancer are asymptomatic at the time of their relapse and, as such, recurrent ovarian cancer is most frequently detected by increased levels of CA125; the sensitivity and specificity of this test for recurrence detection range from ~60% to 94% and ~91% to 100%, respectively. CA125 levels are monitored following completion of the initial treatment, but guidelines regarding the frequency of CA125 and clinical monitoring of patients with ovarian cancer change with different guidelines (5, 18, 19).

The Society of Gynecologic Oncology recommends a review of clinical symptoms and a physical examination of patients following the initial treatment for ovarian cancer every three months with an optional CA125 test and radiographic imaging (CT, PET or MRI) in patients with suspected recurrence (such as those with an increased level of CA125, findings on clinical examination and/or suspicious symptoms) (19). Conversely, the National Comprehensive Cancer Network guidelines recommend follow-up visits every 2–4 months for two years after treatment, including the measurement of CA125 levels; radiographic imaging should be done if recurrence of ovarian cancer is suspected (16). In the following sections, we discuss the role of nuclear imaging in ovarian cancer.

MORPHOLOGICAL IMAGING OF OVARIAN CANCER

Transvaginal ultrasonography (TVUS) combined with power Doppler is the imaging procedure of choice for evaluation of the origin, location, and benign or malignant features in patients presenting with adnexal masses. The suspicion of malignancy on TVUS increases in masses with thick irregular walls, presence of papillary projections and solid echogenic foci, the presence of ascites, peritoneal nodules and tumour neovascularity within solid masses (20). MRI and contrast enhanced CT (CECT) provide an added value in patients with indeterminate lesions on ultrasonography.

CT of the chest, abdomen, and pelvis is the preferred imaging procedure for presurgical evaluation and staging of ovarian cancer with a good specificity; however, the sensitivity for identifying small peritoneal metastases is poor especially for lesions smaller than 1cm where the sensitivity is 25–50%. CECT also has a lower sensitivity for detection of recurrent micro-metastases within normal-sized

lymph nodes (21) and has a high false negative rate of detection of tumour in the small bowel mesentery, subdiaphragmatic space, and porta hepatis (22). CECT also has a role in delineating enhancing components within adnexal masses and detection of peritoneal tumour spread and is usually performed to define the extent of peritoneal disease and to evaluate for distant spread.

MRI is more useful in the detection of disease implanted along the peritoneal surfaces and bowel serosa; however, MRI is of limited the detection of recurrent lesions or metastatic deposits on visceral surfaces especially when post-surgical changes are present (23).

^{18}F-FDG PET/CT

^{18}F-FDG PET imaging is infrequently used at initial diagnosis. It has particularly limited use in premenopausal women due to a high frequency of false positives; however, in a post-menopausal woman the presence of FDG uptake raises the suspicion for ovarian cancer (24). PET imaging has limitations in the detection of small-volume and diffuse miliary peritoneal disease due to individual lesion size and physiological tracer accumulation in the bowel and the bladder. PET is typically reserved for indeterminate lesions on CT/MR that would preclude primary surgery or in suspected recurrence. ^{18}F-FDG PET also has a lower sensitivity in detection of primary or recurrent mucinous carcinoma which often does not demonstrate tracer uptake.

Staging

Ovarian cancer staging is based on surgical and pathologic findings; none of the imaging modalities provides conclusive ovarian cancer staging however imaging helps determine the surgical approach and in the selection of patients who would benefit from neoadjuvant therapies (25). Preoperative assessment of peritoneal metastases remains an important factor for treatment planning and selection of candidates for cytoreductive surgery (CRS) in primary advanced stage (FIGO stages III–IV) epithelial ovarian cancer (26). Diffusion weighted (DW)-MRI has a higher diagnostic accuracy in the staging of patients with high tumour burden than FDG PET/CT; however, both ^{18}F-FDG PET and DW-MRI cannot replace presurgical exploration in the detection of peritoneal disease extent.

^{18}F-FDG-PET/CT is superior to CECT for the detection of carcinomatosis in subdiaphragmatic peritoneal surfaces and in the bowel mesentery in advanced ovarian cancer (27). ^{18}F-FDG PET/CT examination can provide more accurate information on preoperative staging and surveillance for detecting recurrent high grade ovarian cancer. However due to its high false negative rate for microlesions or cystic lesions, surgical staging is still performed even when ^{18}F-FDG-PET/CT is negative.

