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GUIDELINES

# EANM guideline on the role of 2-[$^{18}$F]FDG PET/CT in diagnosis, staging, prognostic value, therapy assessment and restaging of ovarian cancer, endorsed by the American College of Nuclear Medicine (ACNM), the Society of Nuclear Medicine and Molecular Imaging (SNMMI) and the International Atomic Energy Agency (IAEA)

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## Abstract

In most patients with ovarian carcinoma, the diagnosis is reached when the disease is long past the initial stages, presenting already an advanced stage, and they usually have a very bad prognosis. Cytoreductive or debulking surgical procedures, platinum-based chemotherapy and targeted agents are key therapeutic elements. However, around 7 out of 10 patients present recurrent disease within 36 months from the initial diagnosis. The metastatic spread in ovarian cancer follows three pathways: contiguous dissemination across the peritoneum, dissemination through the lymphatic drainage and, although less importantly in this case, through the bloodstream. Radiological imaging, including ultrasound, CT and MRI, are the main imaging techniques in which management decisions are supported, CT being considered the best available technique for presurgical evaluation and staging purposes. Regarding 2-[$^{18}$F]FDG PET/CT, the evidence available in the literature demonstrates efficacy in primary detection, disease staging and establishing the prognosis and especially for relapse detection. There is limited evidence when considering the evaluation of therapeutic response. This guideline summarizes the level of evidence and grade of recommendation for the clinical indications of 2-[$^{18}$F]FDG PET/CT in each disease stage of ovarian carcinoma.

**Keywords** Ovarian cancer · Imaging · PET/CT · $^{18}$F-FDG · Guideline · Clinical indications

## Abbreviations

| | |
|---|---|
| 2-[$^{18}$F]FDG | 2-[$^{18}$F]Fluoro-2-deoxy-D-glucose |
| AOC | Advanced ovarian cancer |
| BOT | Borderline ovarian tumour |
| CEA | Serum carcinoembryonic antigen |
| CT | Computed tomography |
| ceCT | Contrast-enhanced computed tomography |
| EOC | Early-stage ovarian carcinoma |
| EORTC | European Organisation for Research and Treatment of Cancer |
| ESMO | European Society of Medical Oncology |
| ESGO | European Society of Gynaecological Oncology |
| FIGO | International Federation of Gynaecology and Obstetrics |
| IAEA | International Atomic Energy Agency |
| IOTA | International Ovarian Tumour Analysis group |
| LBM | Lean body mass |
| LGSC | Low-grade serous carcinoma |
| PCI | Peritoneal cancer index |
| PET | Positron emission tomography |
| MATV or MTV | Metabolic active tumour volume |
| MRI | Magnetic resonance imaging |
| sBOT(s) | Serous borderline ovarian tumour(s) |

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| | |
|---|---|
| SUL | Standardized uptake value using lean body mass (LBM) |
| SUV | Standardized uptake value |
| TAUS | Transabdominal ultrasound |
| TLG | Total lesion glycolysis |
| TVUS | Transvaginal ultrasound |
| US | Ultrasound or echography |
| VOI | Volume of interest |
| WHO | World Health Organization |

## Preamble

The European Association of Nuclear Medicine (EANM) is a professional non-profit medical association that facilitates communication worldwide among individuals pursuing clinical and research excellence in nuclear medicine. The EANM was founded in 1985.

These guidelines are intended to assist practitioners in providing appropriate nuclear medicine care for patients. They are not inflexible rules or requirements of practice and are not intended, nor should they be used, to establish a legal standard of care.

The ultimate judgement regarding the propriety of any specific procedure or course of action must be made by medical professionals taking into account the unique circumstances of each case. Thus, there is no implication that an approach differing from the guidelines, standing alone, is below the standard of care. To the contrary, a conscientious practitioner may responsibly adopt a course of action different from that set out in the guidelines when, in the reasonable judgement of the practitioner, such course of action is indicated by the condition of the patient, limitations of available resources or advances in knowledge or technology subsequent to publication of the guidelines.

The practice of medicine involves not only the science but also the art of dealing with the prevention, diagnosis, alleviation and treatment of disease.

The variety and complexity of human conditions make it impossible to always reach the most appropriate diagnosis or to predict with certainty a particular response to treatment. Therefore, it should be recognized that adherence to these guidelines will not ensure an accurate diagnosis or a successful outcome. All that should be expected is that the practitioner will follow a reasonable course of action based on current knowledge, available resources and the needs of the patient to deliver effective and safe medical care. The sole purpose of these guidelines is to assist practitioners in achieving this objective.

## Introduction

In most patients with ovarian carcinoma, the diagnosis is reached when the disease is long past the initial stages, presenting already an advanced stage, and they usually have a very bad prognosis. Radiological imaging, including ultrasound, CT and MRI, are the main imaging techniques in which management decisions are supported. Regarding 2-[$^{18}$F]FDG PET/CT, the evidence available in the literature demonstrates efficacy in primary detection, disease staging and establishing the prognosis and especially for relapse detection. There is limited evidence when considering the evaluation of therapeutic response. This guideline summarizes the level of evidence and grade of recommendation for the clinical indications of 2-[$^{18}$F]FDG PET/CT in each disease stage of ovarian carcinoma.

## Background

### Epidemiology

Worldwide data shows that ovarian tumours are among those with high incidence (seventh largest) and are responsible for a high number of cancer-related deaths (eighth highest) [1–3]. Although global incidence rates remain stable over time, in some Eastern Europeans countries, its incidence is the highest [1], and in South-Central Asia, this tumour is the third cause in cancer-related deaths [4]. Globally, 295,400 estimated new cases and 184,800 cancer-related deaths were described in 2018. In the USA, based on the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program statistics for 2017 [4], there were 11.7 new ovarian cancer cases per 100,000 women per year, and there were 7.4 ovarian cancer-related deaths per 100,000 women per year. The European Cancer Information System estimated 45,694 new cases with 32,250 deaths from ovarian cancer in 40 European countries for the year 2018 [5].

Moreover, the survival of the patients is highly impacted by the staging. A recent study based on SEER's database showed a dramatic difference in the 5-year survival of patients with localized disease in comparison to patients with distant dissemination (88.5% versus 37.4%, respectively) for those diagnosed in 2010–2014, being even more impressive in women diagnosed in the 1990s [6].

