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REVIEW ARTICLE

Molecular imaging in the management of cervical cancer

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Positron emission tomography (PET), magnetic resonance imaging (MRI), and integrated 18-fluorodeoxyglucose (^{18}F-FDG) PET/computed tomography are valuable techniques for assessing prognosis, treatment response after the completion of concurrent chemoradiation, suspicious or documented recurrence, unexplained post therapy elevations in tumor markers, and the response to salvage treatment when managing cervical cancer. However, PET plays a limited role in the primary staging of MRI-defined node-negative patients. Currently, ^{18}F-FDG is still the only tracer approved for routine use, but several novel targeting PET compounds, high-Tesla MRI machines, diffusion-weighted imaging without contrast, and dynamic nuclear polarized-enhanced ^{13}C-MR spectroscopic imaging may hold promising applications.
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Introduction

Worldwide, cervical cancer is the third most common form of cancer that afflicts women and the fourth highest cause of cancer mortality in women.[1] Early-stage cervical cancer (IA2—IIA1 according to the 2009 International Federation of Gynecology and Obstetrics [FIGO] staging criteria[2]) can be cured by either radical surgery or radiotherapy, while patients with stage IA1—IB1 can be treated with fertility-preserving surgery. Generally, stage IB2—IV (except IIA1) cancer can be treated with definitive radiation with concurrent platinum-based chemotherapy.[1,3] Accurate clinical staging is crucial for the selection of primary therapy in order to achieve the highest survival rate with the lowest morbidity.

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Nodal metastasis is an independent prognostic factor in cervical cancer patients who are being treated with primary radical surgery[4] or radiotherapy.[5] Because advanced imaging technologies are not available in many countries where cervical cancer is prevalent, the FIGO staging system does not consider pelvic (PLN) or para-aortic lymph nodes (PALN) in the staging criteria for the uniform classification of tumor extent or the comparison of clinical results. FIGO and the National Comprehensive Cancer Network (NCCN) practice guidelines for oncology both advocate the use of imaging methods to define tumor extent when planning treatment options for individual patients.[2,3] Computed tomography (CT) or conventional magnetic resonance imaging (MRI) have been determined by the American College of Radiology Imaging Network and Gynecologic Oncology Group (ACRIN/GOG) to be suboptimal for evaluating the depth of cervical stromal invasion, PLN metastasis, parametrial extension, and visualizing primary tumors.[6,7]

Positron emission tomography (PET) is a molecular imaging technique that uses radiolabeled molecules to visualize molecules, cells, and biological processes in living organisms and humans. The most commonly used radiotracer in clinical practice and for the study of malignant tumors is 18-fluorodeoxyglucose (^{18}F-FDG). ^{18}F-FDG is actively taken up at the cellular level by glucose transporters, then phosphorylated and no longer metabolized. Therefore, it remains trapped within the cell. ^{18}F-FDG-PET is very highly sensitivity for the detection of > 90% of cancers during staging and restaging and for assessing the therapeutic response on follow-up examinations.[8,9] In cervical cancer, radiotracers other than ^{18}F-FDG, such as ^{11}C-choline,[10] ^{60}Cu- or ^{64}Cu-labeled diacetyl-bis(N4-methylthiosemicarbazone) (^{64}Cu-ATSM), have been successfully applied in humans to diagnose hypoxia.[11,12] ^{18}F-FDG is still the only tracer approved for routine clinical use.[9]

This review summarizes recent developments in the use of molecular imaging technology in oncological applications and the use of MRI and ^{18}F-FDG PET in the management of cervical cancer.

Recent advances in molecular imaging technologies

PET imaging

Although FDG is widely used in clinical applications, not all tumors show a significant increase in metabolic activity on FDG-PET imaging. In particular, prostate cancer, neuroendocrine tumors, and hepatic tumors may be virtually invisible on PET. Furthermore, with FDG it is difficult to evaluate malignant lesions in tissues that physiologically take up FDG (such as the central nervous system) or excrete FDG (such as the kidneys and bladder) or differentiate between inflammation and cancer. Therefore, in addition to FDG, several other tracers have been proposed.

