Review

Molecular imaging in the management of gynecologic malignancies

Chyong-Huey Lai a,⁎, Gin Lin b, Tzu-Chen Yen c, Feng-Yuan Liu c

a Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taoyuan, Taiwan

b Department of Medical Imaging and Intervention, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taoyuan, Taiwan

c Department of Nuclear Medicine, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taoyuan, Taiwan

HIGHLIGHTS

• Molecular imaging (PET or MRI) has various impacts in different clinical scenarios.
• Prospective studies with defined endpoints are necessary to evaluate roles of these emerging tools in management of gynecologic malignancies.

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ABSTRACT

Objectives. The purpose of this review is to summarize literature pertaining to clinical roles of positron emission tomography (PET) or integrated PET and computed tomography (PET/CT) scans, magnetic resonance imaging (MRI) and emerging technologies of these two molecular imaging tools for gynecologic malignancies.

Methods. PubMed and MEDLINE databases search for articles published before June 2014 was performed. Only English-language articles were considered. Search terms included “cervical cancer”, “endometrial cancer”, “uterine cancer”, “uterine sarcoma”, “ovarian cancer” and “vulvar cancer”, in association with “FDG”, “PET”, “PET/CT”, “MRI”, “PET/MRI”, “diffusion”, “spectroscopy” and “clinical trial”.

Results. Topics explored included PET, PET/CT and MRI for diagnosis of malignancy, prognostic implications, clinical staging of disease extent, monitoring treatment response, post-therapy surveillance, diagnosis of treatment failure and restaging, and follow-up after salvage therapy in gynecologic malignancies.

Conclusions. Molecular imaging (mainly PET and MRI) plays important roles in the management of gynecologic malignancies. Molecular imaging has various impacts in different clinical scenarios. Emerging technologies will continuously improve our practice. Prospective studies with defined endpoints are necessary to evaluate roles of these novel tools in management of gynecologic malignancies.

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⁎ Corresponding author at: Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, 5 Fu-Shin Street, Kueishan, Taoyuan 333, Taiwan. Fax: +886 3 3288252.
E-mail address: sh46erry@ms6.hinet.net (C.-H. Lai).

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Introduction

Molecular imaging is a means of in vivo visualization of the key molecularly based events, which represents the cancer phenotype and has potential as imaging biomarkers [1] applied in cancer management [2]. Magnetic resonance imaging (MRI) has advanced toward scale beyond the anatomical structures in many aspects. Diffusion-weighted imaging (DWI) measures Brownian motion of molecules and highlights the increased cellularity of cancer tissue, which can be quantitatively evaluated on the apparent diffusion coefficient (ADC) map [3]. Dynamic contrast enhancement (DCE)-MRI makes use of intravascular gadolinium-based contrast agent that is blocked by the tight-junction of the normal blood vessel but leaks out through the neovascularization in the tumor, which provide profuse modeling information such as blood flow, extraction fraction, blood volume, volume of extravascular extracellular space (EES), capillary permeability surface area product and transfer from blood to EES (Ktrans) [4]. MR spectroscopy (MRS) is a technique that can semi-quantitatively acquire chemical composition in a selected region of interest [5]. Nowadays most clinical MR scanners have routine sequences for proton (1H)-MRS measurements, providing a range of metabolic and functional information integrated with complementary MRI localization. Positron emission tomography (PET), on the other hand, can provide functional or metabolic information with specifically labeled radiotracers suitable for different disease scenarios [6]. Integrated PET and computed tomography (PET/CT) scan using 18F-fluorodeoxyglucose (FDG) is now widely used clinically, and many potential radiotracers other than FDG are under development (Table 1). In addition to radiotracers development, imaging parameter breakthrough has translated in clinical application to a new era [8].