### Pathology

An epithelial origin is present in over 90% of malignant ovarian tumours. This pathologic type includes different histologic non-homogeneous types. Traditionally, pathologists have classified ovarian carcinoma into the following subtypes:

- Serous: it represents the most frequent type of advanced ovarian cancers (70–80%).

- Endometrioid: account for around 10–20% of ovarian cancers.
- Clear-cell: account for around 5–10% of ovarian cancers.
- Mucinous.
- Transitional cell.
- Mixed epithelial tumours.
- Undifferentiated tumours.

Borderline tumours represent a grey area, neither benign nor malignant, and account for 10–15% of ovarian tumours.

Regarding the frequency of the mentioned subtypes, there are huge differences when comparing early-stage tumours (clear predominance of non-serous subtypes) and advanced stage tumours (predominance of serous subtype) [7].

When analysing together the histopathology and molecular genetics, ovarian tumours are currently classified in 5 categories: high-grade serous (70%), endometrioid (20%), clear-cell (10%), mucinous (3%) and low-grade serous carcinomas (< 5%). The 5 categories represent clearly different tumours, with different genetic risk factors, epidemiological differences, differences in premalignant or precursor lesions, different spreading patterns, response to chemotherapy and prognosis. Moreover, a relevant proportion of tumours that were classified as primary ovarian carcinomas (especially serous, endometrioid and clear-cell carcinomas) were in fact primary tumours of the fallopian tube and the endometrium, affecting in a second stage the ovary [8].

The last revision of the ovarian cancer World Health Organization (WHO) classification dates back 2014. Both the WHO classification (categorizing histopathologic and molecular tumour types) and the International Federation of Gynaecology and Obstetrics (FIGO) classification (classifying different tumour stages) are the basis of the therapeutic management decisions and the most precise when evaluating prognosis.

Regarding molecular genetics, BRCA1 and BRCA2 (abbreviation for BReast CAncer gene) are tumour suppressor genes that impact the chances of developing cancer, helping repair DNA disruptions that can lead to cancer and the uncontrolled growth of tumours. TP53 mutations are identified in most (96%) high-grade serous carcinomas. Early p53 loss followed by BRCA loss generates deficiency in homologous recombination repair, which in turn sets off chromosomal instability and extensive somatic copy number changes. This is an example of recent advances in molecular pathology, which have greatly improved the understanding of the biology of ovarian carcinomas and evolved patient management [9].

## Patterns of spread

Metastatic spread in ovarian cancer typically follows three different routes: (a) by contiguity to the peritoneum, (b) lymphatic dissemination and (c) haematogenous dissemination.

- Dissemination by contiguity in ovarian cancer makes the peritoneum the most affected tissue because in normal conditions the circulation of peritoneal fluid carries ovarian cells. In the first step, the primary ovarian tumour liberates malignant cells into the peritoneum, where these cells are incorporated into the peritoneal fluid normal flow inside the peritoneal cavity that takes them towards the upper abdominal quadrants. The normal physiology of the peritoneal fluid flow is based on the changes in the subphrenic pressures generated due to the respiratory movements, oscillating between the negative and positive values. These pressure oscillations drive the peritoneal fluid from the paracolic channels cranially to the right subhepatic area and the right subdiaphragmatic area [10]. Ovarian cancer typically disseminates by contiguity to the greater omentum, paracolic channels, Douglas' pouch, perihepatic region (particularly affecting the glissonian capsule), diaphragmatic and bowel surface and, less frequently, mesentery, splenic surface, porta hepatis and gastrosplenic ligament. Macroscopically, peritoneal involvement usually presents as nodules, fusiform lesions or plaques consisting of soft tissue and affecting the peritoneal (parietal or visceral) walls. In the case of serous tumours, they appear as very small calcified lesions.
- Lymphatic dissemination may circulate through three alternative pathways: (a) following the ovarian lymphatic vessels, which is the most frequent pathway, until it arrives at the upper common iliac and paraaortic lymph nodes; (b) following the broad ligament and parametrium, until it arrives at the external iliac and obturator lymph nodes; and (c) very scarcely, following the round ligaments, in the direction of the external iliac and inguinal lymph nodes [11–14].
- Haematogenous dissemination is not as frequent, targeting the liver, lung, spleen, central nervous system and, in few cases, bone [13].

Over 66% of cases are detected when the disease is already advanced due to malignant cells having already reached extrapelvic structures, such as FIGO stages III and IV. The late diagnosis is caused, on one hand, by the typically vague presenting symptoms and, on the other hand, the lack of an effective screening program.

## Staging systems of ovarian cancer: FIGO and AJCC-TNM

At present, the most frequent worldwide staging system adopted for this primary tumour is the FIGO classification

[15, 16]. Initially established in 1973, the last revision dates back to 2014. It defines the features, extent and prognosis of the tumour, in order to achieve the best possible outcome following an optimized and personalized therapeutic approach. The comparison between the American Joint Committee on Cancer (AJCC) tumour–node–metastasis (TNM) and FIGO staging systems is presented in Table 1 [8, 15–17].

It is frequently discussed in the literature the heterogeneity of ovarian cancer, overarching different diseases that have dissimilar aetiology, pathogenesis, pathology and prognosis and that can initially appear affecting the ovaries, the fallopian tubes or the peritoneum. FIGO's 2014 classification includes as a single diagnostic category the tumours affecting ovaries, fallopian tube and primary peritoneal tumours.

## Laboratory

After a complete anamnesis and physical exploration, serum CA-125 is commonly studied in the initial evaluation [7]. In early disease (FIGO stage I), its utility is controversial because it is increased only in around half of the patients. In advanced disease (FIGO stage II or greater), CA-125 presents increased values in around 85% of cases. However, an important issue is the lack of specificity as CA-125 is increased in non-ovarian malignancies (e.g. breast, lung, colon and pancreatic tumours), pregnancy and benign diseases (e.g. cirrhosis, endometriosis, pelvic inflammatory disease and ovarian cysts). Serum carcinoembryonic antigen (CEA) and CA 19–9 values occasionally may help in clarifying the origin of the ovarian tumour, whether if the origin is gastrointestinal or a primary mucinous ovarian cancer. In this regard, endoscopic procedures, such as colonoscopy and/or gastroscopy, may be useful, especially if CA-125/CEA ratio is $\leq 25$ [18], although this is controversial. On the other hand, CA-125 is considered a good marker of tumour recurrence. The correlation between CA-125 levels and the clinical evolution during chemotherapy is very strong. In clinically tumour-free patients, CA-125 values have a prognostic value and can be useful for predicting relapse [19].