^{18}F-FDG PET/CT can provide important prognostic information for patients with ovarian cancer both at diagnosis and at relapse. A significant correlation has been demonstrated between glucose uptake measured by SUVmax of the primary tumour and FIGO classification, as well as the tumour stage, histology (serous vs non-serous carcinoma), presence of nodal or distant metastasis, and poorer

prognosis with a significantly different overall survival (OS) rate between patients with high tracer accumulation (characterized by a SUVmax >13.5) and compared to those with less avid FDG uptake of the primary tumour (28). In a metanalysis, volume-based parameters of ^{18}F-FDG PET/CT were shown to be effective in predicting PFS and OS, patients with a high metabolic tumour volume (MTV) or Total lesion glycolysis (TLG) were at higher risk of disease progression or death (29). Also, the presence of a ^{18}F-FDG PET/CT avid lymph node involvement predicted an increased risk of progression, irrespective of its site (30).

Monitoring response to therapy

^{18}F-FDG PET using EORTC or PERCIST criteria is useful in detecting early tumour response and precedes tumour markers response by 1 month and can also predict second-look surgery outcome and survival (31). FDG PET can predict the outcome after the first cycle of neoadjuvant chemotherapy early, a decrease of >20% in SUVmax after the first cycle of chemotherapy and >55% after the third cycle were found to correlate significantly with overall survival (32). FDG PET CT is superior to morphological imaging in assessing treatment response as molecular imaging with FDG PET identifies residual viable tumour whereas inflammatory lymph nodes or scar tissue may be misinterpreted as residual disease on morphological imaging (Figure 1).

Restaging

The most significant and independent prognostic factor of OS in ovarian cancer patients is the absence or residual disease after primary surgery (28). A positive restaging PET/CT was found to be associated with poor prognosis, and peritoneal spread demonstrated by PET/CT was a significant independent predictor of poor prognosis (33). Moreover, a negative PET/CT has a high negative predictive value (NPV) for the presence of disease and is associated with a very good disease-specific survival rate (Figures 2 and 3).

Suspected recurrence

Ovarian cancer is usually diagnosed at advanced stages. Therefore, it has a poor prognosis, despite effective treatment and complete disease response, recurrence is seen in 50–80% of patients. CA125 levels are the often used for early detection of ovarian carcinoma recurrence with a very high positive predictive value (PPV); however, CA125 is limited by its low specificity and poor sensitivity for small volume disease. In addition, CA125 is not specific for ovarian cancer and is also expressed in other malignant tumors, including lung cancer, colorectal cancer, endometrial cancer, breast cancer, and lymphoma as well as benign pelvic conditions, such as adnexal cyst, endometriosis, uterine fibroids, and pelvic inflammatory disease (34). Also, even though a raised serum CA125 suggests the presence of disease, it gives no information about the location, number, and size of metastatic foci.

PET/CT imaging with ^{18}F-FDG has a very high sensitivity rate of 85–100% for detection of recurrence in ovarian cancer (Figure 3), compared to CECT ^{18}F-FDG

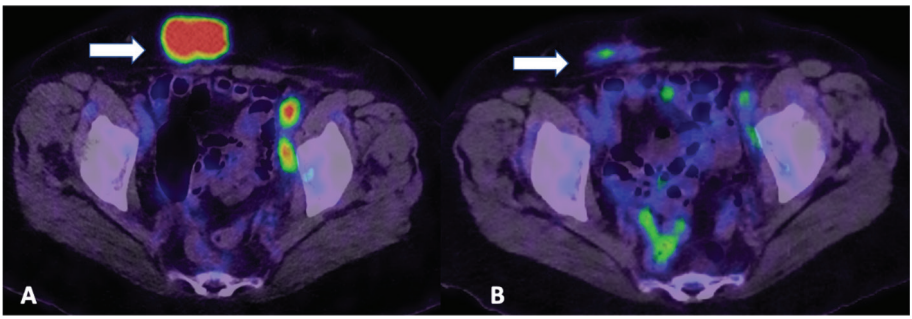

Figure 1. Treatment response evaluation. ^{18}F-FDG PET/CT images obtained from a 68-yr-old patient with recurrent ovarian carcinoma for assessment of treatment response. Image A demonstrates an intensely FDG-avid metastatic abdominal mass on pre-treatment FDG PET/CT, with significant post-treatment improvement noted on Image B.