Diagnosis of malignancy

Molecular imaging may predict the degree of malignancy in ovary tumors or uterine sarcoma sparing endometrium. This function in

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<td>The possibility of imaging parameters to predict surgical-pathological findings listed on FIGO staging/AJCC 2010 7th edition.</td>
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<td>Invasion to lower third of vagina</td>
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<td>Invasion to bladder mucosa</td>
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<td>Extends beyond true pelvis</td>
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<td>Regional pelvic lymph node metastasis</td>
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<td>Distant metastasis para-aortic lymph nodes</td>
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<td>Distant metastasis (including peritoneal spread, involvement of supraclavicular, mediastinal, or lung, liver, or bone)</td>
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<th>Endometrial carcinoma</th>
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<td>Limited to endometrium or invades less than one-half or one-half or more of the myometrium</td>
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<td>Uterine serosa invasion</td>
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<td>Invasion to stromal connective tissue of the cervix</td>
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<td>Adnexal direct extension or metastasis</td>
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<td>Vaginal involvement (direct extension or metastasis)</td>
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<td>Invasion to bowel mucosa</td>
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<td>Regional pelvic lymph node metastasis</td>
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<td>Regional para-aortic lymph node metastasis</td>
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<td>Distant metastasis (includes metastasis to inguinal lymph nodes, intra-peritoneal disease, or lung, liver, or bone. It excludes metastasis to para-aortic lymph nodes, vagina, pelvic serosa, or adnexa)</td>
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<td>Tumor limited to one or both ovary</td>
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Note: Radiotracers listed are a small selection of the many available.

* US Food and Drug Administration-approved radiotracers.
cervical cancer, endometrial cancer or vulvar cancer is less prominent because tissue diagnosis is often made before surgical intervention. Rism et al. showed that FDG-PET/CT is superior to CT or conventional MRI, in distinguishing malignant or borderline tumor from benign ovarian tumors, yielding a sensitivity of 92–100% and a specificity of 85–92.5% in identifying primary ovarian cancer in patients with a pelvic mass and risk of malignancy index (RMI) > 150 [9]. In a recent preliminary report the choline peak on MR spectra was detected in malignant ovarian tumors and was absent in apparently healthy pelvic tissues, which opens new research window for early diagnosis of ovarian cancer [10].

In preoperative diagnosis of uterine leiomyosarcoma, Tanaka et al. demonstrated the presence of high signal on T2-weighted image, any small high-signal areas on T1-weighted image, or areas of unenhanced pocket as imaging features suggestive of leiomyosarcoma or smooth muscle tumors of uncertain malignant potential (n = 12) [11]. Sato et al. reported a combination of signal intensity on DWI and ADC value on MRI, yielding a sensitivity of 100% and a specificity of 94% in imaging diagnosis of leiomyosarcoma (n = 5) [12]. More recently, Yamane et al. showed that 3′-deoxy-3′-[18F]-Fluorothymidine (18F-FLT) PET outperforms FDG-PET (p < 0.01) in differentiation of SUVmax between malignant uterine corpus tumors (n = 5) from benign leiomyoma (n = 10) [13]. To date no adequate evidence has been provided by a large scale or prospective study partly because of rareness of uterine sarcoma. In cervical cancer, radiotracers other than FDG such as 68Ga-cored diacetylaspartate (N4-methylthiosemicarbazone) (68Ga-ATSM) were used to demonstrate hypoxia and 11C-choline for proliferative activity, yet have not gained popularity [14].