## Radiological imaging in ovarian cancer

Randomized clinical trials did not show benefits from screening procedures in ovarian cancer. The only settings where they may be appropriate are high-risk patients both pre- and postmenopausal and especially BRCA-mutated patients. Transvaginal and transabdominal ultrasound are the imaging procedures of choice [19].

Studying ovarian or adnexal masses with the medical imaging methods (ultrasound, US; computed tomography, CT; and magnetic resonance imaging, MRI) is frequent in post- and premenopausal women [20]. Ovarian masses can be either benign or malignant, although they are more frequently benign lesions, such as endometriomas (deep ovarian endometriosis), or corpus luteum cysts (both mainly premenopausal), thecomas, dermoid cysts and serous cystadenomas. Therefore, the impact on the subsequent management decisions of these imaging findings defining the malignancy or not of these masses is very high.

Transvaginal US (TVUS) combined with power Doppler is the initial imaging test (sometimes in combination with transabdominal US, TAUS). There is consensus that it is the imaging procedure of choice in patients with adnexal masses for studying the original location and its benign or malignant features. Characteristics of the masses that are considered as suspicious of malignancy are thick irregular walls or with papillary projections and solid echogenic foci, moreover if appearing associated with ascites or peritoneal nodules [21–24]. In this regard, power Doppler tests may add information to detect tumour neovascularity within solid masses [24].

The International Ovarian Tumour Analysis group (IOTA) has addressed the absence of uniform and standard guidelines in gynaecological ultrasonography as the limiting factor in the early diagnosis. The IOTA rules have introduced a standardized examination technique to define morphological features of ovarian masses. The IOTA simple ultrasound rules categorize ovarian tumours as benign or malignant and establish their application for the early detection of ovarian cancer. The IOTA published both simple rules and complex mathematical models based on logistic regression, allowing reproducible studies, simple to train and apply clinically for estimating the risk of malignancy [25].

However, up to one-fifth (5–20%) of these lesions are classified as indeterminate with ultrasonography. Here, MRI can provide an added value with complementary information [26]. Also, contrast-enhanced CT (ceCT) can be helpful as it can evidence solid enhancing components within adnexal masses and detect peritoneal tumour spread [19].

Regarding MRI, taking into account its main features when analysing T1- and T2-weighted images, indeterminate adnexal masses may be classified in three groups: (a) T1 highly intense masses, (b) solid masses with high or intermediate T2 signal and (c) complex cystic or cystic-solid masses. The first group, based on the loss or absence of signal in fat-suppressed T1-weighted imaging, can lead to mature teratoma and haemorrhagic masses, respectively. In the second group, based on the relationship or not with the uterus, a distinction can be done between uterine leiomyoma and ovarian fibroma, while the gadolinium enhancement can be useful for characterizing solid masses with inhomogeneous low or intermediate T2 signal. Lastly, in the third group and, anyway, in cases of solid components inside the mass, gadolinium enhancement T1-weighted sequences are required in order to establish or refute tumour enhancement

**Table 1** Comparison between AJCC and FIGO staging systems

| AJCC stage | FIGO stage | Stage grouping | | Stage description |
|---|---|---|---|---|
| I | I | T1 | | The cancer is in the ovaries or fallopian tubes without any other spread |
| | | N0 | | |
| | | M0 | | |
| IA | IA | T1a | | Lesion localized inside to one ovary or to one fallopian tube without cancer cells in the fluid or washings from the abdomen and pelvis |
| | | N0 | | |
| | | M0 | | |
| IB | IB | T1b | | Lesions localized inside both ovaries or fallopian tubes without cancer cells in the fluid or washings from the abdomen and pelvis |
| | | N0 | | |
| | | M0 | | |
| IC | IC | | | Lesion in one or both ovaries or fallopian tubes with: |
| | | T1c | T1c1 | Broken capsule during surgery |
| | | | T1c2 | Lesion in the surface of at least one organ or broken capsule before surgery |
| | | | T1c3 | Cancer cells in the fluid or washings from the abdomen and pelvis |
| | | N0 | | |
| | | M0 | | |
| II | II | T2 | | Lesion in one or both ovaries/fallopian tubes with spread to other pelvic organs or primary peritoneal cancer |
| | | N0 | | |
| | | M0 | | |
| IIA | IIA | T2a | | Tumoural extension to the uterus or the fallopian tubes |
| | | N0 | | |
| | | M0 | | |
| IIB | IIB | T2b | | Tumoural extension to the bladder, sigmoid colon or rectum |
| | | N0 | | |
| | | M0 | | |
| IIIA1 | IIIA1 | T1 or T2 | | Tumoural extension as described |
| | | N1 | | Spread to the retroperitoneal (pelvic and/or paraaortic) lymph nodes |
| | | M0 | | |
| IIIA2 | IIIA2 | T3a | | Tumoural extension as described with microscopic extrapelvic peritoneal deposits |
| | | N0 or N1 | | Spread or not to retroperitoneal lymph nodes |
| | | M0 | | |
| IIIB | IIIB | T3b | | Tumoural extension as described with macroscopic (< 2 cm) extrapelvic peritoneal deposits |
| | | N0 or N1 | | Spread or not to retroperitoneal lymph nodes |
| | | M0 | | |
| IIIC | IIIC | T3c | | Tumoural extension as described with macroscopic (> 2 cm) extrapelvic peritoneal deposits |
| | | N0 or N1 | | Spread or not to retroperitoneal lymph nodes |
| | | M0 | | |
| IVA | IVA | Any T | | Pleural effusion with confirmed metastatic cells |
| | | Any N | | |
| | | M1a | | |
| IVB | IVB | Any T | | Spread in extraperitoneal organs or inside the spleen or liver, as well as to lymph nodes different from retroperitoneal lymph nodes |
| | | Any N | | |
| | | M1b | | |

[13, 26, 27]. Other MRI sequences may also be useful for the characterization of these masses [26, 27].

CT from the thoracic apex to the pelvis is considered the preferred imaging procedure for presurgical evaluation and staging. There are publications focusing on which are the crucial imaging findings and diagnostic criteria as well as for generating a structured report for preoperative staging [13, 28].

## Treatment

Cytoreductive (also called debulking) surgical procedures and chemotherapy (platinum-based) are the cornerstones of ovarian cancer therapeutical management.

### Cytoreductive surgery

Primary cytoreductive surgery is aimed to remove completely the tumour before subsequent chemotherapy is administered, while interval cytoreductive surgery is done following neoadjuvant chemotherapy, usually three cycles.