The use of targeted therapeutics has challenged the notion of how imaging techniques assess tumor response to treatment because many new agents are thought to cause cytostasis rather than cytotoxicity. Currently, targeting PET compounds have been developed for oncological studies, but even though tumor size estimation might not correlate well with the true tumor response, PET has merged as the most sensitive imaging tool for the metabolic profiling of individual tumors.[9] These compounds include ^{11}C-acetate (a precursor of membrane fatty acids), ^{11}C-methionine (a precursor of S-adenosylmethionine, which is required for polyamine synthesis), ^{18}F-choline (a substrate of choline kinase in choline metabolism), and ^{18}F-3'-fluoro-3'-deoxy-L-thymidine (^{18}F-FLT) (a substrate of thymidine kinase [TK-2] in DNA synthesis, a specific marker of cell proliferation).

For the evaluation of specific types of tissues or tumors, several PET compounds have been used in clinical trials, either for inclusion criteria or as an endpoint. These include ^{18}F-fluoride (which incorporates into the hydroxyapatite crystals of bone), ^{18}F-3,4-dihydroxyphenylalanine (DOPA) (which is involved in amino acid transport and protein synthesis in neuroendocrine tumors[13]), ^{68}Ga-(tetra-aza-cyclododecane-NN'N''N'''-tetra-acetate-[Tyr]-octreotide) DOTA-TOC/-DOTA-(-1-Nal3-octreotide) NOC (somatostatin analogues, receptor binding [somatostatin receptor type 2 gene (SSTR-II), -V] in neuroendocrine tumors), 16-α-[^{18}F]fluoro-17-β-estradiol (FES) (a specific estrogen-binding receptor involved in breast cancer), ^{18}F-Annexin-V (specifically binds to phosphatidylserine on cell membranes during apoptosis), ^{18}F-FLT (involved in cell proliferation[14]), ^{18}F-RGD-K5 (integrin receptors [$\alpha_v\beta_3$] are present on endothelial cells during neovasculogenesis and angiogenesis[15]), ^{18}F-MISO, ^{64}Cu-ATSM, ^{18}F-EF5 (involved in intracellular reduction, binding, and hypoxia), and immuno-PET with ^{124}I-G250 (used to identify the tumor type when deciding the appropriate therapy for renal cell carcinoma).[16]

Magnetic resonance imaging

Important advances in MRI have taken place in oncology in recent years. In combination with newly developed pulse sequences, perfusion or dynamic contrast-enhanced perfusion-weighted MRI (DCE-PWI) techniques, and diffusion-weighted imaging (DWI), MR imaging has been proven to play a better role in evaluating cervical cancer than conventional MRI.[17,18] Newly developed techniques such as dynamic nuclear polarized (DNP)-enhanced ^{13}C-magnetic resonance spectroscopic imaging (DNP-MRSI), abdominal susceptibility-weighted imaging (SWI), MR imaging, and MR/PET are exciting fields of research. Future applications of MRI are expected to utilize DNP-MRI by using hyperpolarized gases (e.g., ^{13}C and ^{3}He) as contrast agents, which enables MRSI to have 10,000-times the signal-to-noise ratio in comparison to conventional MRI. The technique has been used to image ^{13}C-containing metabolites in tumors (including prostate tumors), cardiac tissue, and the brain.[19]

The future applications of MRI will focus on hyperpolarized DNP-MRSI, DW-MRI, MR/PET,[19] and target-contrasted MR lymphography,[20] which are probably the most promising trends in gynecological-oncological evaluations and management in the near future.

Roles of PET in primary staging, response evaluation, detection, and the management of recurrence

Showalter found that tumor diameters estimated using ^{18}F-FDG-PET (referred to as simply PET hereafter) were

correlated with the pathological tumor diameters of the surgical specimens with a correlation coefficient of 0.757 ($p < 0.0001$).[21] PET and integrated PET/CT are valuable tools for assessing prognosis[22–24] and primary staging,[23–32] the determination of the treatment goal (curative or palliative) in patients with PALN[31] or SLN[32] metastasis as detected by CT/MRI (Table 1 [23–32]) and the treatment response after the completion of concurrent chemoradiation,[33] and documenting recurrent cervical cancer,[34] unexplained post-treatment elevations in tumor markers,[35] and follow-up after salvage therapy.[36] An early study demonstrated the significant sensitivity of PET for detecting PLN metastasis over MRI.[37] Goyal et al reported that using PET/CT alone could avoid multimodality therapy for the treatment of operable stage IB1–IIA1 cervical cancer.[38] Chou et al showed that PET provides significantly better diagnostic efficacy than MRI for detecting PALN metastasis and that the standardized uptake value $(SUV)_{max}$ of primary cervical tumors > 5.3 is an independent and poor prognostic factor in stage I–IIB cervical adenocarcinoma and adenosquamous carcinoma.[39]