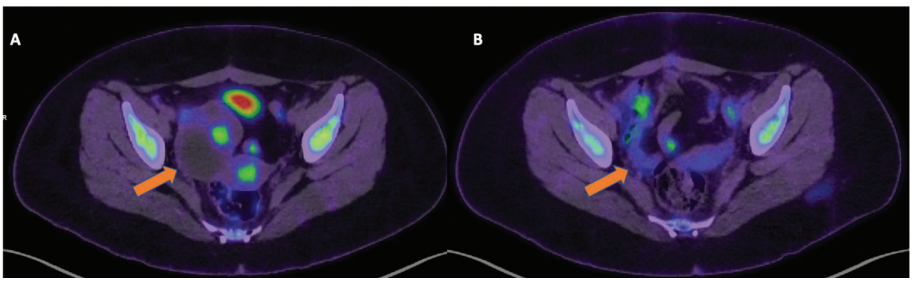

Figure 2. Restaging. FDG PET/CT images obtained from a 19-yr-old patient with atypical serous ovarian carcinoma referred for restaging following a unilateral oophorectomy and a cystectomy. Image A demonstrates a right-sided malignant ovarian tumor with focal areas of increased FDG accumulation on pre-treatment FDG PET/CT, which demonstrates significant post-treatment improvement in Image B.

is more sensitive and more specific; with a sensitivity 91% vs. 84% for CECT and specificity of 91% vs. 65% (35). In addition, ^{18}F-FDG PET/CT gives information about the extent and location of disease which helps in deciding the best treatment approach (23). In comparison to CA-125, CECT, and MRI, FDG PET/CT showed a better sensitivity in detecting ovarian cancer recurrence and distant spread (28); in addition, ^{18}F-FDG PET/CT can identify recurrence earlier before morphological changes occur, because recurrence is characterized by hypermetabolism (36). ^{18}F-FDG PET/CT upstages patients which leads to change in management of a significant proportion of patients by detecting extra-abdominal metastases or sites of diseases anatomically inaccessible for cytoreductive surgery. In a study by Fulham et al., surgery was avoided in 54% of patients who were initially candidates for surgery before the PET/CT; chemotherapy was added to the treatment of 16% and avoided in 13% (37). ^{18}F-FDG PET/CT impacts management by allowing for the selection of the most appropriate treatment and avoids the morbidity and mortality as well as cost associated with the invasive procedure.

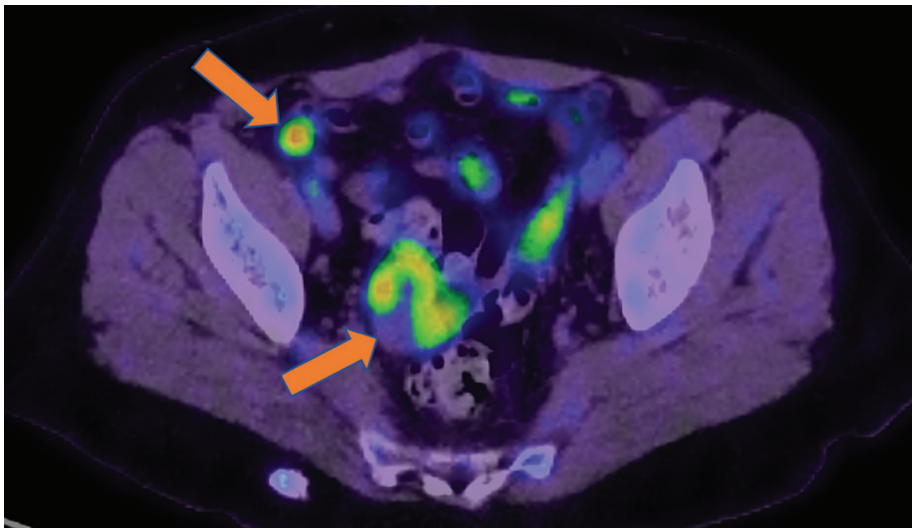

Figure 3. Restaging. ^{18}F-FDG PET/CT images obtained from a 69-yr-old patient with Stage IIIC ovarian carcinoma, post debulking surgery and completion of 3rd line chemotherapy, referred for restaging (in the absence of baseline imaging). Arrows indicate the metabolically active primary ovarian tumor in the right adnexa and a right-sided metastatic iliac lymph node.

