



Molecular Imaging for Radiotherapy Planning and Response Assessment for Cervical Cancer

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Positron emission tomography (PET) with ^{18}F fluorodeoxyglucose (FDG) leverages imaging contrast from accelerated and aberrant glucose metabolism, which is a hallmark of cancer. FDG-PET is essential for assessing involved lymph nodes and distant metastases for cervical cancer. It is also utilized for target delineation in radiation treatment planning, with investigations into functional bone marrow sparing intensity modulated radiation therapy. Tumor heterogeneity in FDG-uptake is part of a radiomics approach to potentially escalate treatment to radiation-resistant tumors. Standardizing posttreatment PET surveillance could also allow early surgical salvage of recurrent tumors. The future of molecular imaging in cervical cancer will require development of novel PET tracers to personalize treatments based on tumor biology. *Semin Nucl Med* 49:493-500 © 2019 Elsevier Inc. All rights reserved.

The clinical usefulness of positron emission tomography (PET) with ^{18}F fluorodeoxyglucose (FDG) for cervical cancer radiotherapy planning and treatment response has been explored since the mid-1990s at Washington University in St. Louis. While the cost of FDG-PET is a significant barrier to clinics in developing countries,¹ pretreatment FDG-PET is now part of the standard of care in the United States² for evaluating cervical cancer extent and determining treatment options. It also has been utilized for treatment planning and therapy response monitoring. The following review will detail the current literature in support of the use of FDG-PET in deciding treatment alternatives, treatment planning, and response assessment for cervical cancer. Ultimately, novel radiopharmaceuticals and/or PET-adaptive radiotherapy planning may help generate improved outcomes for the most advanced cervical cancer patients.

Treatment Options

Assessing for Lymph Nodes and Distant Metastases

The National Comprehensive Cancer Network recommends a pretreatment FDG-PET for all International Federation of

Gynecology and Obstetrics (FIGO) IB2-IVB cervical cancer patients to assist with treatment planning.² FDG-PET is sensitive to metabolically-active metastatic lymph nodes which may appear morphologically normal or indeterminate on computed tomography (CT) or magnetic resonance imaging (MRI).³⁻⁵ A recent secondary analysis of prospective trials including 153 cervical cancer patients found that FDG-PET had a positive- and negative-predictive value of 79% and 93%, respectively.⁶ Kidd et al found 47% of 560 cervical cancer patients had FDG-avid lymph nodes, which independent of FIGO stage was associated with worse cause-specific survival.⁷ The rate of lymph node involvement increases with higher FIGO stage, but even early stage FIGO IB1-IIA had 19%-50% rates of pelvic lymph node involvement.⁷

Prior to FDG-PET, the most common sites of distant organ metastases determined by autopsy studies included the lung, liver, bone, and brain.^{8,9} Recent data have brought to light the unexpected frequency of peritoneal/omental metastases detected by FDG-PET at diagnosis of cervical cancer. In the prospective study by Gee et al, among 21 patients with FDG-avid distant metastases, 8 (38%) lung, 7 (33%) peritoneal, and 1 (5%) bone metastases were detected and confirmed pathologically. In our cohort of cervical cancer patients staged with FDG-PET, we identified 70 patients with distant organ metastases. The sites of distant disease were lung alone (35%), multiple sites (25%), omentum alone (16.5%), bone alone (16.5%), and liver alone (7%).¹⁰ Therefore, omental/peritoneal metastases are not uncommon and should not be discounted as nonspecific findings during treatment planning.

