SYSTEMATIC REVIEW

The role of 18F-FDG PET/CT in endometrial adenocarcinoma: a review of the literature and recent advances

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Abstract

Purpose To provide a substantial coverage on the role of 18F-FDG PET/CT in endometrial cancer (EC), and identify the key issues which make its use recommended with both low level of evidence and low strength of recommendation in accordance with the last consensus conference.

Methods A comprehensive literature computer search was performed on PubMed/MEDLINE and Cochrane Library databases up to June 2020. Included studies had to focus on 18F-FDG PET/CT in EC, with regard to staging, follow-up and prognostic value. Review guidelines, systematic review, meta-analyses and original papers were included.

Results The 18F-FDG PET/CT is affected by suboptimal soft tissue differentiation, with sensitivity and specificity in tumor staging ranged from 77 to 85% and 79 to 96%. The sensitivity and the specificity of 18F-FDG PET/CT performed at staging for lymph node metastases ranged from 63 to 73% and 96 to 97%. For distant metastases, sensitivity and specificity of 18F-FDG PET/CT performed at staging ranged from 63 to 80% and 93 to 96%. After treatment, better performance emerged for EC recurrent with sensitivity ranged from 92 to 98% and specificity ranged from 89 to 94%. Maximum standardized uptake value (SUVmax) and metabolic volumetric parameters, such as total lesion glycolysis (TLG) and metabolic tumor volume (MTV), resulted to be significantly related to prognosis.

Conclusion Despite evidence-based data about the diagnostic performance are increasing, the low sensitivity represents the main limitation of 18F-FDG PET/CT imaging utilization for the detection of primary tumor and lymph node metastases. Better performances were observed for distant metastasis and EC recurrence. Further randomized prospective studies are needed to increase both the low level of evidence and low strength of recommendation for using 18F-FDG PET/CT in EC. Promising results emerged from PET/MRI.

Keywords Endometrial cancer · PET/CT · Pelvic lymph node metastasis · Para-aortic lymph node metastasis · Systematic review · Meta-analysis

Introduction

Endometrial carcinoma (EC) is the most common gynecologic malignancy in the developed country, and the incidence is increasing [1]. The prognosis is mostly determined by grade and stage. The International Federation of Gynecology and Obstetrics (FIGO) and the American Joint Committee on Cancer TNM staging systems [2, 3] are the most important prognostic factors in EC, with 67% 5-years survival for patients with localized disease, 20% with regional disease, and 9% with distant metastasis [2–6]. Consequently, the accurate pre-surgical assessment of the burden of malignancy is critical to evaluate the extent of surgery and to predict the outcome. In this context, non-invasive pre-surgical

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imaging techniques would be beneficial in indicating a tailored treatment.

The burden of malignancy affects surgery

The standard surgical approach consists of laparotomy, peritoneal washing, extrafascial hysterectomy, bilateral salpingo-oophorectomy and partial colpectomy [7]. However, a wider maximal surgical cytoreduction should be recommended for patients with advanced EC [7]. In fact, Bristow et al. reported that the median survival rate of patients undergoing optimal surgery was 34.3 months, a statistically significant advantage compared to patients with > 1 cm residual tumor (11.0 months, $P = 0.0001$) [8]. Therefore, for putative FIGO stages III (local or regional tumor spread) and IV (distant metastases and/or invasion of the bladder/bowel), surgical treatment consists of the resection of tumor and metastatic lesions [9].

Moreover, pelvic and para-aortic lymphadenectomy is recommended for patients with suspicious nodes at surgical exploration and resulted efficient to increase overall survival (OS) in EC patients with high-risk for extra-uterine disease and poor outcome [10]. Such risk factors include macroscopic extrauterine disease, deep myometrial invasion greater than 50% or G3 tumor grade. If a lymphadenectomy is performed, systematic removal of pelvic and para-aortic nodes up to the level of the renal veins should be considered [11]. On the other hand, for low-risk EC surgical approach is debated. In fact, in a prospective multicenter randomized trial (NCT00482300), the 5-years disease-free survival (DFS) and OS rates were similar between lymphadenectomy arm (81% and 85.9%) and no-lymphadenectomy arm (81.7% and 90.0%) in patients with preoperatively supposed stage I–II EC [12]. Moreover, lymphadenectomy in low-risk EC could increase morbidity and cost of care without discernible benefits [13]. Interestingly, Dong et al. proposed a prediction model to help clinicians in decision-making and reduce overtreatment and medical costs [14].

Pre-surgical non-invasive imaging techniques

More effectively, non-invasive pre-surgical imaging techniques would be beneficial in indicating the necessity of more radical hysterectomy from low-risk to high-risk patients. For this purpose, local ultrasound is the gold standard in evaluating the depth of myometrial invasion (FIGO stage I) and cervical involvement (FIGO stage II) [15, 16]. Nevertheless, contrast-enhanced magnetic resonance imaging (MRI) can accurately determine FIGO stages I and II, depict pelvic and para-aortic lymphadenopathy and the extent of local and regional disease spread, such as serosal, adnexa, vaginal or parametrial involvement (FIGO stage III). Finally, MRI can find an extension to the pelvic wall,

invasion of bladder or bowel mucosa and involvement of inguinal lymph nodes (FIGO stage IV). In addition, CT is used to assess the extra-pelvic disease, even if depicting the invasion of myometrial, adjacent organs and nodal metastasis could be possible [11, 17].