Complete cytoreduction, or R0, is defined as the result of a surgical procedure that has cleared all macroscopic tumour, leaving no macroscopic residual disease. There is evidence that complete cytoreduction is the best independent prognostic factor in advanced ovarian cancer. Thus, a precise presurgical staging is key for defining the management plan. If complete cytoreduction is feasible with an acceptable surgical morbidity, primary debulking surgery should be offered [29–31].

According to the European Society for Medical Oncology (ESMO)-European Society of Gynaecological Oncology (ESGO) recommendations [29, 30], a multidisciplinary team working in a centre specialized in ovarian cancer must be in charge of patient selection for either primary debulking surgery or neoadjuvant chemotherapy. Radiological imaging or diagnostic laparoscopy must be part of the standard diagnostic and staging algorithm. Exclusion criteria from primary surgery, based on ESGO guidelines on ovarian cancer surgery [31], when the tumour has spread with the following findings, among other factors, in the diagnostic work-up are extensive and profound invasion of the root of small intestine mesentery; diffuse carcinomatosis of the small intestine with such an extensive dissemination that surgical clearance would produce a short bowel syndrome (the intestine left measuring less than 1.5 m); gastric/duodenal, head or middle part of the pancreas diffuse disease/profound invasion; tumour affecting coeliac trunk, hepatic arteries, left gastric artery; central or multisegmental hepatic secondary lesions; multiple lung secondary lesions (preferably pathologically confirmed); non-resectable lymphadenopathies; and central nervous system secondary lesions.

### Nodal staging

With regard to nodal staging, there has been a paradigm change in the last few years. In early-stage ovarian carcinoma (EOC), ESMO-ESGO guidelines indicate that the required management includes nodal staging surgery. In presurgical stage I patients, this surgical procedure must encompass a bilateral pelvic and paraaortic lymphadenectomy up to the left renal vein (independently of the surgical approach). In any case, given the low prevalence of lymphatic infiltration in certain pathology subtypes (e.g. mucinous carcinoma of expansile subtype or low-grade serous carcinoma, LGSC), there are doubts and discussion regarding the indication for staging surgery in these patients (ESMO-ESGO recommendation, level of evidence, IV; strength of the recommendation, A) [29, 30]. When referring to lymph node dissection with the aim of restaging, the procedure can be eluded when nodal status will not change clinical or therapeutic decisions (ESMO-ESGO recommendation, level of evidence, V; strength of the recommendation, B) [29, 30]. In the case of serous borderline ovarian tumours (sBOTs) with peritoneal implants, there is evidence that residual disease has a prognostic value. In this situation, both from a staging point of view and a therapeutical objective, it is of utmost importance to aim at an entire removal of peritoneal implants. In the case of stage II/III sBOTs, there is no evidence of improved evolution following lymphadenectomy (level of evidence, IV; strength of the recommendation, B) [29, 30]. Finally, regarding the cases with advanced ovarian cancer (AOC), the recently published lymphadenectomy in ovarian neoplasms (LION) trial [32] provided evidence on the limitations of lymphadenectomy. Available first-level evidence, coming from randomized clinical trials, is limited regarding the utility of systematic pelvic and paraaortic lymphadenectomy that has, however, been broadly applied in the surgical treatment of patients with advanced ovarian cancer. The LION trial demonstrated that, in advanced ovarian cancer cases with intraabdominal macroscopically complete resection and normal lymph nodes both before and during surgery, systematic pelvic and paraaortic lymphadenectomy in cases with advanced ovarian cancer was not associated with improved survival (overall or progression-free) compared to no lymphadenectomy but was associated with more postsurgical complications [32].

### Systemic treatment

The first-line ovarian cancer treatment and standard-of-care chemotherapy is the carboplatin/paclitaxel combination. Bevacizumab and poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors are now incorporated in the management guidelines. In addition to standard chemotherapy, some patients may be treated with molecularly targeted therapies. The addition of bevacizumab, an antiangiogenic drug, should be considered in patients with stage III–IV ovarian cancer. The use of maintenance therapy with olaparib, an oral PARP inhibitor, demonstrated significant advantages regarding progression-free survival especially in patients with initially diagnosed advanced ovarian cancer with BRCA1/2 mutation, as shown in the SOLO1 trial [29, 30, 33].

Around 70% of cases will recur in the first 3 years. In these patients, the progression-free interval after finishing the preceding line of chemotherapy is strongly associated with the prognosis and probability of response to second-line chemotherapy and subsequent chemotherapy lines.

Traditionally, patients that present disease progression in the first 6 months after finishing platinum-based chemotherapy are considered to be platinum-resistant and are unlikely to benefit from a re-challenge by platinum-based chemotherapy, while patients presenting progressive disease in the time interval of more than 6 or even 12 months are considered platinum-sensitive and likely to respond to platinum therapy. This concept, developed when alternatives to platinum re-treatment were scarce, presents limitations and was discontinued at the fifth Ovarian Cancer Consensus Conference of the Gynecologic Cancer InterGroup (GCIG) [34]. Bevacizumab could be recommended both combined with platinum-based therapy and, after, as maintenance therapy in those cases presenting a platinum-free interval (PFI) over 6 months and in combination with second- or third-line non-platinum chemotherapy (weekly paclitaxel, PLD, topotecan) in patients with shorter PFI. PARP inhibitors (olaparib, niraparib and rucaparib) could be recommended as maintenance therapy after a response to platinum-based second or higher line of treatment. Their benefit is highest in patients presenting BRCA mutation, although those without BRCA mutation also benefit of the therapy. Furthermore, in selected cases presenting a first relapse, complete cytoreductive surgery followed by chemotherapy achieves better progression-free survival (PFS) and makes the beneficial effect extensive to the next chemotherapy line [29, 30].

In the era of precision medicine, research focuses on looking for targeted therapies for the different histological subtypes with their specific molecular features and different chemosensitivity and also variable CA-125 expression and positron emission tomography (PET) imaging semiology with dedicated radiopharmaceuticals. The targeted treatments being investigated are immune checkpoint inhibitors, PARP inhibitors, hormone receptor modulators and antiangiogenic agents [29, 30].