Normal CA125 levels cannot exclude disease relapse, and it has been demonstrated that, among patients with ovarian cancer said to be in complete clinical remission, a progressive low-level increase in serum CA125 levels is strongly predictive of disease recurrence. FDG PET/CT had a 90.9% detection rate for recurrent ovarian cancer in a group of patients with low-level increased serum CA125 levels (33). In addition, FDG PET/CT is able to detect recurrence early, before elevation in CA125 and morphological changes on NECT, in a study where symptomatic patients were followed up due to suspected recurrence despite normal CA125 and negative CECT results but with positive PET/CT results (initially considered false positive results) were confirmed to have recurrence 2 years later.

Radiotherapy planning

Intensity-modulated radiation therapy (IMRT) provides ideal dose distribution to the clinical target volume (CTV) while reducing the dose to adjacent normal tissue, thereby enhancing the effects of radiotherapy and decreasing complications. However, in recurrent disease, reported local relapse rates after CT-based IMRT are still high, due to geographic misses. Recurrent lesions of ovarian cancer often lie on the surface of the colon and rectum, sigmoid mesocolon, perirectal tissues, bladder, and cul-de-sac and present as minimal nodularity on CT scan which is often missed as it is difficult to distinguish from adjacent organs. In addition, some small lymph node metastases may be missed due to their size whereas FDG PET/CT can detect foci of disease even in normal size lymph nodes.

In a study by Du et al comparing CT and FDG PET/CT-based radiotherapy planning, changes in gross tumour volume (GTV) delineation were found in 7 patients (35%) based on FDG PET/CT information compared with CT data (38). In these patients, the average increase in GTV was 21.6%, due to the incorporation of additional lymph node metastases, minimal recurrent nodularity, and extension of the metastatic tumour beyond that defined by CT. Thus ^{18}F-FDG PET/CT has a role in radiotherapy planning as it allows for more accurate estimation of the GTV to be targeted compared to CECT, better target delineation, results in the better therapeutic response and less toxicity of the treatment received to adjacent normal tumours. In the following sections, we describe various PET tracers.

^{11}C Methionine in ovarian cancer

C-11 methionine (MET) is most widely studied amino acid tracer, whose uptake in tumours is mediated by neutral L-amino acid transporters to meet the demand of accelerated protein and RNA synthesis in malignant tumours (39). Yoshikawa et al. compared ^{18}F FDG PET/CT with ^{11}C Methionine in 18 patients with ovarian cancer, MET showed similar sensitivity (92.9%) and specificity (75%) as ^{18}F FDG PET however ^{11}C MET was limited in the detection of liver lesions due to high physiological tracer accumulation in liver tissue (40). Moreover, the diagnostic accuracy of FDG and MET PET were superior to conventional imaging modalities such as CT or MRI.

[^{18}F] 3′deoxy-3-fluorothymidine (FLT) in ovarian cancer

^{18}FLT is a radiolabelled analogue of thymidine that has been used for imaging tumour cell proliferation in humans. ^{18}FLT is retained in proliferating tissues through the activity of the enzyme thymidine kinase-1 (*TK-1*), which phosphorylates ^{18}FLT to ^{18}FLT-5 phosphate, trapping it within the cell (41). In a pilot study of 6 patients who were imaged with^{18}FLT, Scott et al. found a positive correlation between tracer accumulation and the Ki67 proliferation index. Low grade uptake was seen in benign disease processes likely due to increased proliferation of lymphocytes at sites of inflammation as well as increased perfusion and vascular permeability in other benign disease processes.

^{68}Ga- fibroblast activation protein inhibitor (FAPI)

Fibroblast activation protein (FAP) is a type II serine protease that is expressed by cancer-associated fibroblasts (CAFs), which are part of the stroma in many tumours promoting cancerous growth and are associated with poor prognosis. Dendl et al. evaluated 31 patients with gynaecological malignancies with ^{68}Ga-FAPI PET/CT of which 9 had ovarian cancer, there was high tracer uptake resulting in sharp contrasts in primary and metastatic lesions and higher TBRs than ^{18}F-FDG-PET/CT. In addition, ^{68}Ga-FAPI uptake was not seen in normal ovaries (42).

^{68}Ga Pentixafor

Pentixafor is a peptide that targets chemokine receptor 4 (CXCR4), which is overexpressed in the tumour micro-environment and promotes tumour growth,

metastasis, angiogenesis, and cancer cell-microenvironment interaction (43) and is associated with more aggressive tumour behaviour and poorer prognosis. CXR4 is expressed in ovarian cancer primary tumours and its ligand CXCL 12 is expressed in the ascitic fluid (44). In a meta-analysis of 7 studies, it was shown that CXCR4 expression correlated with more advanced disease and poorer overall survival (45). ^{68}Ga Pentixafor has been shown to avidly accumulate in solid tumours including ovarian cancer (46). There may be potential to target ovarian cancer with therapies targeting CXCR4 such as CXCR4 antagonists and ^{177}Lu Pentixather.