In this pre-operatively setting, the debate has challenged the use of anatomic assessments solely relying on tumor morphologic information, not taking into account metabolic tumor characteristics, that may prove highly relevant for the clinical phenotype [18]. However, there are not enough randomized studies assessing the role of 18F-FDG PET/CT in EC and current knowledge still derived from retrospective studies, experts in the field and individual experiences. Further, there have been no wide reports of cost-effectiveness [19]. Therefore, in 2016, 18F-FDG PET/CT scan was considered with both low level of evidence (IV) and low (C) strength of recommendation from the last European Society for Medical Oncology (ESMO), European Society of Gynecologic Oncology (ESGO) and European SocieTy for Radiotherapy and Oncology (ESTRO) consensus conference on EC [11, 20, 21].

In this regard, a cumulative approach could be helpful to provide gathering evidence for or against the use of 18F-FDG PET/CT technique in EC. Herein, we review current literature on 18F-FDG PET/CT in EC with respect to staging, follow-up and prognostic value.

Materials and methods

This review is based on the available consensus recommendations for the use of 18F-FDG PET/CT and current clinical diagnostic criteria. In addition, a comprehensive literature computer search was performed on PubMed/MEDLINE and Cochrane library databases. We used a search algorithm based on a combination of terms ("endometr*") AND ("PET" OR "positron emission tomography") AND ("meta-analysis" OR "systematic review"). No beginning date limit was used. Search process was conducted until June 2020.

Included studies had to focus on 18F-FDG PET/CT in EC. Reviews, meta-analyses and original papers were included. According to primary tumor, lymph node metastases, distant metastases, prognostic value and EC recurrence, their respective latest meta-analysis was collected and a standard pro forma used to extract the following data: the basic study characteristics (authors, year of publication, number of original studies included, number of patients included) and diagnostic performance measures (pooled sensitivity and specificity with a 95% confidence interval, and index of heterogeneity (I^2) [5, 23–26].

I^2 value indicated the reproducibility of report values and reflected the extent of inconsistency of findings across studies which constitute each meta-analysis. A small I^2 value was

interpreted as meaning that the performance was comparable across studies, while a large I^2 value as meaning that the performance size varies substantively across studies. I^2 values of 25%, 50%, and 75%, corresponded to small, moderate, and large amounts of heterogeneity.

Data not derived from the most recent meta-analyses were not collected in the spreadsheet to avoid overlapping of the studies. Studies for which an English translation could not be obtained were excluded.

Results

Performing the computer literature search about the use of 18F-FDG PET/CT in the EC, six meta-analyses [5, 18, 23–26] were found. However, the main findings of the five latest meta-analyses, each taking into account 18F-FDG PET/CT with regard to primary tumor, lymph node metastases, distance metastases, recurrence disease and prognostic value, were selected and presented in Table 1 [5, 23–26]. The 18F-FDG PET/CT results were affected by suboptimal soft tissue differentiation with low sensitivity in tumor staging. The best sensitivity and specificity were reported for the detection of distant metastases. Accordingly, all guidelines agree in considering 18F-FDG PET/CT useful to assess suspected recurrent and to detect distant metastases as indicated based on clinical symptoms, physical findings, or abnormal laboratory findings (Table 2).

Discussion

The main findings of the selected evidence-based articles are discussed here below, taking into account the role of 18F-FDG PET/CT for primary tumor, lymph node metastasis, distant metastasis, follow-up and prognostic value.

The role of 18F-FDG PET/CT in T staging

Despite high pooled specificity (89%) and sensitivity (81%), the presence of heterogeneity across 16 studies (I^2 of 57% and 85% for specificity and sensitivity, respectively) which were collected by a meta-analysis (including a total of 807 patients) was an important issue to be considered. The non-malignant physiological uptake of 18F-FDG PET/CT in the normal endometrium was most likely the cause of sub-optimal pooled sensitivity [25].

However, in a multicenter prospective comparative study, among 318 consecutive women, 18F-FDG PET/CT, MRI and trans-vaginal two-dimensional ultrasound (2D-US) were found to have quite a similar accuracy in assessing myometrial invasion (FIGO stage I) with 61%, 66% and 72%, respectively [16]. More recently, Husby et al. also suggested that measurement of metabolic tumor volume may represent a new tool to assess deep myometrial invasion [27]. Further, Sudo et al. reported that 18F-FDG PET/CT diagnostic value may need adjustment based on the anatomical information provided by MRI before surgery to improve

Table 1 18F-FDG PET/CT performances for endometrial cancer reported by meta-analyses