### Follow-up

Clinical evaluation and CA-125 are the standard in the follow-up of ovarian cancer after primary treatment [28]. The indications and application of imaging procedures (ultrasound, chest–abdomen–pelvis CT, whole-body MRI or PET/CT) have to be based on sound clinical indications, deriving either from symptoms, signs or increasing CA-125 values [29, 30]. In patients in which there is suspicion of relapse, CT is the preferred technique, although PET/CT can be a valid alternative if performed with contrast enhancement, as the contrast-enhanced CT component is mandatory in this setting to accurately evaluate peritoneal carcinomatosis.

## PET/CT procedure

### 2-[$^{18}$F]FDG PET/CT acquisition

The 2-[$^{18}$F]FDG PET/CT procedure has been described in the EANM guideline [35]. In ovarian cancer it is important to effectively search for cancer deposits in the regions where this tumour spreads more frequently, namely, the peritoneum, the lymphatic system and the bloodstream.

If ceCT can be done as part of the 2-[$^{18}$F]FDG PET/CT, it may be evaluated by the multidisciplinary tumour board to avoid performing an additional separate diagnostic CT.

It is generally considered helpful to obtain multiphase contrast-enhanced CT imaging in patients with known/suspected ovarian cancer, especially for the evaluation of the liver, lymph nodes, mesentery, omentum, pleura and lungs. All available patient CT dose reduction methods should be considered, including automatic exposure control and iterative reconstruction.

### Data extraction and analysis

Qualitative PET/CT categorizes the findings into malignant, indeterminate or benignant. 2-[$^{18}$F]FDG uptake is visually compared with the background and with other structures, such as the mediastinum and the liver. Based on the degree of 2-[$^{18}$F]FDG uptake and the particular context of the study (clinical indication, previous treatments and concomitant processes), the findings are categorized into the aforementioned qualitative values.

Quantitative PET/CT may be applied as a diagnostic or prognostic tool (i.e. single measurement) or for therapy response assessment (i.e. longitudinal studies). Metrics include standardized uptake values (SUV, general acronym) computed either using the body weight (SUV) or the lean body mass (SUL), metabolic active tumour volume (MATV or MTV) and total lesion glycolysis (TLG), defined as MATV × SUVmean. In fact, MATV is the volume inside a user- or algorithm-defined volume of interest (VOI) used to circumscribe the metabolically active tumour. Several techniques have been proposed to determine the limits of the VOI, threshold-based or algorithm-based [36], while TLG calculated by multiplying MATV by the mean SUV of all voxels in the MATV incorporates both 2-[$^{18}$F]FDG uptake and size of the tumour, also known as whole metabolic burden of the tumour [37].

The use of quantitative 2-[$^{18}$F]FDG PET/CT parameters as imaging biomarkers in centres that have several PET/CT systems or in trials involving different PET/CT systems

requires a minimum standardization to make these parameters comparable between patients, independently of the PET/CT scanner acquiring the images.

Delineation of MATVs may be affected by similar errors as occur when calculating SUVs, leading to one of the main causes of variability, which is variations in the delineation methodology of lesions [38]. MATVs also allow extraction of heterogeneity features. However, radiomic features are greatly affected and sensitive to a few confounding factors, being image reconstruction settings an example, and this translates into challenges when aiming at its clinical implementation [39, 40].

It is therefore recommended to comply with harmonizing standards such as the EANM/EARL program, one of the international harmonization programs aiming at using 2-[$^{18}$F]FDG PET/CT as a quantitative imaging biomarker [41]. Radiomics should also follow the definitions of the image biomarker standardization initiative (IBSI).

In addition to harmonization issues, attention should be paid to avoid including ureters or bladder when computing MATV in patients with bulky disease (Fig. 1).

Therapy assessment should be performed according to either the European Organisation for Research and Treatment of Cancer (EORTC) PET response criteria or PERCIST [42–44]. In addition to the use of the area harbouring the highest uptake, it is recommended to explore peritoneal index-adapted PERCIST classification where the 5 target lesions would be based on one of the scores that have been developed for assessing the extension of peritoneal carcinomatosis. Several scores for laparotomic assessment of tumour/carcinomatosis extension have been described: the Sugarbaker score or the peritoneal cancer index (PCI) and the Aletti, Fagotti and Eisenkop scores, which attribute a score to several anatomical regions of the abdomen [45, 46].

## 2-[$^{18}$F]FDG PET/CT indications

- Initial diagnosis and staging
- Prognostic value
- Treatment planning
  - Evaluation of tumour resectability
  - Predictive value before upfront debulking surgery or interval debulking surgery
  - Predictive value before chemotherapy
- Therapy assessment
  - Chemotherapy
- Relapse detection
  - Non-conclusive radiological imaging
  - Negative radiological imaging with increased tumour markers
- Follow-up