**Clinical staging of disease extent**

Precise clinical staging is crucial for selection of primary therapy for cervical cancer. Generally, International Federation of Gynecology and Obstetrics [FIGO] stages IA1–IA2A diseases can be treated with either primary surgery or radiotherapy (RT), while stages IB2 to IV (except IA1) diseases can be treated with definitive radiation with concurrent platinum-based chemotherapy [14]. MRI was found useful to confirm the absence of residual tumor in the cervix after a cone biopsy with negative margins in selection of patients for fertility-sparing radical trachelectomy [15]. Results of the intergroup study American College of Radiology Imaging Network (ACRIN) 6651/Gynecologic Oncology Group (GOG) 183 showed that, in patients with early-stage cervical cancer scheduled for curative radical hysterectomy, MRI is superior to CT by receiver operating curve (ROC) analysis (area under the curve [AUC] 0.80 vs. 0.66, respectively; p < 0.01), for evaluating uterine body involvement and measuring tumor size [16], and has a sensitivity of 53% and a specificity of 74% in detection of parametrial invasion (≥ IIB) [17]. A European multicenter trial to evaluate tumor delineation by MRI in early-stage cervical cancer showed that, the agreement between MRI and histology was good for classifying tumors as ≤ 2 cm, or ≤ 4 cm, and detecting deep stromal invasion (kappa values of 0.77, 0.76, 0.77, respectively), but only moderately accurate in assessing parametral invasion (kappa values of 0.52, 0.45, respectively) [18].

Data from the ACRIN 6651/GOG 183 study showed MRI has only a sensitivity of 37% but a specificity of 94% in detecting pelvic lymph node (LN) metastases [19]. Lin et al. has demonstrated a combination of size and relative ADC values on DVI being useful in detecting pelvic LN (PLN) metastasis in patients’ population mixed with cervical and endometrial cancer, trying to provide a better sensitivity (25% vs. 83%) and maintain a similar specificity (98% vs. 99%), as compared with conventional MRI [20]. Chou et al. [21] showed that FDG-PET detected only one of the 10 MRI-negative pelvic metastatic LNs in patients with primary, non-bulky, stages IIA2 to IIA cervical cancer. The PET false-negative PLN containing micro-metastasis measured a short axis diameter of only 0.5–6 mm [21]. Kitajima et al. compared DVI and FDG-PET/CT in evaluation of LN metastasis in cervical and endometrial cancer, showing that DVI has a higher sensitivity (83.3% vs. 38.9%) but a lower specificity (51.2% vs. 96.3%) than FDG-PET/CT [22]. Kim et al. evaluated the additional diagnostic value of FDG-PET and MRI fusion in the detection of metastatic LNs in cervical cancer patients, with the sensitivity and specificity of FDG-PET/CT and fused FDG-PET/MRI being 44.1%, 93.9% and 54.2%, 92.7% respectively [23].

Detection of paraaortic LN (PALN) metastasis is an important issue because extended-field RT is indicated based on PALN positivity, although it remains controversial whether extraperitoneal paraaortic lymphadenectomy should be performed [24]. In patients having negative findings of PALN on CT or MRI, the sensitivity and specificity of FDG-PET/CT were 33–36% and 94–96%, respectively, using laparoscopic paraaortic lymphadenectomy histology as a gold standard [25,26]. In patients with stage IB/IB cervical adenocarcinoma or adenosquamous carcinoma, the diagnostic efficacy in identifying metastatic PALN was significantly higher in FDG-PET than in MRI, with a sensitivity of 66.7% and a specificity of 100%, based on surgical histopathology [27]. Tsai et al. demonstrated that pretreatment FDG-PET improves the detection of extrapelvic metastasis on MRI, mainly PALN, and helps to select patients for extended-field RT, albeit not translating into survival benefit, even with a reduced rate in PALN relapse [28].

For patients who present with distant metastatic disease (i.e., stage IVB), primary treatment is often cisplatin-based chemotherapy. In these situations, individualized RT may be considered for pelvic disease and other symptoms. For newly diagnosed cervical cancer FIGO stage ≥ IB, FDG-PET/CT has a sensitivity of 100% and a specificity of 94% in detecting distant metastases [29]. Liu et al. demonstrated the superiority of FDG-PET over CT and MRI for detecting hematogenous bone metastasis in FIGO stage III/IV or positive LN metastasis cervical cancer patients upon primary staging [30]. However, FDG-PET/CT should be interpreted cautiously for isolated mediastinal involvement in newly diagnosed cervical cancer patients, because 75% of the mediastinal LNs with increased FDG uptake were eventually confirmed histopathologically to be granulomatous changes only and free of tumor [31].