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Definitive Surgery vs Radiation in Early Stage Cervical Cancer

In the late 1980s, Landoni et al demonstrated equivalent survival for FIGO stage IB-IIA cervical cancer patients treated with radical surgery or definitive radiation, but 63% of surgical patients required adjuvant radiation and leg edema was significantly worse in the surgical arm.¹¹ Further studies showed bulkier invasive disease with LVSI warranted adjuvant radiation,¹² and chemoradiation was essential for disease that had spread to the lymph nodes.¹³ Definitive chemoradiation is now standard of care for FIGO IIB-IVA disease.² As the role of surgery continues to be debated for FIGO IB2-IIA cervical cancer,^{11,14} FDG-PET assessment of lymphatic spread could help in selecting surgical management vs chemoradiation alone. The 2018 updated FIGO staging now allows FDG-PET and other advanced imaging to assess for regional lymph node metastasis, and positive nodes are classified as stage III.¹⁵

Definitive vs Palliative Radiation in FIGO IVB Cervical Cancer

Prospective evidence now supports the existence of oligometastatic disease in multiple cancer primaries, and definitive radiation to up to five sites of disease improves survival.¹⁶⁻¹⁸ A retrospective National Cancer Database study of 3169 patients with metastatic cervical cancer found pelvic radiation and brachytherapy improved overall survival (OS) three-fold over chemotherapy alone.¹⁹ In smaller single institution series, it appears that carefully selected patients with metastatic disease limited to the supraclavicular nodes and thorax benefit most from aggressive treatment.²⁰⁻²⁴ Prior to the current practice of treating all oligometastatic sites of disease, patients with multiple sites of metastases had a median OS of 3 months.¹⁰ It is now our general practice to recommend definitive radiation to all sites of disease to patients with FDG-avid metastases limited to lymph nodes, bone, or omentum, though each patient needs to be individually evaluated and biopsy of distant disease should be obtained when possible. For patients with a large tumor burden and life expectancy not longer than 6 months, palliative pelvic radiation can be compressed to three monthly courses of 14.8 Gy in four fractions given twice daily, for a total dose of 44.4 Gy.²⁵⁻²⁷ Two palliative weekly brachytherapy ring treatments are also effective for stopping acute tumor bleeds,²⁸ prior to enrolling on hospice care.

Radiotherapy Planning

Patient Simulation and PET Image Fusion for External Radiation Planning

The following sections will describe our definitive radiation treatment planning methods incorporating FDG-PET with intensity-modulated radiation therapy (IMRT) and high dose rate brachytherapy. The clinical outcomes of this treatment paradigm have previously been reported.²⁹⁻³⁴

In the Radiation Oncology Department, three gold fiducial markers are placed to demarcate the inferior and lateral

borders of the tumor. The CT simulation scan is performed with the patient immobilized in a thermoplastic body mold. Often the same body mold is used for her pretreatment FDG-PET study. The CT simulation is then fused to the diagnostic PET and pelvic MRI for treatment planning.³⁴

Delineating the Metabolic Tumor Volume and Treatment Volumes for Pseudo Split-Field Pelvis Treatment

Our institution's approach to cervical cancer treatment has been to intentionally reduce dose to the central pelvis from the external irradiation plan so that the majority of dose to the cervix primary tumor is delivered by an intracavitary brachytherapy boost. Historically, opposed anterior-posterior megavoltage beams would target the whole pelvis, prescribed to 50.4 Gy, and a step-wedge was placed to block the central pelvis after 20 Gy had been delivered. Since 2005, we have used IMRT to create a pseudo split-field pelvis plan. The lateral pelvis is prescribed 50.4 Gy and the central pelvis receives 20 Gy, spread over 28 daily fractions.³⁵ External radiation is delivered 4 days a week, and tandem and ovoid high dose rate brachytherapy is administered once weekly for 7 weeks total of treatment. If patients can tolerate chemotherapy, concurrent weekly bolus cisplatin 40 mg/m² is given.³⁶