In contrast, the same group found that PET plays a limited role in the primary staging of MRI-defined node-negative stage I–II patients.[40] Ryu et al[41] used PET in routine posttherapy surveillance ($n = 249$) and found that among 80 patients with positive PET scans, only 28 demonstrated confirmed recurrence (false-positive rate of 65%). When Havrilesky et al[42] used PET to evaluate clinically suspicious recurrence, the positive predictive value was 85.7% (Table 2).[6,34–38,40–42,47,48] A randomized controlled study on the use of PET to evaluate MRI-defined pelvic node-positive patients prior to chemoradiation did not show a significant survival benefit of using additional PET arm, which reflects the importance of cost-effective research on molecular imaging tools.[28] Schwarz et al found PET/CT to be useful for monitoring treatment responses during concurrent chemoradiation.[43] The role of using PET with FDG or other novel targeted radiopharmaceuticals for predicting or monitoring the response will become more important in the future.[44]

Roles of MRI in differential diagnosis, staging, and response assessment

Patients with a histological diagnosis of adenocarcinoma or adenosquamous carcinoma by cervical biopsy should be differentially diagnosed as cervical or endometrial origin because the treatment strategies for these two sites are different. Vagas et al showed that when two radiologists were independently and retrospectively asked to determine the tumor origin from MRI studies of 48 patients (32 endometrial and 16 cervical cases), and the odds ratios of the tumor originating from the site were 4.80–6.35 greater than they would have been if no other information was available.[45] Rockall et al[46] used nanoparticle-enhanced MRI to evaluate 29 cervical cancer patients using ultrasmall particles of iron oxide (USPIO) followed by lymphadenectomy. The sensitivity (SN) of detecting LN metastasis was significantly better using USPIO (93%) compared with using size criteria alone (29%) on a nodal basis. Hori et al compared 3-Tesla (3T) versus 1.5T MR without DWI and

found a significantly better signal-to-noise ratio and mean tumor-to-cervical contrast-to-noise ratios using 3T MR in comparison with 1.5T MR, but the LN metastasis detection efficacies were similar.[47]

Lin et al[48] used 3T MRI with DWI, fusion, and T2-weighted imaging. The combination of size and apparent diffusion coefficient (ADC) differences (3T MRI with DWI) resulted in better sensitivity (25% vs. 83%) and similar specificities (98% vs. 99%) for the diagnosis of LN metastasis in comparison with conventional MRI (Table 2). A French study using 1.5T MRI and DWI at 8 weeks (range: 4–20 weeks) indicated residual tumors after radiotherapy/concurrent chemoradiation (RT/CCRT).[49] The mean ADC was $1.62 \pm 0.21 \times 10^{-3}$ mm^2/second (standard deviation [SD] $= 1.45 \times 10^{-4}$ mm^2/second) for those with residual disease ($n = 5$) versus $1.76 \pm 0.33 \times 10^{-3}$ mm^2/second (SD $= 1.99 \times 10^{-4}$ mm^2/second) for those with complete remission (CR) ($n = 44$; $p = 0.09$). Using 1.7×10^{-3} mm^2/second as a cut-off value for the mean ADC, all patients with histologically proven residual disease had a value $\leq 1.7 \times 10^{-3}$ mm^2/second.[49]