Author	Year	Study no	Patient no	Sensitivity% (95% CI); I^2%	Specificity % (95% CI); I^2%	DFS (CI); I^2%
Performance for primary lesion						
Kakhki [25]	2013	16	807	81 (77–85); 88	89 (79–96); 57	Na
Performance for metastatic lymph node						
Hu [26]	2019	19	1431	LNM: 68 (63–73); 57	LNM: 96 (96–97); 98	Na
				PLN: 61 (52–69); 44	PLN: 96 (95–97); 44	Na
				PALN: 70 (58–79); 58	PALN: 92 (90–94); 58	Na
Performance for distant metastases						
Bollineni[a] [5]	2015	13	861	72 (63–80); 18	94 (93–96); 28	Na
Performance for endometrial cancer recurrent						
Kadkhodayan[b] [24]	2013	11	541	95 (92–98); 28	92 (89–94); 35	Na
Performance for prognostic value						
Ghooshkhanei [23]	2014	10	771	Grade: 88 (47–100); 2	Grade: 49 (32–65); 85	HR 7.4 (2–19)[c]; 0
				MI: 82 (75–88); 0	MI: 51 (40–61); 85	
				Low vs High risk: 74 (68–80); 53	Low vs High risk: 46 (38–54); 84	

LNM total lymph node metastases, *PLN* pelvic lymph nodes, *PALN* paraaortic lymph nodes, *No.* numbers, I^2 heterogeneity index across studies collected by each meta-analysis, *DFS* disease-free survival, *HR* pooled hazard ratio of pre-operative SUVmax

[a]The included studies lack histologic confirmation of all putative metastases based on 18F-FDG PET/CT [5]

[b]The results are patients based

[c]the DFS was reported for 264 patients [23]

Table 2 Guidelines for endometrial cancer

Clinical guidelines	Clinical indications
ESMO (2013)	[18F]2-fluoro-2deoxy-D-glucose–positron emission tomography (18F-FDG PET)/CT could be useful for the assessment of suspected recurrent endometrial cancer
	18F-FDG PET/CT could be useful to detect distant metastases accurately
SGO (2017)	18F-FDG PET/CT scan may be useful if there is a suspicion for recurrent disease
	In intermediate- to high-risk patient for extrauterine disease, 18F-FDG PET/CT can evaluate for extrauterine disease and may improve the outcomes by allowing administration of adjuvant chemotherapy following completion of radiation therapy (2014)
ESMO-ESGO-ESTRO Consensus Conference (2016)	As optional preoperative work-up in clinical stage I, grade 1 and 2, 18F-FDG PET/CT should be considered to assess ovarian, nodal, peritoneal or metastatic disease (level of evidence IV; grade of reccomendation C)
NCCN (2020)	In the initial workup, PET/CT may be used to assess disease extent and to evaluate for metastatic disease as indicated based on clinical or abnormal laboratory findings
	Consider whole-body PET/CT for suspected recurrence as clinically indicated

ESMO European Society for Medical Oncology, *SGO* Society of Gynecologic Oncology's, *ESTRO* European Society of Radiation Oncology, *NCCN* National Comprehensive Cancer Network, Level of evidence IV, based on retrospective cohort studies or case–control studies, grade of recommendation C, insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs)

pre-surgical treatment planning [28]. Lastly, thanks to its superior soft tissue contrast, integrated 18F-FDG PET/MRI was more sensitive to the diagnosis of myometrial invasion than 18F-FDG PET/CT, with an overall accuracy of 81.8% and 45.9%, respectively [29]. To date, however, due to the lack of prospective randomized studies comparing 18F-FDG PET/MRI with local ultrasound or MRI alone, the last National Comprehensive Cancer Network guideline for EC considered only whole body 18F-FDG PET/CT if metastasis and/or recurrence are suspected.

With regard to cervical invasion (FIGO stage II), although 18F-FDG PET/CT, MRI and 2D-US modalities were acceptable with negative predictive value of 82–85%, none of these were sensitive enough (29% for 2D-US, 33% for MRI and 43% for PET/CT) [16].

In addition, 18F-FDG PET/CT showed to be helpful in identifying tumor lesions in vagina, adnexa (FIGO stage III), bladder, rectum and more rarely sigmoid colon [30] (FIGO stage IV). Likewise, the ability of 18F-FDG PET/CT to recognize a spreading disease is relevant when MRI cannot be performed (e.g. claustrophobic patients, adverse events to contrast agent, some metal prosthesis). However, diffusion-weighted MRI can provide some accurate information for preoperative evaluation in patients in whom MRI contrast agents are contraindicated [31, 32]. Finally, in patients with incidental increasing uptake, 18F-FDG PET/CT could identify the affected area for biopsy to confirm diagnosis.

Much more prospective studies are essential to confirm the role of 18F-FDG PET/CT in T staging.

The role of 18F-FDG PET/CT in N staging

The last meta-analyses reported high specificity (96%) and quite low sensitivity (68%) for detecting lymph node metastases. However, differently from what was observed in T staging, the smaller values of I^2 reported could be interpreted as meaning that the effect sizes (such as sensitivity and specificity) are better comparable across nineteen studies [26]. More recently, the sensitivity of 18F-FDG PET/CT to detect metastatic lymph nodes was confirmed to be low (45%), but with a specificity of 91% in high-risk EC patients [33]. This low sensitivity may be explained by the tendency of this technique to underestimate standardized uptake values in lymph node smaller than 5 mm due to the partial volume effect [34, 35]. Notwithstanding, a better accuracy was estimated in identifying para-aortic (77%) instead of pelvic (73%) lymph nodes metastases [26]. Further, better sensitivity (93%) and negative predictive value (approximately 100%) emerged for lymph nodes ≥ 10 mm [18].