For endometrial cancer, Antonsen et al. reported a Danish multicenter prospective comparative study showing the prediction of myometrial invasion, the sensitivity and specificity being 93% and 49% for FDG-PET/CT, and 87% and 57% for conventional MRI [32]. Lin et al. demonstrated fused T2-weighted and high-b-value DWI at 3T can provide accurate information for preoperative evaluation of myometrial invasion, with a sensitivity of 86% and a specificity of 100% [33]. Regarding the detection of cervical invasion, the sensitivity of both FDG-PET/CT and MRI was suboptimal (43% and 33%, respectively) [32].

For preoperative diagnosis of LN metastases in patients with endometrial carcinoma, the sensitivity and specificity of FDG-PET/CT were 67–74% and 93–94% respectively, superior to those of MRI, 59% and 93%, proven by surgical staging [32,34]. Suzuki et al. reported that FDG-PET had a sensitivity superior to CT/MRI, in detection of extraperitoneal lesions excluding retroperitoneal LNs (83.3% vs. 66.7%), although there was no difference in the specificity among the modalities (100%) [35]. FDG-PET also had a higher specificity (100%) compared with CT/ MRI (85.7%), but still could not detect LN metastatic lesions smaller than 0.6 cm in short-axis diameter [35]. Ho et al. [36] showed that FDG-PET is beneficial in excluding falsely inoperable carcinosarcoma for curative therapy and in making a decision on palliation for better quality of life instead of aggressive treatment.

Regarding ovarian cancer, Hyninen et al. showed a substantial number of patients with advanced ovarian cancer stages IIIC–IV showing supra-diaphragmatic nodal metastasis in pre-treatment FDG-PET/CT, suggesting that the route of ovarian cancer cells from the peritoneal cavity to the lymphatic system permeates the diaphragm mainly to the cardiophrenic node and continues to the parasternal LNs [37]. A meta-analysis demonstrated that, FDG-PET or FDG-PET/CT (sensitivity, 73.2%; specificity, 96.7%) is more accurate than CT (sensitivity, 42.6%; specificity, 95.0%) or MRI (sensitivity, 54.7%; specificity, 88.3%) in the detection of LN metastasis in
of recurrent disease as detected by conventional CT or MRI, but had responses to primary treatment or salvage therapy, there is no evidence to provide a surrogate biomarker of treatment response in advanced disease. Cohn et al. showed that ADC values was reproducible and showed a significant reduction in tumor volume on MRI and PET/CT scans in patients with cervical cancer [40]. Yen et al. defined the priority of using FDG-PET in cervical cancer patients after a definitive treatment with documented failure or unexplained elevated tumor marker in serum. Primary radiation treatment, SCC-Ag ≥ 4 ng/mL, and the presence of symptoms at recurrence were significant factors of poor survival. FDG-PET may offer maximal benefits by selecting appropriate recurrent cervical cancer patients for salvage therapy with precise restaging information [54].

In patients with cervical carcinoma who experienced confirmed treatment failure but who were feasible candidates for curative salvage therapy, FDG-PET was significantly superior to CT/MRI (sensitivity: 92% vs. 60%) in identifying metastatic lesions, and led to treatment plan modifications in 55% of the participants [55]. The benefits of FDG-PET exceed those of CT-MRI mainly because of the ability of FDG-PET to identify extra-pelvic metastases and its higher sensitivity and specificity [56]. Overall FDG-PET has a positive impact on 46% patients in cervical cancer patients with histologically documented recurrence after curative salvage therapy or unexplained tumor marker elevation [57].