Comparisons between different imaging modalities

Ho et al[50] investigated the correlation between ADCs measured using 3T MRI with DWI and SUV from PET in 33 patients with primary cervical cancer. The relative ADC_{min} ($rADC_{min}$) was defined as the ratio between ADC_{min}/ADC_{mean} and was found to be significantly and inversely correlated with the relative SUV_{max} ($rSUV_{max}$) as defined by the ratio between SUV_{max}/SUV_{mean} ($r = -0.526$, $p = 0.0017$). A significant inverse correlation between $rADC_{min}$ and $rSUV_{max}$ was observed between patients with adenocarcinoma and adenosquamous carcinoma ($r = -0.685$, $p = 0.0012$) and those with well- to moderately differentiated tumors ($r = -0.631$, $p = 0.0050$).[50] A prospective study evaluated the use of lymphangiography, CT/MRI, and PET imaging for the detection of lymph node metastasis in patients receiving primary chemoradiotherapy for cervical cancer.[51] Agreement between imaging was most consistent in the common iliac LN ($p < 0.001$) and the least consistent in the PALN ($p = 0.41$). Disease-free and overall survival rates were most accurately predicted by PET.[51] A Korean retrospective study ($n = 83$) reviewed patients with cervical cancer who had undergone both preoperative MRI and PET/CT before radical surgery and lymphadenectomy. The sensitivity, specificity, and accuracy of detecting LN metastasis were 64.3%, 69.1%, and 67.5% for MRI and 28.6%, 83.6%, and 65.1% for PET/CT, respectively. The area under the curve (AUC) for the MRI and PET/CT ROC curves were 0.667 and 0.561, respectively ($p = 0.013$). MRI showed significantly higher sensitivity for detecting metastatic LNs than PET/CT ($p = 0.006$).[52] However, learning curve issues result in serious variations between diagnostic efficacies.

Benchmark examples of new MRI and PET technologies and clinical endpoints in oncology

With the development of new technologies and new targeting imaging drugs for use in MRI, PET, and single-photon

Table 1 Summary of the literature on the staging of locally advanced cervical cancer using CT/MRI and PET.

Authors	Year	Study	Patient number/FIGO stage	Purpose	Gold standard	Results
Yen et al[23]	2008	Prospective	70/untreated with PLN or PALN	SUV_{max} in PET or PET/CT as prognostic factor	5-year OS 5-yeay RFS	FIGO stage III/IV ($p = 0.008$) and $SUV_{max} >3.3$ at PALN ($p = 0.008$) are independent prognostic factors
Kidd et al[24]	2010	Retrospective	560/stage IA—IVB; before primary surgery, RT/CCRT	LN staging by PET	PLN and PALN: treated with RT/CCRT: unproven PLN and PALN: treated with surgery or ScLN: histological evidence	HR for recurrence: PLN 2.40 (95% CI, 1.63–3.52), PALN 5.88 (95% CI, 3.80–9.09), and ScLN 30.27 (95% CI, 16.56–55.34)
Grigsby et al[25]	2001	Retrospective	101 before RT/CCRT	LN staging, PET compared with CT	PLN and PALN: unproven SLN: histology evidence	CT: PLN-positive, 20%; PALN-positive, 7% PET: PLN-positive, 67%; PALN-positive, 21%; SLN-positive, 8%
Yamashita[26]	2005	Retrospective	71/FIGO IIB—IIIB	CT or MRI/before CCRT or NAC+RT	Histology or follow-up	15 CR/MRI-defined PALN-positive 5-year PFS: PALN-pos, 19.8% 5-year OS: PALN-pos 49.9%
Kim et al[27]	2009	Prospective	79/stage IB—IVA before lymphadenectomy	PET/CT vs. PET/MR fusion	Histology	PET/CT vs. PET/MR fusion: Sv, 44.1%; Sp, 93.9% vs. Sv,54.2%; Sp, 92.7%; AUC:0.690 vs. 0.735, $p = 0.0259$
Tsai et al[28]	2010	Prospective, randomized controlled trial	66 PET+ vs. 63 PET-	Additional extrapelvic mets, distant mets-free survival, OS	Image-guided biopsy or follow-up	11% additional extrapelvic mets; 4-year OS: PET+ vs. PET-, 79% vs. 85%, $p = 0.65$
Ramirez et al[29]	2011	Prospective	60/IB2-IVA CT/MRI PALN negative	LN staging, PET compared with laparoscopic extraperitoneal PALN dissection	Surgery	14 true positive at PALN: 6 PET+ for PALN; 6 of 27 (22%) PLN+, PALN- by PET; 3 of 26 (12%) PLN-, PALN- by PET
Kang et al[30]	2011	Prospective	Training cohort, 62; testing cohort, 54/IB2-IVA before CCRT	Laparoscopic staging PALN-negative PLN-positive by PET	Distant failure	FIGO stage > IIB and SCCAg > 2.4 ng/mL for training cohort PLN-positive by PET for distant failure: 100% Sv for training set and testing set
Chao et al[31]	2008	Prospective	47/untreated with limited PALN, ScLN, ILN metastasis	Clinical impact of PET or PET/CT	Histology or metabolic biopsy	44.7% positive impact 2-year OS: PALN, 50.9%; ScLN, 24.7%
Qiu et al[32]	2007	Retrospective	33/stage IVB (ScLN mets)	Clinical impact of PET or PET/CT, prognostic factors	Histology	SCC-Ag < 15 ng/mL ($p = 0.021$), staging including PET ($p = 0.006$) with better prognosis