On the other hand, among CT, MRI, diffusion-weighted magnetic resonance imaging (DW-MRI) and 18F-FDG PET/CT, the last one had the highest specificity while DW-MRI the highest sensitivity [36]. Reasonably, fused PET/DW-MRI showed better sensitivity (89%) than 18F-FDG PET-CT (70%), with quite a similar specificity (91% and 90%, respectively) [35]. Moreover, fused 18F-FDG PET/MRI showed the same performance of 18F-FDG PET/contrast-enhanced CT, combining the individual advantages of MRI and 18F-FDG PET/CT [37]. Accordingly, a meta-analysis on diagnostic performance of PET/MRI in gynecological malignancies ($I^2 = 0\%$) confirmed high sensitivity (87%) and specificity (88%) [38]. The 18F-FDG PET/MRI could provide added benefit to surgeons when selecting appropriate patients for lymphadenectomy [39, 40].

Given the low sensitivity and high false-negative rate, it is still debated if 18F-FDG PET/CT alone can provide benefit to surgeons when selecting appropriate patients for lymphadenectomy. Nevertheless, the high specificity could

be helpful in preoperative phase to guide surgical procedure [41]. Recently, nodal staging detection sensitivity was increased by the computation of imaging features on the primary tumor in a radiomic approach [42]. Moreover, the first-in-human study of positron lymphography, where 18F-FDG is injected interstitially in women with uterine and cervical cancer (clinical trials identifier NCT02285192 which is estimated to be completed in November 2020), demonstrated its feasibility and ability to identify patients with nodal metastases. However, more studies are needed to investigate their potential clinical utility.

The role of 18F-FDG PET/CT in M staging

18F-FDG-PET/CT could be useful to detect distant metastases accurately and the last meta-analysis indicated a sensitivity and specificity of 95% and 91%, respectively [5, 11]. Importantly, for those patients who are candidates for radiation therapy, either curative or palliative, 18F-FDG-PET/CT provided more accurate delineation of metastatic lesions allowing radiation dose escalation that may have improved the effectiveness in local tumor control. Accordingly, 18F-FDG PET/CT has been reported to be of particular value in the detection of occult metastatic disease for inguinal lymph nodes, abdomen, thorax and bone. While the suspicion of distant metastases was documented by conventional imaging, 18F-FDG PET /CT can identify metastatic lesions. In fact, metabolic tracers such as 18F-FDG can overcome the limitations of anatomical imaging since functional changes evaluated by 18F-FDG PET/CT imaging usually precede anatomical changes assessed by CT or MRI [24]. Finally, the usefulness of a whole-body imaging technique such as 18F-FDG PET/CT can be helpful in the detection of atypical sites of metastasis, such as sellar/suprasellar region, therefore being of help in guiding towards the correct diagnosis [43].

This performance in recognizing patients with distant metastases can have high clinical impact on the management of EC patients [44]. It can change the treatment plan in patients who had equivocal findings on conventional imaging, thus affecting the performance status of the patient.

The role of 18F-FDG PET/CT in follow-up

In addition to the ability in local and extra-pelvic staging, 18F-FDG PET/CT was found to be a more useful modality than conventional imaging and CA-125 in recognizing true recurrence in patients with endometrial cancer [45–53]. On this topic, the meta-analysis of Kadkhodayan et al. included 541 patients and showed pooled sensitivity and specificity for the detection of overall recurrence of 95% and 92%, respectively, also highlighting a changed treatment plan in 22–35% of patients [24]. Interestingly, Kitajima et al. compared low-dose non-enhanced CT and full-dose contrast-enhanced CT in integrated 18F-FDG PET/CT studies for restaging and found that sensitivity, specificity and accuracy did not significantly differ between the two methods [54]. Despite the high performance the location of recurrence can affect the performance of 18F-FDG PET/CT. In fact, for para-aortic lymph node, the sensitiviy was reported as sub-optimal (80%), but with high specificity (100%). While higher values have been shown for local recurrence, pelvic lymph nodes and distant metastases (with sensitivity of 91, 98%, 96% and specificity of 98, 96%, 97%, respectively). Nevertheless, the literature that focused on this topic was mainly retrospective and bias related to the choice of the reference standard and interpretations existed [55].

The prognostic value of 18F-FDG PET/CT

The most studied prognostic markers were the maximum standardized uptake value (SUVmax) and metabolic volumetric parameters, such as total lesion glycolysis (TLG) and metabolic tumor volume (MTV).

Several authors agreed that 18F-FDG uptake is higher in patients with more aggressive endometrial tumors [56]. In particular, patients with grade III, lymphovascular invasion, cervical invasion and deep myometrial invasion resulted in a statistically higher pooled average SUVmax [23]. Consistently, Nakamura et al. found that SUVmax significantly correlated with glucose transporter-1 expression ($P < 0.001$) [57]. Further, MTV and TLG were found to be significantly related to deep myometrial invasion, presence of lymph node metastases and high histologic grade [27].