IMRT requires target volumes to be delineated for inverse planning. A metabolic tumor volume (MTV) is defined based on the primary tumor's maximum standard uptake value (SUVmax). The MTV is semiautomatically drawn by the treatment planning software to encompass the 40% SUVmax intensity threshold.^{37,38} In about 25% of cases, the MTV will have to be manually shaved off the bladder due to FDG retention in the urinary bladder. The MTV, without any additional margin, is prescribed 20 Gy. The pelvic vessels are contoured starting at the bifurcation of the aorta, including the internal and external iliac vessels, down to the level of the midfemoral heads. The clinical treatment volume (CTV) includes the pelvic vessels expanded uniformly by 7 mm, excluding bone. In a series of 244 FIGO IIB cervical cancer patients from China treated with IMRT and chemotherapy, almost all lymph nodes >0.5 cm in size detected by CT were located within 1 cm from pelvic vessel and para-aortic vessels.³⁹ Obturator nodes are not typically near vessels, but can be included by joining the external and internal iliac CTVs with a 1.5-2 cm wide bar along the pelvic sidewall. Notable, presacral nodes were rare (2/244 patients),³⁹ which supports our practice of omitting presacral nodal coverage with IMRT. Any metabolically active lymph nodes are included in the CTV. If para-aortic lymph nodes are FDG-avid, the aorta and inferior vena cava are additionally contoured up to the level of the renal veins and expanded 7 mm for the CTV. The planning treatment volume (PTV) is a uniform 5-7 mm expansion of the CTV to account for patient setup uncertainty.⁴⁰ Normal structures such as the small bowel, bladder, and rectum are contoured on the simulation CT scan as avoidance structures. A typical IMRT plan is shown in Figure 1, where 95% of the PTV is covered by at least 90% of the prescription dose. Notably, our approach is different from that proposed by the Groupe