THERANOSTICS IN OVARIAN CANCER

The current standard of care for the treatment of ovarian carcinoma consists mainly of cytoreductive surgery in conjunction with platinum-based chemotherapy and taxanes. Although this therapeutic strategy has been shown to improve both progression-free- and overall survival, the chemotherapy-related toxicity is not insignificant. Nephrotoxicity and neurotoxicity are important adverse effects and resistance and recurrence still occur in many patients despite these treatment strategies. An unmet need therefore remains for a treatment modality that targets tumour and metastatic involvement in the absence of significant systemic side effects.

It would be valuable to have a way of evaluating whether the intended treatment approach is likely to succeed or not, prior to its administration. Baseline imaging could potentially be acquired by selecting tracers that detect the specific pathological entities to be targeted by the chosen treatment modality. Examples include imaging of angiogenesis, HER2neu expression, Fibroblast Activation Protein expression and likely platinum biodistribution. The following section provides a brief outline of some of the most interesting current and future theranostic approaches, which is by no means exhaustive.

^{195}Pt-Cisplatinum

In a phase 0 pilot study that consisted of 10 healthy volunteers, Zeevaart and colleagues evaluated the normal biodistribution of 195Pt-Cisplatinum. The researchers found that blood and urine values varied widely amongst participants, reflecting the differences in individual metabolism. Most of the urinary tracer excretion occurred in the first 5 hours and this initial time period was integral to determining the fate of cisplatinum in a particular patient. They produced a GMP-compliant product that was well tolerated by all participants. The authors highlighted that imaging of cisplatinum could potentially be used as a tool to individualise patient doses. In addition, it could potentially serve to predict resistance to platinum and to avoid futile treatment with its significant associated costs and adverse effects (47).

^{131}I-labeled monoclonal antibodies/ anti-CEA

Crippa et al. investigated the use of 131I-Mov 18 monoclonal antibody in a group of 30 patients with ovarian cancer. They divided the patients in two groups and

compared the IV route (n=20) to the intra-peritoneal route (n=10). Although the intra-peritoneal route of administration resulted in a higher tumour uptake, with an improved target to background ratio, they also reported occasional persistent, non-specific pelvic tracer accumulation. Diagnostic sensitivity was 73% with a specificity of 100% and no significant differences were detected when comparing the two routes of administration. Sensitivity and specificity for abdominal- and pelvic lesions were unfortunately significantly lower as demonstrated in previous studies. The authors commented that 131I-Mov 18 provided an interesting monoclonal antibody option for radio-immunotherapy of ovarian cancer. They suggested that the intra-peritoneal route was not necessarily advantageous in the diagnostic setting (considering its invasive nature), but that it could potentially provide an advantage in the therapeutic setting (48).

The production of CEA by epithelial ovarian cancer provides another attractive theranostic target, which has been investigated by several groups. In a phase 1 trial involving 14 patients with refractory epithelial ovarian cancer, Juweid et al administered escalated doses of I-131-labeled anti-CEA monoclonal antibodies in a theranostic approach, where CEA expression was established with a preceding diagnostic scan. No dose-limiting toxicity was observed up to a dose of 40 mCi/m^2. Although the sample size was insufficient to convincingly demonstrate a therapeutic advantage, the authors suggested that 131-I-MN-14 IgG provided a suitable imaging approach in ovarian cancer. A theranostic approach could potentially translate into a therapeutic advantage for chemo-refractory patients, especially in those with limited or microscopic disease involvement. Possibilities for the therapeutic radionuclide partner include Y-90 and Re-186 in addition to I-131 (49).

^{99m}Tc-MIBI

In a small study by Kurata et al, eleven patients with a clinical suspicion of ovarian carcinoma were evaluated pre-operatively with the aim of detecting multi-drug resistant (MDR)- and apoptosis-related proteins. Patients were imaged with ^{99m}Tc-MIBI at two time points (10 mins and 2 hrs) from which a washout percentage was calculated. MDR- and apoptosis-related proteins were assessed in all surgically excised tumours and quantified with immunohistochemistry staining. Six patients were definitely diagnosed with ovarian cancer post-laparotomy and 5 of these demonstrated MIBI uptake on both the early- and the delayed images. The authors concluded that the MIBI washout rate could significantly be correlated to YB-1 and Bax expression. This could potentially have important clinical implications in prioritizing patients for chemotherapy in order to avoid likely treatment failure (50).