More contradictory results emerged on 18F-FDG PET/CT value for DFS and OS. On the one hand, multivariate analyses revealed that SUVmax was an independent prognostic factor for OS and superior to CA-125 serum levels and ADCmin MRI [58–60]. Further, MTV was shown to be significantly correlated with DFS [23] and OS in EC patients with stage IVB [61]. Interestingly, some authors reported cut-off values to categorize patients as high or low risk. Namely both the OS and DFS in patients with a higher SUVmax (≥ 7.30) were found to be significantly reduced compared with those with a lower SUVmax [62]. In another study, EC patients with SUVmax ≥ 17.7 correlated with lower overall survival [56]. Likewise, cut-off values were reported to be correlated with clinical–pathological risk factors and tumor aggressiveness [63] and risk of treatment failure [59, 63–65].

On the other hand, a systematic review (including 771 patients) did not confirm 18F-FDG PET/CT value for OS. Moreover, no significant relationship was found between 18F-FDG PET/CT (SUVmax, MTV and TLG) parameters and OS or DFS [66]. But primarily, a major concern still remains the very short follow-up in most studies. In fact, EC

is known to have a generally good prognosis and a follow-up should exceed 5 years to see any differences [23].

Recent advances included the applications based on integrated functional biologic parameters, such as the SUV to apparent diffusion coefficient (derived from DW-MRI) ratio [67] or PET-intravoxel incoherent motion MRI, which could define an optimal prognostic parameter in EC patients [68, 69].

Conclusion

The low sensitivity and suboptimal soft tissue differentiation represented the main limitation on the use of 18F-FDG PET/CT imaging for the detection of EC primary tumor and lymph node metastases. Especially the pelvic metastatic lymph nodes and those lesser than 5 mm suffered from a low detection rate, also due to the partial volume effect inherent in PET/CT modality. However, high specificities ensure higher positive predictive values in the tumor and lymph node staging, particularly in para-aortic lymph node metastases. Better performance emerged for detection and localization of distant metastasis or recurrence in post-therapy follow up. In this context, high sensitivity and specificity could suggest important change of treatment planning. In addition, 18F-FDG PET could be useful for its prognostic value. However, the studies did not provide robust scientific evidence for the use of 18F-FDG PET in EC patients risk stratification. Further randomized prospective studies are needed to increase both the low level of evidence and low strength of recommendation for using 18F-FDG PET/CT in EC. Finally, promising results emerged from 18F-FDG PET/DW-MRI technique, where PET specificity can benefit from high sensitivity inherent in MRI modality, which can provide better soft tissue characterization and evaluate microstructure changes.

Compliance with ethical standards

References

1. SEER Statistics (2020) Cancer statistics review, 1975–2016. https://seer.cancer.gov/archive/csr/1975_2016/. Accessed 24 May 2020

2. FIGO Committee on Gynecologic Oncology (2014) FIGO staging for carcinoma of the vulva, cervix, and corpus uteri. Int J Gynaecol Obstet. https://doi.org/10.1016/j.ijgo.2014.02.003

3. Amin MB, Greene FL, Edge SB et al (2017) The Eighth Edition AJCC Cancer Staging Manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin. https://doi.org/10.3322/caac.21388

4. Santaballa A, Matías-Guiu X, Redondo A et al (2018) SEOM clinical guidelines for endometrial cancer. Clin Transl Oncol. https://doi.org/10.1007/s12094-017-1809-9

5. Bollineni VR, Ytre-Hauge S, Bollineni-Balabay O et al (2016) High diagnostic value of 18F-FDG PET/CT in endometrial cancer: Systematic review and meta-analysis of the literature. J Nucl Med. https://doi.org/10.2967/jnumed.115.170597

6. SEER Statistics (2020) Cancer statistics review, 1975–2017. https://seer.cancer.gov/csr/1975_2016/. Accessed 24 May 2020

7. Gadducci A, Cosio S, Genazzani AR (2014) Treatment planning in endometrial cancer treatment planning in endometrial cancer. Cancer Therapy 1:373–391

8. Bristow RE, Zerbe MJ, Rosenshein NB et al (2000) Stage IVB endometrial carcinoma: the role of cytoreductive surgery and determinants of survival. Gynecol Oncol. https://doi.org/10.1006/gyno.2000.5843

9. Haldorsen IS, Salvesen HB (2016) What is the best preoperative imaging for endometrial cancer. Curr Oncol Rep. https://doi.org/10.1007/s11912-016-0506-0

10. Kim HS, Suh DH, Kim MK et al (2012) Systematic lymphadenectomy for survival in patients with endometrial cancer: a meta-analysis. Jpn J Clin Oncol. https://doi.org/10.1093/jjco/hys019

11. Colombo N, Preti E, Landoni F et al (2013) Endometrial cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. https://doi.org/10.1093/annonc/mdt353

12. Panici PB, Basile S, Maneschi F et al (2008) Systematic pelvic lymphadenectomy vs no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. J Natl Cancer Inst. https://doi.org/10.1093/jnci/djn397