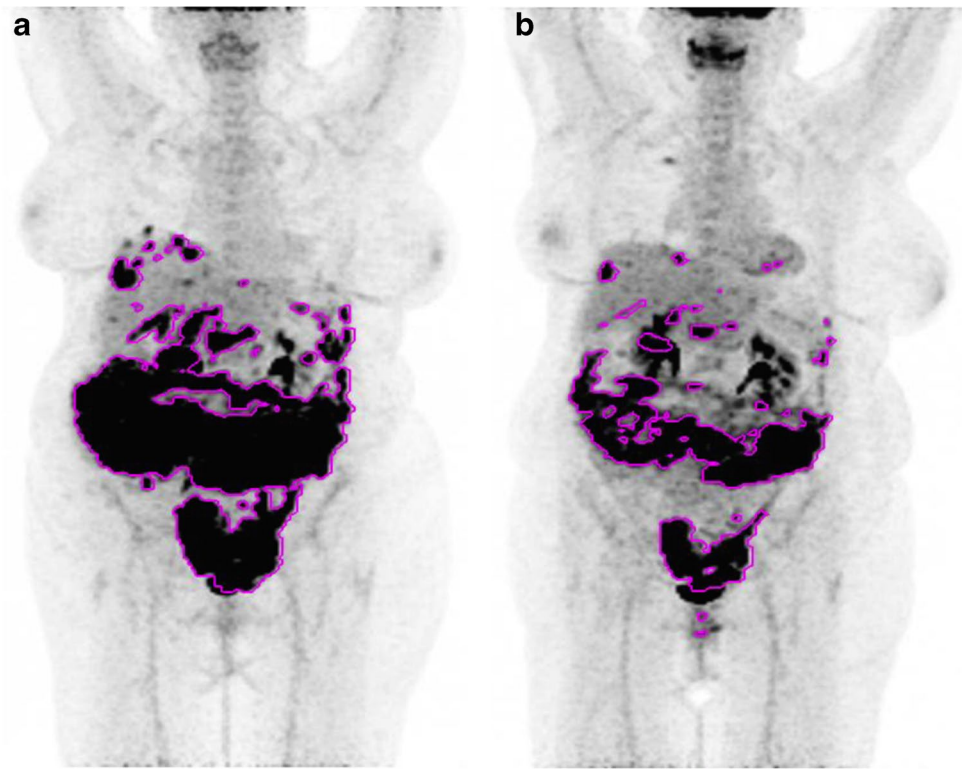


**Fig. 1** Example of metabolic active tumour volume (MATV) delineation in a patient with stage IIIc FIGO ovarian cancer enrolled in the CHIVA trial [95] in the chemotherapy plus placebo arm. Attention should be paid to avoid including the ureters or bladder in the tumour burden when drawing MATV. Early therapy assessment 2-[$^{18}$F]FDG PET/CT (**b**) was performed 20 days after baseline scan (**a**), after the first cycle of treatment. This patient was classified as stable metabolic disease as per PERCIST therapy response criteria. Maximum intensity projections (MIP) of 2-[$^{18}$F]FDG PET are presented

Each indication has been reviewed, assigning a level of evidence and a recommendation grade (Table 2) following the National Institute for Health and Clinical Excellence (NICE) adaptation, as previously used [47, 48], as follows:

## Levels of evidence

The level of evidence is a rating of the literature data on which the recommendations formulated are based. The level depends on the type and quality of studies available and degree of consistency across their results. Details of the levels of evidence used are presented below:

- Level I: There are good-quality meta-analyses or good-quality randomized trials with cross-consistent results. New data will most likely not change confidence in the estimated effect.
- Level II: There is good-quality evidence (randomized trials (B1) or prospective or retrospective studies (B2) with overall cross-consistent results. New data may impact confidence in the estimate of effect or may change the estimate.
- Level III: The studies available carry methodological weaknesses, and/or the results of the studies are not always cross-consistent. New data will most likely impact confidence in the estimate of effect and will likely change the estimate.
- Level IV: There are no data or only case series. There is a great deal of uncertainty as to the estimated effect.

## Grades of recommendation

- A: At least one meta-analysis, systematic review or randomized controlled trials (RCT) directly applicable to the target population and demonstrating overall consistency of results
- B: A body of evidence including high-quality systematic reviews of case–control or cohort studies, directly applicable to the target population, and demonstrating overall consistency of results
- C: A body of evidence including well-conducted case–control or cohort studies with a low risk of confounding or bias, directly applicable to the target population and demonstrating overall consistency of results
- D: Non-analytic studies, e.g. case reports, case series and expert opinion

**Table 2** Clinical indications, levels of evidence and grade of recommendation for 2-[$^{18}$F]FDG PET/CT in ovarian cancer

| Clinical indication of 2-[$^{18}$F]FDG PET/CT in ovarian cancer | Level of evidence | Grade of recommendation |
|---|---|---|
| Initial diagnosis and staging in patients presenting with a pelvic mass | III | Grade C |
| Prognostic value | I | Grade B |
| Treatment planning | IV | Grade C |
| Therapy assessment | II | Grade B |
| Relapse detection | I | Grade A |

## Initial diagnosis and staging in patients presenting with a pelvic mass

Level of evidence: III

Recommendation: grade C

Many publications have focused on the diagnostic efficacy of 2-[$^{18}$F]FDG PET/CT for ovarian cancer in patients presenting with a pelvic mass, aiming at ameliorating management decisions identifying patients in whom surgical intervention is indicated (positive PET). With the aim of detecting ovarian tumours in fifty consecutive patients presenting a pelvic mass and had a surgical intervention scheduled, Castellucci et al. [49] reported comparable sensitivity for 2-[$^{18}$F]FDG PET/CT and TVUS (around 87–90%), but 2-[$^{18}$F]FDG PET/CT presented better specificity. In another prospective study of 97 patients presenting pelvic masses, Risum et al. reported high specificity of 2-[$^{18}$F]FDG PET/CT for detecting malignant disease related to ovarian cancer as well as high sensitivity (92.5% and 100%, respectively) [50]. Nam et al. [51] in 133 women obtained 2-[$^{18}$F]FDG PET/CT accuracy (92%), better than pelvic power Doppler US (83%) and CT/MR (74%) in differentiating benign vs borderline/malignant adnexal masses.

The pathophysiologic bases of the aforementioned observations include glucose transporter 1 (GLUT-1) overexpression and microvessel density/tumour proliferation, both being indicators of tumour aggressiveness and worse prognosis. Therefore, researchers indicate that 2-[$^{18}$F]FDG PET/CT helps ameliorate patient selection for surgery and as guidance for cytoreductive surgery [52, 53]. Moreover, staging with 2-[$^{18}$F]FDG PET/CT coincided with surgical staging in 78% of cases, indicating 2-[$^{18}$F]FDG PET/CT may be applied in the presurgical staging of patients in which ovarian cancer is suspected [51]. Thus, even if Yamamoto et al. and Kitajima et al. [54, 55] confirmed high 2-[$^{18}$F]FDG PET/CT sensitivity and specificity in differentiating malignant from benign ovarian masses, their reports present low diagnostic efficacy when discriminating between borderline–malignant and benign lesions. Furthermore, even after positive findings when analysing the diagnostic value of 2-[$^{18}$F]FDG PET/CT in ovarian cancer, Fenchel et al. [56] and Tanizaki et al. [57] described false-negative and false-positive results. The false-negative patients appeared because of the absent or low 2-[$^{18}$F]FDG accumulation

in early tumours and clear-cell, mucinous and cystic carcinomas (compared with serous carcinoma and epithelial carcinoma) [58–60]. The false-positive results commonly appeared associated to 2-[$^{18}$F]FDG accumulation in benign conditions, such as cystadenomas, endometriomas and acute inflammatory processes, or in premenopausal ovaries deriving from cyclic functional activity changes.

As in other fields of oncology, it is a well-known fact that there is an overlap between the degree of 2-[$^{18}$F]FDG uptake in malignant, borderline–malignant and benign lesions. Thus, 2-[$^{18}$F]FDG PET/CT has a good diagnostic accuracy in discriminating ovarian cancer from benign tumours, this not being the case when trying to differentiate borderline–malignant from benign tumours because of its comparatively lower diagnostic accuracy in this context [57].