Park et al. evaluated the clinical impact of FDG-PET or PET/CT in the post-therapy surveillance of endometrial carcinoma. In patients with suspected disease recurrence, the sensitivity and specificity of FDG-PET and/or PET/CT in detecting recurrence in these patients was 100% and 83.3%, respectively. In asymptomatic patients for routine post-therapy surveillance, the sensitivity and specificity of FDG-PET or PET/CT were both 100%. FDG-PET and/or PET/CT were highly effective in discriminating true recurrence in patients with suspected recurrence, highly sensitive in detecting recurrence in asymptomatic patients, and had impacts on clinical decisions in a considerable portion of patients [58]. Chao et al. reported that, in primary advanced (stage III/IV), or suspicious/document recurrent endometrial cancer or surveillance after salvage therapy, FDG-PET plus MRI or CT was significantly superior to MRI or CT alone in overall lesion detection, detection of pelvic nodal/soft tissue metastases and detection of extrapelvic metastases (AUC 0.949 vs. 0.872; p = 0.004). Positive clinical impact was more often seen among those for suspicious/document recurrence or post-salvage surveillance (70%) than primary staging (22.2%) [59].

Antonsen et al. found that preoperative SUVmax of endometrial tumor is significantly higher in patients with high FIGO stages, deep myometrial invasion, cervical invasion, LN metastasis and high-risk tumors. However, the sensitivity and specificity of the SUVmax in staging endometrial cancer is not high enough to reliably replace surgical staging [46]. The preoperative SUVmax is also superior to ADCmin of the primary tumor as a predictor of disease recurrence and survival in patients with endometrial cancer [47]. Liu et al. reported that MTV by FDG-PET/CT is prognostic for stage IB endometrial carcinoma [48], with 4 patients with total body MTV above 450 mL (or total body TLG above 2700 g) having a median survival of 2 months, while the remaining patients having a median survival of 47 months.

Response evaluation, surveillance, and the management of recurrence

Imaging is indicated in patients with symptoms or findings that are suspicious for recurrence but not routinely recommended for surveillance [49]. According to the NCCN Guidelines, in patients at high risk for locoregional failure, a combined PET/CT scan (e.g., 3–6 months after treatment) or other radiologic imaging may be useful for detecting asymptomatic disease that is potentially curable [49]. deSouza et al. assessed tumor response to neoadjuvant chemotherapy prior to radical hysterectomy in FIGO stages IB–IIB previously untreated cervical tumors >10 cm², and found a significant reduction in tumor volume on MRI and –CH₂ triglyceride levels on MRS after neoadjuvant chemotherapy [50]. Furthermore, Harry et al. showed that ADC values was reproducible and showed a significant correlation with eventual clinical response, hence has potential to provide a surrogate biomarker of treatment response in advanced cervical cancers [51].

In patients with cervical cancer who experienced complete responses to primary treatment or salvage therapy, there is no evidence of recurrent disease as detected by conventional CT or MRI, but had serum squamous cell carcinoma antigen (SCC-Ag) level elevation on two consecutive occasions. Chang et al. demonstrated that FDG-PET expedited the detection (94%) of recurrence [52]. Chung et al. reported that the overall sensitivity and specificity of post-treatment FDG-PET/CT were 94.7% and 87.8% [53]. Yen et al. defined the priority of using FDG-PET in cervical cancer patients after a definitive treatment with documented failure or unexplained elevated tumor marker in serum. Primary radiation treatment, SCC-Ag ≥ 4 ng/mL, and the presence of symptoms at recurrence were significant factors of poor survival. FDG-PET may offer maximal benefits by selecting appropriate recurrent cervical cancer patients for salvage therapy with precise restaging information [54].