13. Dowdy SC, Borah BJ, Bakkum-Gamez JN et al (2012) Prospective assessment of survival, morbidity, and cost associated with lymphadenectomy in low-risk endometrial cancer. Gynecol Oncol. https://doi.org/10.1016/j.ygyno.2012.06.035

14. Dong Y, Cheng Y, Tian W et al (2019) An externally validated nomogram for predicting lymph node metastasis of presumed Stage I and II endometrial cancer. Front Oncol. https://doi.org/10.3389/fonc.2019.01218

15. Goldstein A, Mcintosh L, Masciocchi M et al (2018) Endometrial cancer staging: imaging. Review. https://doi.org/10.1594/ecr2018/C-1268.Accessed25June2020

16. Antonsen SL, Jensen LN, Loft A et al (2013) MRI, PET/CT and ultrasound in the preoperative staging of endometrial cancer—a multicenter prospective comparative study. Gynecol Oncol. https://doi.org/10.1016/j.ygyno.2012.11.025

17. Parsyan A, Banerjee S (2014) Gynecologic cancers. In: Parsyan A (ed) Translation and its regulation in cancer biology and medicine. Springer, Dordrecht. https://doi.org/10.1007/978-94-017-9078-9_32

18. Chang MC, Chen JH, Liang JA et al (2012) 18F-FDG PET or PET/CT for detection of metastatic lymph nodes in patients with endometrial cancer: A systematic review and meta-analysis. Eur J Radiol. https://doi.org/10.1016/j.ejrad.2012.01.024

19. Rocha A, Domínguez AM, Lécuru F et al (2016) Indocyanine green and infrared fluorescence in detection of sentinel lymph nodes in endometrial and cervical cancer staging—a systematic review. Eur J Obstet Gynecol Reprod Biol. https://doi.org/10.1016/j.ejogrb.2016.09.027

20. Colombo N, Creutzberg C, Amant F et al (2016) ESMO-ESGO-ESTRO consensus conference on endometrial cancer: diagnosis,

treatment and follow-up. Int J Gynecol Cancer. https://doi.org/10.1097/IGC.0000000000000609

21. Burke WM, Orr J, Leitao M et al (2014) Endometrial cancer: a review and current management strategies: Part II. Gynecol Oncol. https://doi.org/10.1016/j.ygyno.2014.06.003

22. Melsen WG, Bootsma MCJ, Rovers MM et al (2014) The effects of clinical and statistical heterogeneity on the predictive values of results from meta-analyses. Clin Microbiol Infect. https://doi.org/10.1111/1469-0691.12494

23. Ghooshkhanei H, Treglia G, Sabouri G et al (2014) Risk stratification and prognosis determination using 18F-FDG PET imaging in endometrial cancer patients: a systematic review and meta-analysis. Gynecol Oncol. https://doi.org/10.1016/j.ygyno.2014.01.039

24. Kadkhodayan S, Shahriari S, Treglia G et al (2013) Accuracy of 18-F-FDG PET imaging in the follow up of endometrial cancer patients: systematic review and meta-analysis of the literature. Gynecol Oncol. https://doi.org/10.1016/j.ygyno.2012.10.022

25. Kakhki VRD, Shahriari S, Treglia G et al (2013) Diagnostic performance of fluorine 18 fluorodeoxyglucose positron emission tomography imaging for detection of primary lesion and staging of endometrial cancer patients: systematic review and meta-analysis of the literature. Int J Gynecol Cancer. https://doi.org/10.1097/IGC.0000000000000003

26. Hu J, Zhang K, Yan Y et al (2019) Diagnostic accuracy of preoperative 18F-FDG PET or PET/CT in detecting pelvic and para-aortic lymph node metastasis in patients with endometrial cancer: a systematic review and meta-analysis. Arch Gynecol Obstet. https://doi.org/10.1007/s00404-019-05207-8

27. Husby JA, Reitan BC, Biermann M et al (2015) Metabolic tumor volume on 18F-FDG PET/CT improves preoperative identification of high-risk endometrial carcinoma patients. J Nucl Med. https://doi.org/10.2967/jnumed.115.159913

28. Sudo S, Hattori N, Manabe O et al (2015) FDG PET/CT diagnostic criteria may need adjustment based on MRI to estimate the presurgical risk of extrapelvic infiltration in patients with uterine endometrial cancer. Eur J Nucl Med Mol Imaging. https://doi.org/10.1007/s00259-014-2964-7

29. Bian LH, Wang M, Gong J, Liu HH et al (2019) Comparison of integrated PET/MRI with PET/CT in evaluation of endometrial cancer: a retrospective analysis of 81 cases. PeerJ. https://doi.org/10.7717/peerj.7081

30. Jeffrey A, Soni A (2017) A rare case of endometrial cancer metastatic to the sigmoid colon and small bowel. Case Rep Gastrointest Med. https://doi.org/10.1155/2017/9382486

31. Lin G, Ng KK, Chang CJ et al (2009) Myometrial invasion in trial cancer: diagnostic accuracy of diffusion-weighted 3-T MR imaging-initial experience. Radiology. https://doi.org/10.1148/radiol.2503080874