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; PET, positron emission tomography; MRI, magnetic resonance imaging; CT, computed tomography; CCRT, concurrent chemoradiation; PLN, pelvic lymph node; PALN, paraaortic lymph node; ScLN, supraclavicular lymph node; ILN, inguinal lymph node; SUV, standardized uptake value; mets, metastasis; OS, overall survival; RFS, recurrence-free survival; Sv, sensitivity; Sp, specificity; NAC, neoadjuvant chemotherapy; HR: hazard ratio.

Table 2 Summary of literature on using MRI and PET for treating early-stage cervical cancer or posttherapy surveillance.

Authors	Year	Study	Patient number/FIGO stage	Purpose	Gold std	Results
Mitchell et al[6]	2006	Prospective	208 stage I—II before surgery	Diagnostic efficacy, patient-based LN staging, depth, tumor size MRI vs. CT	Histology by surgery	MRI and CT inaccurate for depth of invasion; uterine body involvement AUC of ROC: MRI vs. CT, 0.80 vs. 0.66, $p = 0.01$)
Lai et al[34]	2004	Prospective	40 documented recurrence/persistent potentially curable	Primary end point: % improvement in restaging	Surgery or clinical follow-up	55% modified treatment due to PET; detecting metastatic lesions: dual-phase PET vs. MRI/CT ($p < 0.0001$)
Chang et al[35]	2004	Prospective	27/initial stage I—IV after primary treatment	Restaging at SCC elevation when CT/MRI (-)	Histology or clinical follow-up	Sv, 94% (17/18); Sp 86%, (6/7); PPV, 89% (17/19); NPV, 88% (7/8)
Lin et al[36]	2006	Prospective	26 curable re-recurrences or unexplained SCCAg, CEA elevation after salvage therapy	Clinical impact of using PET in addition to CT/MRI	Biopsy/surgery or clinical follow-up	12 (46.2%) Pts with positive impact Poor prognosis for AD/ASC, SCCAg > 4 ng/mL, site of re-recurrence at central/pelvis or distant+pelvis 36M survival 80% for score 0
Reinhart et al[37]	2001	Prospective	35 untreated	Diagnostic efficacy, Patient-based LN staging and LN sites-based PET vs. MRI	Histology by surgery	Patient-based PET vs. MRI, Sv = 0.91 vs. 0.73, $p > 0.05$ LN sites-based, PPV = 0.90 vs. 0.64, $p < 0.05$
Goyal et al[38]	2010	Prospective	80/stage IB1—IIA before surgery	PET to detect PLN mets	Histology by surgery	PET PLN detection: Sv, 58.3%;, Sp, 92.8%; PPV, 77.7%; NPV, 83.8%; postoperative RT reduced from 30% to 12.5%
Chou et al[40]	2006	Prospective	IA2-IIA MRI LN(-) $n = 60$	PET to detect PLN metastasis	Histology by surgery	16.7%, PLN mets; Sv, 10%; Sp, 94%; PPV, 25%; NPV, 84%; FN micrometastasis 0.5×0.5—7×6 mm
Ryu et al[41]	2003	Retrospective	249 posttherapy surveillance	To detect asymptomatic early recurrence	Histology or clinical follow-up	80 pts with PET-positive: PPV, 35%;Sv, 90.3%; Sp, 76.1%
Havrilesky et al[42]	2003	Retrospective	28	Detecting recurrence when clinically suspicious	Histology or clinical follow-up	Sv, 85.7%; Sp, 86.7%; PPV, 85.7%; NPV, 86.7%
Hori et al[47]	2009	Prospective	31/stage IA1—IIB before surgery	1.5T vs. 3.0T MRI detecting PLN mets	Histology by surgery	No difference
Lin et al[48]	2008	Prospective	50/stage I—II before surgery	3T-MR size vs. size+ADC	Histology by surgery	Combined size and ADC; Sv, 85%; AUC 0.965 vs. size alone Sv, 25%; AUC, 0.679; $p = 0.015$