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Emerging molecular imaging techniques

PET/MR

The recently introduced hybrid PET/MR might improve the diagnostic performance of PET/CT, based on the major strengths of MRI over CT, including superior soft tissue contrast, multiplanar image acquisition and functional imaging capability through specialized techniques. Moreover, the absence of radiation using MR might be particularly beneficial in pediatric, young adult, or pregnant patients [8]. Initial results (n = 19) in cervical cancer from hybrid PET/MR including Grueneisen et al. revealed a significant inverse correlation between SUVmax and ADCmin of primary tumors (R = −0.342, p < 0.05) and associated primary LN metastases (R = −0.692, p < 0.001), measured in a hybrid PET/MR system, whereas recurrent cervical cancer lesions did not show a significant correlation [67]. Hybrid PET/MR has also been applied for radiation treatment planning in cervical cancer patients but the results are controversial. Zhang et al. reported that tumor volume discrepancies were observed between MR-GTV (manually T2-weighted) and PET-GTV (auto-contoured by 40% SUV threshold) [68], but a strong volume concordance between FDG-PET, and T2-weighted and DWI was reported by Sun et al. [69]. Cost-effectiveness analysis should be used as an end point in researches using new PET and MRI technologies.

PET texture analysis

Texture analysis is an image process technique analyzing a set of quantified metrics to represent the spatial arrangement of intensities in a volume of interest on PET. Coarseness, contrast and heterogeneity are frequently encountered metrics [70]. Although there is currently no evidence of connection between image texture and tumor heterogeneity at the cellular level, many researchers have tried texture analysis techniques on functional PET or structural CT and MR images to find potential parameters for prognosis and treatment response, as alternatives to traditional parameters such as tumor volume and SUV. Yang et al. had conducted a pilot study with 20 cervical cancer patients treated with combined chemoradiation and suggested some texture parameters may be better than SUV in predicting treatment outcome during the early phase of treatment [71]. However, by finding a few potential ones from a pool of numerous parameters with mathematical variation in a limited set of patients, further prospective, large-scale studies have to be performed with the exact same parameters to validate their true utility. Texture analysis on functional and structural medical images is a complicated field with potentiality and with many questions to be clarified [72].

Dynamic nuclear polarization (DNP)

Dynamic nuclear polarization (DNP) is a novel imaging technique which uses specialized instrumentation to provide signal enhancements of over 10,000-folds of magnitude for stable isotope carbon-13 (13C) enriched compounds [73]. Hyperpolarized [1-13C]pyruvate has been used to study the real-time flow of pyruvate to lactate non-invasively following anticancer therapies in xenograft models. In addition to pyruvate, hyperpolarized 13CO2− has been demonstrated to measure extracellular pH in lymphoma xenograft and [1,4-13C2]glutarate showed the potential as an indicator of necrotic cell death [73]. The first clinical trial of DNP-MRS has recently demonstrated the use of hyperpolarized [1-13C]pyruvate to examine prostate cancer metabolism in human [74], and paves the way to rapid translation of this exciting technology to clinical research and perhaps clinical practice.

Chemical exchange saturation transfer (CEST) imaging

Chemical exchange saturation transfer (CEST) imaging is an emerging MRI approach in which exogenous or endogenous compounds containing either exchangeable protons or exchangeable molecules are selectively saturated and after transfer of this saturation, detected indirectly through the water signal with enhanced sensitivity [75]. By measuring the uptake of unlabeled glucose to be measured through the chemical exchange of protons between hydroxyl groups and water, Walker-Samuels et al. demonstrated that CEST was sensitive to tumor glucose accumulation in colorectal tumor models and could distinguish tumor types and potentially assessing response to therapy in the clinic [76]. CEST using amide proton transfer imaging added to a standard MR at 3T has been reported to have significantly increased signal intensity in brain tumor of 12 patients [77], yet there is no boundary to apply this technique in the field of gynecologic oncology.

Conclusions

In summary, molecular imaging (mainly PET and MRI) has played important roles in gynecologic oncology, for tumor detection, primary staging, treatment planning, prediction of prognosis, as well as response evaluation, surveillance, and the management of recurrence. Emerging imaging technologies will continuously improve our practice. Such development will aid decision-making in personalized medicine and precisely guide radiation treatment plan or real-time surgical interventions, which will directly impact on patient survival. No single imaging tool will universally apply in different tumor types. Prospective studies with defined endpoints are necessary to evaluate the roles of these emerging tools in management of gynecologic malignancies.

Conflicts of interest statement

None declared.

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