32. Huang YT, Huang YL, Ng KK et al (2019) Current status of magnetic resonance imaging in patients with malignant uterine neoplasms: a review. Korean J Radiol. https://doi.org/10.3348/kjr.2018.0090

33. Stewart KI, Chasen B, Erwin W et al (2019) Preoperative PET/CT does not accurately detect extrauterine disease in patients with newly diagnosed high-risk endometrial cancer: a prospective study. Cancer. https://doi.org/10.1002/cncr.32329

34. Rezaee A, Schäfer N, Avril N et al (2017) PET/CT in cancer: an interdisciplinary approach to individualized imaging. In: Gynecologic cancer. Springer, Dordrecht. https://doi.org/10.1016/B978-0-323-48567-8.00009-2

35. Stecco A, Buemi F, Cassarà A et al (2016) Comparison of retrospective PET and MRI-DWI (PET/MRI-DWI) image fusion with PET/CT and MRI-DWI in detection of cervical and endometrial cancer lymph node metastases. Radiol Medica. https://doi.org/10.1007/s11547-016-0626-5

36. Liu B, Gao S, Li S (2017) A comprehensive comparison of CT, MRI, positron emission tomography or positron emission tomography/CT, and diffusion weighted imaging-MRI for detecting the lymph nodes metastases in patients with cervical cancer: a meta-analysis based on 67 studies. Gynecol Obstet Invest. https://doi.org/10.1159/000456006

37. Kitajima K, Suenaga Y, Ueno Y et al (2014) Fusion of PET and MRI for staging of uterine cervical cancer: comparison with contrast-enhanced 18F-FDG PET/CT and pelvic MRI. Clin Imaging. https://doi.org/10.1016/j.clinimag.2014.02.006

38. Virarkar M, Devine C, Bassett R et al (2020) Update on diagnostic performance of PET/MRI in gynecological malignancies: a systematic review and meta-analysis. J Belgian Soc Radiol. https://doi.org/10.5334/jbsr.1981

39. Queiroz MA, Kubik-Huch RA, Hauser N et al (2015) PET/MRI and PET/CT in advanced gynaecological tumours: initial experience and comparison. Eur Radiol. https://doi.org/10.1007/s00330-015-3657-8

40. Kitajima K, Suenaga Y, Ueno Y et al (2013) Value of fusion of PET and MRI for staging of endometrial cancer: comparison with 18F-FDGcontrast-enhanced PET/CT and dynamic contrast-enhanced pelvic MRI. Eur J Radiol. https://doi.org/10.1016/j.ejrad.2013.05.005

41. Budak E, Yanarateş A (2019) The value of PET/CT in determining lymph node metastasis of endometrial cancer. Ginekol Pol. https://doi.org/10.5603/GP.2019.0098

42. De Bernardi E, Buda A, Guerra L et al (2018) Radiomics of the primary tumour as a tool to improve 18F-FDG-PET sensitivity in detecting nodal metastases in endometrial cancer. EJNMMI. https://doi.org/10.1186/s13550-018-0441-1

43. Salvatore B, D'Amico D, Fonti R (2018) Metastasis to the sellar/suprasellar region in a patient with endometrial carcinoma detected by 18F-FDG PET/CT. Clin Nucl Med. https://doi.org/10.1097/RLU.0000000000002037

44. Al-Ibraheem A, AlSharif A, Abu-Hijlih R et al (2019) Clinical impact of 18F-FDG PET/CT on the management of gynecologic cancers: one center experience. Asia Ocean J Nucl Med Biol. https://doi.org/10.22038/AOJNMB.2018.11208

45. Chung HH, Kang WJ, Kim JW et al (2008) The clinical impact of [18F]FDG PET/CT for the management of recurrent endometrial cancer: correlation with clinical and histological findings. Eur J Nucl Med Mol. https://doi.org/10.1007/s00259-007-0687-8

46. Saga T, Higashi T, Ishimori T et al (2003) Clinical value of FDG-PET in the follow up of post-operative patients with endometrial cancer. Ann Nucl Med. https://doi.org/10.1007/BF02990022

47. Sironi S, Picchio M, Landoni C et al (2007) Post-therapy surveillance of patients with uterine cancers: value of integrated FDG PET/CT in the detection of recurrence. Eur J Nucl Med Mol Imaging. https://doi.org/10.1007/s00259-006-0251-y

48. Kitajima K, Murakami K, Yamasaki E et al (2009) Performance of integrated FDG-PET/contrast-enhanced CT in the diagnosis of recurrent uterine cancer: comparison with PET and enhanced CT. Eur J Nucl Med Mol Imaging. https://doi.org/10.1007/s00259-008-0956-1

49. Ryu SY, Kim K, Kim Y et al (2010) Detection of recurrence by 18F-FDG PET in patients with endometrial cancer showing no evidence of disease. J Korean Med Sci. https://doi.org/10.3346/jkms.2010.25.7.1029

50. Ozcan Kara P, Kara T, Kaya B et al (2012) The value of FDG-PET/CT in the post-treatment evaluation of endometrial carcinoma: a comparison of PET/CT findings with conventional imaging and CA 125 as a tumour marker. Rev Esp Med Nucl Imagen Mol. https://doi.org/10.1016/j.remn.2011.06.001