A meta-analysis including 8 studies and 594 patients reported an joint sensitivity and specificity for metastasis of 0.72 (95% confidence interval [CI] = 0.61–0.81) and 0.93 (95% CI = 0.85–0.97), respectively [61]. Heterogeneity analysis showed high values both for sensitivity (97.57%) and specificity (96.74%). In sensitivity analyses, studies using laparotomy as the gold standard evidenced better sensitivity and specificity (0.77, 95% CI = 0.67–0.87, and 0.96, 95% CI = 0.92–0.99, respectively) than those including diagnostic laparoscopy (0.62, 95% CI = 0.46–0.77, and 0.84, 95% CI = 0.69–0.99, respectively). Better specificity was demonstrated in studies that confirmed surgical findings using pathology (0.95, 95% CI = 0.90–0.99) than in a study not applying pathology confirmation (0.69, 95% CI = 0.24–1.00). Studies with a lower prevalence of the 2-[$^{18}$F]FDG-avid subtype showed better specificity (0.97, 95% CI = 0.94–1.00) than those with a higher prevalence (0.89, 95% CI = 0.80–0.97).

## Prognostic value

Level of evidence: I

Recommendation: grade B

The assessment of the prognosis is key for patient management planning. There is broad evidence confirming the prognostic value of 2-[$^{18}$F]FDG PET/CT in ovarian cancer, with many meta-analyses published in the last years [58, 62–73]. MTV and TLG from 2-[$^{18}$F]FDG PET/CT were significant prognostic factors in these patients. Although there was clinical heterogeneity and methodological differences between studies, patients with a high MTV or TLG present more risk of disease progression or death [61].

2-[$^{18}$F]FDG PET/CT is a diagnostic procedure useful for the accurate detection of not previously known metastases. Moreover, it gives an insight into tumour biology and behaviour and, thus, the potential influence of these aspects on the prognosis. Several studies have evidenced significant associations between primary tumour SUVmax and FIGO stage, pathology (serous/non-serous carcinoma), metastatic lymphadenopathies and a bad prognosis with a significantly worse overall survival rate between cases with high and low primary tumour SUVmax [63, 74, 75]. Mucinous and clear-cell ovarian cancer shows a significantly lower SUVmax than in serous carcinomas [63]. The explanation for this can be found in the pathophysiology, based on different glucose transporter concentrations in the different tumour subtypes. Cho et al. [52] described a strong association between membrane GLUT-1 overexpression in the primary tumour and bad overall survival and also ovarian cancer aggressiveness. Other prognostic factors prior to treatment are volumetric metabolic PET parameters, such as MTV and TLG [64].

Chung et al. [76] observed that MTV and TLG were statistically significant independent prognostic factors in ovarian cancer associated with progression-free interval. Lee et al. [64] showed that TLG was an independent prognostic factor for disease progression following cytoreductive surgery. Gallicchio et al. reported similar data for MTV [77]. Risum et al. [70] showed that stage IIIC/IV disease on 2-[$^{18}$F]FDG PET/CT was associated with worse overall survival and proposed using 2-[$^{18}$F]FDG PET/CT criteria for referring ovarian cancer patients to neoadjuvant chemotherapy before surgery. Therefore, 2-[$^{18}$F]FDG PET/CT helps finding previously unknown metastatic lesions but also helps evaluating the risk of residual cancer following surgical treatment, in summary, improving patient management.

## Treatment planning

- Evaluation of tumour resectability
- Predictive value before upfront debulking surgery or interval debulking surgery
- Predictive value before chemotherapy

Level of evidence: IV

Recommendation: grade C

In these clinical situations, the available evidence is limited [78–85], including retrospective studies. In women with advanced stage ovarian cancer, no firm conclusions can be drawn regarding the replacement of diagnostic CT by 2-[$^{18}$F]FDG PET/CT or contrast-enhanced or diffusion-weighted (DW) MRI to assess incomplete debulking surgery. 2-[$^{18}$F]FDG PET/CT and MRI are commonly available in hospitals, and they suggested there was a high specificity and moderate sensitivity to assess incomplete debulking. Potential advantages included the ability of 2-[$^{18}$F]FDG PET/CT to detect extra-abdominal (distant) disease and the soft tissue contrast of MRI for (small) lesion detection. Importantly, the level of evidence is insufficient to advise routine addition of 2-[$^{18}$F]FDG PET/CT or MRI to clinical practice [84].

As mentioned above in the "Treatment" section, there has been a paradigm change with regard to nodal staging.

First, in early-stage ovarian carcinoma, the indication for staging surgery may be questioned, whereas when referring to lymph node dissection for restaging purposes, the procedure may be avoided if the nodal status does not alter patient management [29, 30]. Second, in the case of serous borderline ovarian tumours (sBOTs) with peritoneal implants, there is no proven benefit of lymphadenectomy in stage II/III sBOTs [29, 30]. Third, in patients with advanced ovarian cancer (AOC), after intraabdominal macroscopically complete resection and presenting normal lymph nodes both before and during surgery, systematic pelvic and paraaortic lymphadenectomy did not correlate with better overall or progression-free survival than no lymphadenectomy but was associated with an increased incidence rate of postsurgical morbidity and complications [32], as well as increased costs. Because of this, to ameliorate patient selection for those who will benefit from lymphadenectomy, a presurgical imaging test providing an accurate nodal staging was proposed [86]. Many studies have shown 2-[$^{18}$F]FDG PET/CT has a better diagnostic performance in detecting metastatic lymph nodes compared with ceCT only [87]. A meta-analysis by Yuan et al. [88] (including 882 patients from 18 studies) showed that 2-[$^{18}$F]FDG PET/CT had better accuracy than both ceCT and MR in detecting metastatic lymphadenopathies, with sensitivity and specificity values of 73% and 96% for 2-[$^{18}$F]FDG PET/CT, 42% and 95% for ceCT and 54% and 88% for MRI, respectively, with significant differences reached only in sensitivity. Signorelli et al. [86] confirmed the previous results. These studies evidence that 2-[$^{18}$F]FDG PET/CT may be a precise imaging test for selecting patients could benefit from systematic lymphadenectomy. Thus, the high negative predictive value (NPV) may avoid lymphadenectomy in many cases, reducing to a minimum the surgical complications.