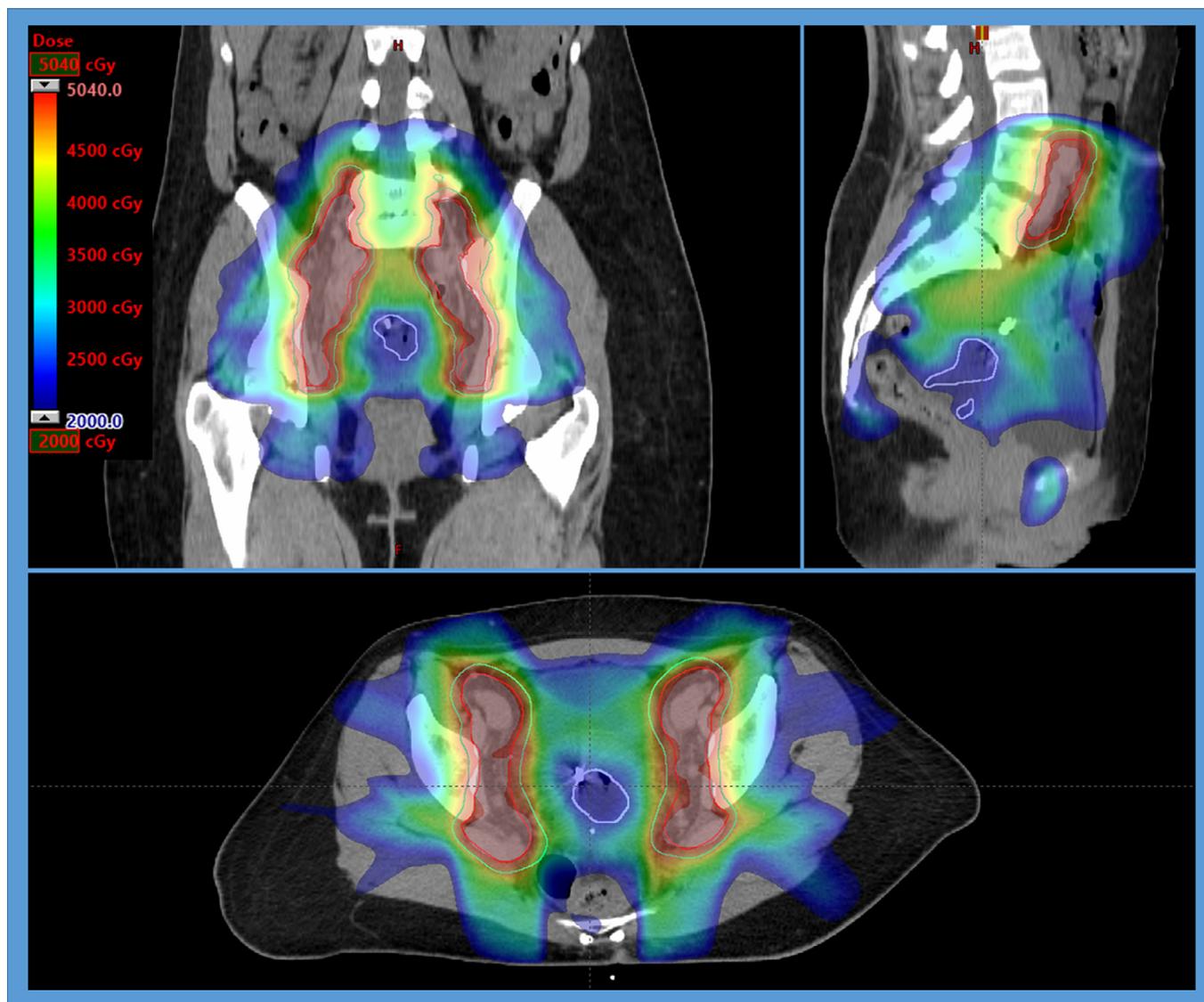


Figure 1 IMRT external beam plan shown in coronal (upper left), sagittal (upper right), and axial (bottom) panes. Dose from 20 to 50.4 Gy is shown in colorwash. The CTV (red), PTV (cyan), and MTV (white) are outlined in each view.

Européen de Curiethérapie and the European Society for Radiotherapy and Oncology (GEC-ESTRO) paradigm.⁴¹ Key differences are outlined in [Table 1](#).

Boosting Metabolically Active Lymph Nodes

FDG-avid para-aortic lymph nodes are a negative prognostic factor.⁷ Prior trials investigating higher dose and/or altered fractionation to the entire pelvis/para-aortic PTV have been too toxic with no change in survival.⁴² Focal radiation boosts of involved lymph nodes is an attractive use of IMRT. A Korean study found boosting the involved lymph nodes in 11 patients did not change the objective complete response rate (about 80%) compared to the 35 that did not get a boost.⁴³ Similarly, Hata et al observed that 50.4 Gy controlled 76/78 (97%) of involved pelvic lymph nodes <3 cm, and 55.4 Gy controlled 33/33 (100%) of lymph nodes ≥3 cm.⁴⁴ Concurrent chemotherapy may, in part, allow adequate control of smaller para-aortic lymph nodes at

total radiation doses of 50.4 Gy.⁴⁵ A Taiwanese study of 72 cervical cancer patients with biopsy-proven pelvic, para-aortic, and/or supraclavicular nodes boosted the entire pelvic and para-aortic fields with IMRT to 54 Gy, followed by a sequential boost of FDG-avid nodes (SUVmax > 4.5) to 59.4-64.8 Gy. Patterns of failure after definitive IMRT and concurrent cisplatin indicated out-of-field or distant failure was the most frequent (25%), followed by in-field (11%) or combined (4%) failure.²⁴ Our practice is to employ a simultaneous integrated boost for lymph nodes ≥3 cm to a dose of 60 Gy in 28 fractions.^{46,47} The nodal MTV is contoured without any further geometric expansion as the nodal boost volume.