^{131}I-trastuzumab

Another potential target for a theranostic approach, is the expression of HER-2, which is overexpressed in a number of ovarian cancer cells (including serous, mucinous and clear cell epithelial). Trastuzumab is a monoclonal antibody that targets the extracellular domain of HER2/neu protein to inhibit the proliferation of ovarian cancer cells. Labelling to ^{177}Lu/ ^{22}Th for therapeutic application,

has been linked to tumour cytotoxic effects in pre-clinical studies. Iodine-131 provides another attractive label with its beta- and gamma emissions that enables both imaging and treatment. A recent publication by Deng et al illustrates the proof of principle both in vitro and in vivo, confirms sufficient tumour uptake and cell death by apoptosis. As such, ^{131}I-trastuzumab provides an attractive theranostic possibility for ovarian cancer with over-expression of HER-2 (51).

^{177}Lu-labelled anti-L1 cell adhesion molecule (L1CAM) monoclonal antibody

Lindenblatt and colleagues evaluated the use of ^{177}Lu-labelled anti-L1 cell adhesion molecule (L1CAM) monoclonal antibody chCE7 in combination with Paclitaxel in an animal model of ovarian cancer. The researchers demonstrated improved overall survival by the addition of Paclitaxel to radionuclide therapy with negligent toxicity and concluded that this therapeutic combination could potentially benefit patients with ovarian cancer, especially those with malignant ascites (52).

^{211}At-monoclonal murine antibody fragments

Treatment with an alpha emitter, such as astatine, offers the opportunity to treat small metastatic lesions, such as peritoneal metastases, without significant radiation to neighbouring tissues or systemic toxicity. In a phase 1 study involving 12 participants by Hallqvist and colleagues, ^{211}At was labelled to fragments of a mouse monoclonal antibody (MX35). The therapeutic radionuclide was administered via the intraperitoneal route to patients with relapsed ovarian cancer in escalating doses. The median overall survival was 35 months and mostly low-grade toxicity was reported (53).

^{99m}Tc/^{188}Re-FAPI

In a recent study, Lindner et al. evaluated the use of SPECT imaging with ^{99m}Tc-FAPI in combination with ^{188}Re as the therapeutic partner in this novel theranostic approach. They identified FAPI-34 as the peptide with the best potential for SPECT imaging with high target to background contrast and fast clearance. Possible therapeutic partners include ^{90}Y-FAPI-46 or ^{188}Re, which could potentially benefit patients with ovarian cancer (54).

Other possibilities

Various additional imaging strategies involving the visualization of major role players in the selection of the most appropriate chemotherapeutic agent, such as the expression of NIS (55), vascular cell adhesion molecule-1(VCAM-1), IL-6 (56, 57) and others have been reported. These imaging modalities could potentially play an important role in selecting the most appropriate next treatment, with the highest likelihood of a favourable treatment response and in the subsequent evaluation of treatment response.

CONCLUSION

Ovarian cancer remains an important cause of morbidity and mortality worldwide and is unfortunately often detected only when the disease has already progressed to an advanced stage. To date, there is no feasible screening strategy and practice guidelines recommend a combination of imaging modalities that depends on the clinical setting. ^{18}F-FDG PET/CT has the greatest potential to add value and change patient management in the clinical settings of suspected disease recurrence, disease prognostication, treatment response evaluation and radiation treatment planning. Promising future tracers for PET imaging include ^{11}C Methionine, ^{18}F-FLT, ^{68}Ga-FAPI and ^{68}Ga-Pentixafor. Current therapeutic options offer modest survival benefits with significant side effects, creating the need for improved, effective personalised targeted therapies. A significant advantage could be obtained by imaging prior to administering the planned targeted therapy in order to assess the likelihood of a positive treatment response. Possibilities for such personalised theranostic approaches include ^{195}Pt-Cisplatinum, ^{131}I-labeled monoclonal antibodies/ anti-CEA,^{131}I-trastuzumab, ^{99m}Tc/^{188}Re-FAPI, ^{177}Lu-anti-L1 cell adhesion molecule (L1CAM) monoclonal antibody and ^{211}At-based therapies.

Conflict of Interest: The authors declare no potential conflicts of interest with respect to research, authorship and/or publication of this manuscript.

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