51. Sharma P, Kumar R, Singh H et al (2012) Carcinoma endometrium: role of 18-FDG PET/CT for detection of suspected

recurrence. Clin Nucl Med. https://doi.org/10.1097/RLU.0b013e31824d24fa

52. Park JY, Kim EN, Kim DY et al (2008) Clinical impact of positron emission tomography or positron emission tomography/computed tomography in the posttherapy surveillance of endometrial carcinoma: evaluation of 88 patients. Int J Gynecol Cancer. https://doi.org/10.1111/j.1525-1438.2008.01197.x

53. Lebron L, Ma W, Larson SM et al (2009) F18-FDG PET/CT for detection of recurrent endometrial cancer. J Nucl Med 50:1702

54. Kitajima K, Suzuki K, Nakamoto Y et al (2010) Low-dose non-enhanced CT versus full-dose contrast-enhanced CT in integrated PET/CT studies for the diagnosis of uterine cancer recurrence. Eur J Nucl Med Mol Imaging. https://doi.org/10.1007/s00259-010-1440-2

55. Albano D, Zizioli V, Odicino F et al (2019) Clinical and prognostic value of 18 F-FDG PET/CT in recurrent endometrial carcinoma. Rev Esp Med Nucl Imagen Mol. https://doi.org/10.1016/j.remn.2018.09.005

56. Walentowicz-Sadlecka W, Malkowski B, Walentowicz P et al (2014) The preoperative maximum standardized uptake value measured by 18F-FDG PET/CT as an independent prognostic factor of overall survival in endometrial cancer patients. Biomed Res Int. https://doi.org/10.1155/2014/234813

57. Nakamura K, Kodama J, Okumura Y et al (2010) The SUVmax of 18F-FDG PET correlates with histological grade in endometrial cancer. Int J Gynecol Cancer. https://doi.org/10.1111/IGC.0b013e3181c3a288

58. Nakamura K, Joja I, Fukushima C et al (2013) The preoperative SUVmax is superior to ADCmin of the primary tumour as a predictor of disease recurrence and survival in patients with endometrial cancer. Eur J Nucl Med Mol Imaging. https://doi.org/10.1007/s00259-012-2240-7

59. Nakamura K, Hongo A, Kodama J et al (2011) The measurement of SUVmax of the primary tumor is predictive of prognosis for patients with endometrial cancer. Gynecol Oncol. https://doi.org/10.1016/j.ygyno.2011.06.026

60. Musto A, Grassetto G, Marzola MC et al (2014) Role of 18F-FDG PET/CT in the carcinoma of the uterus: a review of literature. Yonsei Med J. https://doi.org/10.3349/ymj.2014.55.6.1467

61. Liu FY, Chao A, Lai CH et al (2012) Metabolic tumor volume by 18 F-FDG PET/CT is prognostic for stage IVB endometrial carcinoma. Gynecol Oncol. https://doi.org/10.1016/j.ygyno.2012.03.021

62. Yahata T, Yagi S, Mabuchi Y et al (2016) Prognostic impact of primary tumor SUVmax on preoperative 18F-fluoro-2-deoxy-D-glucose positron emission tomography and computed tomography in endometrial cancer and uterine carcinosarcoma. Mol Clin Oncol. https://doi.org/10.3892/mco.2016.980

63. Brunetti J (2013) PET/CT in gynecologic malignancies. Radiol Clin North Am. https://doi.org/10.1016/j.rcl.2013.05.006

64. Lee HJ, Ahn BC, Hong CM et al (2011) Preoperative risk stratification using 18F-FDG PET/CT in women with endometrial cancer. Nuklear Medizin. https://doi.org/10.3413/nukmed-0375-10-12

65. Wu C, Chen R, Zhou X et al (2020) Preoperative evaluation of residual tumor in patients with endometrial carcinoma by using 18F-FDG PET/CT. J Cancer. https://doi.org/10.7150/jca.39423

66. Yanarateş A, Budak E (2019) Prognostic role of PET/CT in endometrial cancer. Ginekol Pol. https://doi.org/10.5603/GP.2019.0085

67. Tsuyoshi H, Tsujikawa T, Yamada S et al (2020) FDG-PET/MRI with high-resolution DWI characterises the distinct phenotypes of endometrial cancer. Clin Radiol. https://doi.org/10.1016/j.crad.2019.10.018

68. Tsujikawa T, Yoshida Y, Kudo T et al (2009) Functional images reflect aggressiveness of endometrial carcinoma: estrogen receptor expression combined with 18F-FDG PET. J Nucl Med. https://doi.org/10.2967/jnumed.108.060145

69. Xu C, Li X, Shi Y et al (2020) Combinative evaluation of primary tumor and lymph nodes to predict pelvic lymphatic metastasis in cervical cancer: an integrated PET-IVIM MRI study. Cancer Imaging. https://doi.org/10.1186/s40644-020-00298-y

70. Kitajima K, Murakami K, Yamasaki E et al (2008) Performance of FDG-PET/CT in the diagnosis of recurrent endometrial cancer. Ann Nucl Med. https://doi.org/10.1007/s12149-007-0087-y