PET for Bone Marrow Sparing IMRT

Lymphopenia^{48,49} and neutrophilia^{50,51} have been associated with poor survival in cervical cancer, and there is growing evidence that prolonged large-volume radiation therapy has

Table 1 Outline of Locally Advanced Cervical Cancer Radiation Treatment Planning of Two Established Systems

	Mallinckrodt (As of 2019) ³²	GEC-ESTRO EMBRACE II ⁴¹
IMRT simulation and contouring	<p>CT simulation fused with FDG-PET and pelvic MRI.</p> <p>FDG-PET used to delineate MTV and involved lymph nodes.</p> <p>MTV: 40% SUVmax isocontour of primary tumor.</p> <p>CTV: 7 mm expansion off pelvic \pm para-aortic vessels (if para-aortic nodes are FDG-avid); includes FDG-avid lymph nodes with no extra margin.</p> <p>PTV: 5 mm expansion from CTV with daily cone-beam CT imaging.</p>	<p>CT simulation fused with pelvic MRI, FDG-PET optional.</p> <p><i>FDG-PET optionally used</i> to delineate involved lymph nodes. Lymph nodes need to be surgically assessed.</p> <p>GTV initial: gross tumor volume delineated by preradiation MRI T2 sequence.⁸⁴</p> <p>CTV-tumor high risk: GTV initial + cervix.</p> <p>CTV-tumor low risk: entire uterus, parametria, upper vagina, and potential spaces between the bladder and rectum.</p> <p>CTV-elective small pelvis for node-negative IA, IB1, IIA1 tumors: internal + external iliac, obturator, presacral nodes.</p> <p>OR</p> <p>CTV-elective large pelvis for intermediate risk (neither low nor high risk) tumors: small pelvis + common iliac to aortic bifurcation; inguinal nodes for distal vagina involvement; mesorectal nodes if involved or at risk.</p> <p>OR</p> <p>CTV-elective large pelvis + paraaortics for high risk tumors (≥ 1 pathologically involved node at or above common iliac OR ≥ 3 pathologically involved nodes): large pelvis + para-aortic nodes to renal vein and 3 cm cranial to the highest involved node.</p> <p>PTVs: 5 mm expansion from CTV-tumor and CTV-elective volumes with daily cone-beam CT imaging.</p>
IMRT planning objectives for targets.	<p>IMRT 50.4 Gy in 28 fractions delivered 4 days a week for 7 weeks to the PTV.</p> <p>The MTV is prescribed 20 Gy in 28 fractions.</p> <p>Simultaneous integrated boost to lymph nodes ≥ 3 cm-60 Gy with IMRT.</p> <p>95% coverage of PTV with 90% of prescription dose.</p> <p>Complete all treatment <56 days.</p>	<p>IMRT 45 Gy in 25 fractions delivered 5 days a week for 5 weeks to the PTV.</p> <p>Simultaneous integrated boost to pathologically involved lymph nodes to 60 Gy EQD₂ from both IMRT and brachytherapy.</p> <p>95% coverage of PTV with 95% of prescription dose.</p> <p>Complete all treatment <50 days.</p>
Selected normal tissue constraints for IMRT.	<p>Small bowel bag V40 Gy < 30%.</p> <p>Rectum V40 Gy < 60%.</p> <p>Bladder V45 Gy < 50%.</p>	<p>Small bowel V40 Gy < 250 cm³.</p> <p>Rectum V40 Gy < 75%.</p> <p>Sigmoid D_{max} < 105%.</p> <p>Bladder V40 Gy < 60%.</p>
Image-guided brachytherapy.	<p><i>Starts with first week of IMRT, six weekly implants.</i></p> <p>Tandem and ovoid implant.</p> <p>CT and MR planning scan for each implant. GTV is contoured based on DWI and T2 sequence on MRI.^{31,85}</p>	<p><i>Starts after 5 weeks of IMRT, dose and fractionation per institution.</i></p> <p>Tandem and ovoid implant, optional interstitial needles.</p> <p>CT and MR planning scan before first implant. <i>GTV residual</i> is contoured based on T1 with and without contrast, T2 sequence on MRI.⁸⁶</p>

Table 1 (Continued)