It is known that 2-[$^{18}$F]FDG PET/CT can ameliorate presurgical staging by detecting extra-abdominal spread not detected by radiological procedures [51, 89, 90] including lymphadenopathies situated outside the abdominopelvic area as well as unsuspected extraovarian tumours [49, 51]. Locations of metastatic lesions found by 2-[$^{18}$F]FDG PET/CT were predominantly supradiaphragmatic [90]. Moreover, the presurgical staging of advanced disease with PET has evidenced that up-staging from stage III to IV happens in a high proportion of cases [91]. In addition, 2-[$^{18}$F]FDG PET/CT improves the identification of stage III/IV patients for whom complete debulking is not possible. There is evidence that stage IV cases with diverse volumes of residual disease may have similar evolutions; thus, an early detection of stage IV can be useful for changing the therapeutic approach.

With regard to 2-[$^{18}$F]FDG PET/CT and its indication or not for assessing peritoneal carcinomatosis when staging ovarian cancer, there is certain controversy, but several studies have reported promising results. ceCT is the most accurate. 2-[$^{18}$F]FDG PET/CT seems to have an acceptable diagnostic accuracy for tumour implants greater than 5 mm, although in any case a detailed review of the CT images of the 2-[$^{18}$F]FDG PET/CT should be done, comparing with previous CT images, for an adequately evaluation of the status of the disease in the peritoneum. In cases with peritoneal carcinomatosis with evident 2-[$^{18}$F]FDG uptake, an apron sign or shield sign can be detected, appearing as 2-[$^{18}$F]FDG uptake along the anterior abdomen (on occasions related to increased peritoneal thickening or omental fat stranding on ceCT) [92].

## Therapy assessment

Level of evidence: II

Recommendation: grade B

There are few clinical trials evaluating the role of 2-[$^{18}$F]FDG PET/CT in the assessment of therapy response. Chundury and colleagues [80] explored the role of 2-[$^{18}$F]FDG PET/CT in order to evaluate the efficacy of intensity-modulated radiation therapy (IMRT) in women treated for recurrent ovarian cancer. Among 17 patients, 11 showed a partial metabolic response, while in six a complete metabolic response was observed. Furthermore, among 11 patients with partial metabolic response, in only two cases recurrence was observed at the site of IMRT, while of the 6 patients with complete metabolic response recurrence was found in only one woman at the site of IMRT.

In three studies, 2-[$^{18}$F]FDG PET/CT was used to assess neoadjuvant chemotherapy response [85, 93, 94]. Vallius et al. [85] reported that patients with normalization of SUVmax after 3 courses had higher probabilities to benefit from additional 3 courses. The study from Hynninen et al. [93] did not confirm the ability of 2-[$^{18}$F]FDG PET/CT to distinguish responders from non-responders compared to morphological imaging, due to residual 2-[$^{18}$F]FDG activity. In fact although 2-[$^{18}$F]FDG uptake at the end of the treatment tended to be confirmed in case of relapse, this residual activity was observed even in RECIST complete responders. In another study, Vallius et al. [94] described that a decrease in MATV < 85% permitted identifying cases with stable or progressive disease (as per RECIST 1.1) after neoadjuvant chemotherapy for inoperable EOC with a sensitivity and specificity of 70% and 78%, respectively, and that MTV decrease was associated with PFS. More recently, an ancillary PET study from the CHIVA trial [95] demonstrated that 2-[$^{18}$F]FDG PET/CT using EORTC or PERCIST criteria was useful to evaluate early tumour response and predict second-look surgery outcome, PFS and OS. In this study, neither MATV nor TLG was useful in predicting survival.

### Relapse detection

- Non-conclusive radiological imaging
- Negative radiological imaging with increased tumour markers

Level of evidence: I
Recommendation: grade A

There is broad evidence regarding this indication [96–100]. Several meta-analyses have reported the high performance of 2-[$^{18}$F]FDG PET/CT in suspected recurrent disease with a better diagnostic accuracy than radiological imaging, especially in the context of increasing CA-125 serum levels [26, 88, 101]. Furthermore, ESMO guidelines on ovarian cancer indicate that 2-[$^{18}$F]FDG PET/CT may indicate locations of disease not detected on CT. The main role of 2-[$^{18}$F]FDG PET/CT is to contribute in selecting patients for secondary debulking surgery, by excluding cases with additional sites of disease not detected on CT and not treatable with cytoreduction [7].

Increased serum CA-125 is very accurate for indicating that there is active recurrent disease. Nevertheless, normal serum CA-125 does not permit excluding a relapse. Thus, there is evidence that in ovarian cancer patients in complete clinical remission, a progressive low-level elevation in serum CA-125 (staying under the upper normal threshold) is highly predictive of relapse [102]. The role of 2-[$^{18}$F]FDG PET/CT in these cases with a low-level elevation of serum CA-125 has been studied with promising results [103–106].

The available studies confirm the utility of 2-[$^{18}$F]FDG PET/CT to change treatment management, on one hand guiding the indications to otherwise unplanned therapies and, on the other hand, saving from performing previously planned diagnostic procedures, with values ranging between 30 and 57% [107–110]. The available reports coincide with findings from the US National Oncology PET Registry, showing that changes in management were done in 38% to 45% of cases who were restaged with 2-[$^{18}$F]FDG PET/CT [111, 112].

### Follow-up

Follow-up is not indicated unless there is suspicion of relapse and negative radiological imaging [29, 30].

## Conclusion

2-[$^{18}$F]FDG PET/CT is an established imaging technique in oncology in general and in gynaecological cancer in particular. Given the high incidence and aggressiveness of ovarian cancer, a guideline focusing on the role of 2-[$^{18}$F]FDG PET/CT in this tumour was developed. The evidence available in the literature was reviewed for each clinical indication, assigning a level of evidence and a recommendation grade following the NICE adaptation. In conclusion, 2-[$^{18}$F]FDG PET/CT is most useful in relapse detection (level of evidence I, grade of recommendation A), followed by its prognostic value (level of evidence I, grade of recommendation B). There is less evidence for therapy assessment (level of evidence II, grade of recommendation B) and very scarce or low quality evidence for initial diagnosis and staging in patients presenting with a pelvic mass (level of evidence III, grade of recommendation C) and treatment planning (level of evidence IV, grade of recommendation C). Finally, multidisciplinary collaboration is especially important to obtain the best possible outcome, as well as weighting the need for personalizing diagnosis and therapy to the individual patient.

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## Declarations

**Ethics approval** This article does not contain any studies with human participants performed by any of the authors.

**Conflict of interest** The authors declare no competing interests.

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