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; PET, positron emission tomography; MRI, magnetic resonance imaging; CT, computed tomography; CCRT, concurrent chemoradiation; PLN, pelvic lymph node; OS, overall survival; SCCAg, squamous cell carcinoma antigen; ADC, apparent diffusion coefficient; mets, metastasis; Sv, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; RT radiotherapy; M: months; FN: false negative; AD/ASC: adenocarcinoma and adenosquamous carcinoma.

emission computed tomography (SPECT), these techniques can provide sensitive and serial noninvasive information regarding tumor characteristics. The merging of MRI and PET technologies that can be applied to cervical cancer, as summarized in Table 3.[19,54—62]

If we use breast cancer as an example, most clinical data have been gathered on the visualization of general processes such as the detection of tumor blood flow using 3T MRI contrast-enhanced dynamic studies, glucose metabolism using ^{18}F-FDG-PET, and DNA synthesis using ^{18}F-FLT.[53] Increasingly, more breast cancer-specific targets are being imaged such as the estrogen receptor (ER), growth factors, and growth factor receptors. Imaging of the ER using FES-PET has shown a good correlation between FES uptake into tumors and ER density. Using ^{111}In-trastuzumab SPECT to image human epidermal growth factor receptor 2 (HER2) has shown that in most patients with metastatic HER2 overexpression, more lesions are detected than with conventional staging procedures. The PET tracer [89]Zr-trastuzumab has shown excellent, quantifiable, and specific tumor uptake. The use of ^{111}In-bevacizumab in SPECT and [89]Zr-bevacizumab in PET imaging have been developed for the imaging of vascular endothelial growth factor (VEGF) as an angiogenic marker.[54,55] Lastly, tracers for the EGFR, IGF-1R, platelet-derived growth factor receptor (PDGFR)-β receptors and the tumor necrosis factor (TGF)-β ligand are under development.[56] The use of radio-immunoconjugates for immuno-PET offers high tumor-to-

Table 3 Summary of the merging of MRI and PET technologies that can be applied to cervical cancer.

New technologies	Advantages	Disadvantages	Example
PET imaging of angiogenesis, proliferation, apoptosis, VEGF, EGFR, HER2, somatostatin receptor type 2 gene and type 5 gene (sstr-2/sstr-5)	Provide a variety of PET tracers targeting specific molecular entities allowing the noninvasive measurement of biological processes	Need repeated scans due to the shifting of signaling pathways during treatment; no NDA approved available so far	Breast cancer; can help for treatment planning in the future[54—57]
Radioimmunoconjugates for immuno-PET	High tumor-to-background tissue contrast with high specificity, tumor response	Large decrease in radiolabeled antibody mediated by Fc receptor	Prostate cancer, colorectal cancer[56,58]
[13]C and ^{15}N MRI	Real time ^{13}C, ^{15}N images using DNP or PHIP Increased sensitivity with S/N ratio enhancements >10,000-times for ^{13}C, [15]N Selective ^{13}C, ^{15}N metabolic imaging.	Instrumentation is expensive	High-contrast imaging of the lungs in clinical trial on prostate cancer patients[19,59]
PET/MR	Higher resolution than CT, no radiation dose, and provides better functional information	The adverse effects of scattered and accidental gamma coincidences on the quantitative accuracy of PET, as well as artifacts caused by the inherent crosstalk between activity and attenuation estimation	The disadvantages can be reduced using enhanced decay event localization provided by time-of-flight PET, accurate correction for accidental coincidences, and a reduced number of unknown attenuation coefficients[60]
Susceptibility-weighted imaging (SWI)	Useful for emphasizing blood vessels, for example, vein- and iron-accumulated lesions; clinical applicable for trauma, tumor hypoxia, stroke, calcifications vessel density, and blood flow	Algorithms applied to other tumor types may not apply to cervical cancer	Clinically useful for breast cancer at baseline and after 2 courses of NAC showed promise[61]
Histogram analysis of ADC for DWI MRI	As compared with average ADC, histogram analysis of ADCs can offer different calculation of DWI	Algorithms applied to other tumor types may not apply to cervical cancer	Response to first 3 courses of chemotherapy correlated well with histogram analysis of ADC for DWI MRI in ovarian cancer[62]

NDA, new drug application; PET, positron emission tomography; MRI, magnetic resonance imaging; NAC, neoadjuvant chemotherapy; DWI, diffusion-weighted image; Fc, fragment crystallizable; DNP, dynamic nuclear polarized; PHIP, 2-Amino-1-methyl-6-phenylimidazo [4,5-b]pyridine; S/N, signal to noise ratio; ADC, apparent diffusion coefficient.

background tissue contrast in immuno-PET and can be used as a tool for monitoring and quantifying tumor responses with high specificity.[57,58]

The simultaneous reconstruction of activity and attenuation in PET/MR is attractive, yet there are downsides to this technology, such as the fact that MR does not measure photon attenuation and, thus, does not provide easy access to this valuable information.[59] A major challenge in cancer biology is the monitoring and understanding of cancer metabolism *in vivo* with the end goal of improving diagnosis and treatment.[60] Crucial metabolites may be present in low concentrations and are, therefore, beyond the detection limit of traditional MR methods. Hyperpolarized molecules can be generated in aqueous solution and infused *in vivo* where metabolism generates products that can be imaged,[60] which hold vast potential; however, we are still a long way from developing clinical applications. Li et al[61] used intrinsic susceptibility-weighted MR imaging in patients with primary breast cancer to assess the relationship between the baseline transverse relaxation rate (R2*), changes in the T2* relaxivity ($\triangle$ R2*), and the response to neoadjuvant chemotherapy (NAC). Their results suggest that an increase in R2* after two cycles of NAC correlates with the pathologic response and that therapy-induced uncoupling of the relationship between R2* and relative blood volume (rBV) and relative blood flow (rBF) is consistent with the responding tumors becoming hypoxic shortly after beginning treatment.

A prospective study evaluated apparent ADC histograms in order to assess the chemotherapeutic response of patients with metastatic ovarian or primary peritoneal cancer, demonstrating that all ADCs increased after the first and third cycles ($p < 0.001$) while skew and kurtosis decreased after the third cycle ($p < 0.001$ and 0.006, respectively) in responders but not in nonresponders.[62] Chen et al used 3T MRI to assess the response to NAC in correlation with the molecular markers HER2, ER, and Ki67. The mean MR imaging-pathologic size discrepancy was 0.5 cm $\pm$ 0.9 for HER2-positive cancer and 2.3 cm $\pm$ 3.5 for HER2-negative cancer ($p = 0.009$). In the HER2-negative group, the size discrepancy was smaller for hormone receptor-negative cancers than for hormone receptor-positive cancers (1.0 cm $\pm$ 1.1 vs. 3.0 cm $\pm$ 4.0, $p = 0.04$).[63]

Cost-effective analyses should be encouraged as an endpoint in research on the use of new diagnostic tools, such as new PET and MRI technologies. Comparisons of alternative or threshold values will lead to the identification of the most efficient ways to maximize health at the population level.[64] FDG-PET has been used to evaluate patients with head and neck cancer using distant metastasis as the risk factors and has been determined to be cost-effective.[65] FDG-PET demonstrated 95.9% accuracy for restaging patients with Hodgkin's lymphoma after first-line therapy, and the ICER was -$3,268 US dollars.[66]

Conclusion

^{18}F-FDG is still the only tracer approved for routine use. Currently, several novel targeting PET compounds have been developed for oncological studies, either for clinical use or at different stages of clinical evaluation. The results

of using nanoparticle contrast media-enhanced MRI, high-Tesla machines, diffusion-weighted imaging without contrast, and spectroscopy are promising. The role of using molecular imaging (e.g., new MRI and PET technologies) as an early predictor of response to treatment is an emerging utility that requires more clinical investigations. Cost-effective analysis should be encouraged as an endpoint in research regarding the use of new diagnostic tools, such as new PET and MRI technologies.

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