	Mallinckrodt (As of 2019) ³²	GEC-ESTRO EMBRACE II ⁴¹
	High dose rate Ir-192 source. Empirical planning to achieve constant dose rate to point A (typically 6.5 Gy × 6 fractions). Dose to GTV and organs at risk are tracked with each implant. ⁸⁷	High dose rate Ir-192 source. Forward or inverse planning acceptable to meet planning objectives. CTV high risk adapted (HRA): GTV residual + cervix + residual disease on physical exam. CTV intermediate risk adapted (IRA): 1 cm lateral and craniocaudal expansion and 0.5 cm anterior/posterior expansion on CTV-HRA, includes GTV initial.
Brachytherapy planning objectives for targets.	GTV D90 > 100 Gy (EQD ₂) GTV mean dose > 260 Gy (EQD ₂).	GTV residual D98 > 95 Gy (EQD ₂). CTV-HRA D98 > 75 Gy (EQD ₂). CTV-IRA D98 > 60 Gy (EQD ₂).
Selected normal tissue constraints for IMRT + brachytherapy.	Rectum D2cc < 75 Gy (EQD ₂). Bladder D2cc < 90 Gy (EQD ₂).	Small bowel D2cc < 70 Gy (EQD ₂). Rectum D2cc < 65 Gy (EQD ₂). Sigmoid D2cc < 70 Gy (EQD ₂). Bladder D2cc < 80 Gy (EQD ₂).

Abbreviations: CTV, clinical treatment volume; D_{max}, maximum point dose; D2cc, maximum dose to at least 2cc of the organ at risk; EQD₂, equivalent dose in 2 Gy fractions (assumes tumor $\alpha/\beta = 10$ and normal tissue $\alpha/\beta = 3$); GTV, gross tumor volume; MTV, metabolic tumor volume; Point A, point 2 cm above the cervical os and 2 cm lateral to the tandem; PTV, planning treatment volume; VXXGy, percent organ volume receiving at least XX Gy.

inadvertently been reducing levels of these radiosensitive immune cells in various primary cancers.⁵²⁻⁵⁶ To reduce the impact of prolonged radiation on the immune system, bone marrow sparing IMRT using PET to delineate metabolically active marrow has been spearheaded by our colleagues at the University of California, San Diego.⁵⁷ The pelvic bones are contoured from the superior aspect of L5 to the ischial tuberosities. The functional bone marrow subvolume is autocontoured as the bone marrow regions with an SUV greater than the mean pelvic bones SUV value. Mean dose to the functional bone marrow is constrained, with a mean dose goal of less than 15 Gy; additional goals are that bone marrow subvolume receiving ≥ 10 Gy (V10) < 90% and V20 < 75%. The INTERTECC phase 2 trial showed that these patients had a significant reduction in grade ≥ 3 neutropenia (8.6% vs 27.1%, $P = 0.04$) and nonsignificantly lower incidence of leukopenia (31.4% vs 43.8%, $P = 0.25$).⁵⁸ The ongoing INTERTECC 3 (NCT01554397) is a randomized phase 3 trial comparing standard IMRT to bone-marrow-sparing IMRT with concurrent cisplatin. By reducing bone marrow toxicity, patients may be able to tolerate more intense chemotherapy regimens such as adding gemcitabine to cisplatin.⁵⁹ It will also be important to keep the immune system intact as various immune checkpoint inhibitors are tested for adjuvant therapy.

Treatment Response

Prognosis From Pretreatment PET Heterogeneity and Tumor Shrinkage During Radiation

Ideally, FDG-PET could be used to identify tumors that are radiation resistant and need dose escalation during brachytherapy. Kidd and Grigsby examined the tumor volume fall-off (dV) per incremental change in SUV threshold (dT) from

40% to 80% SUVmax in 72 cervical cancer patients. The magnitude of dV/dT was positively correlated with the primary tumor size ($R^2 = 0.88$), and both larger dV/dT and initial tumor size were associated with worse pelvic control and OS.⁶⁰ Yang et al utilized gray-level run length encoding and gray-level zone size encoding analyses of SUV as a measure of FDG uptake heterogeneity in the primary tumor. Both tumor FDG uptake and heterogeneity decreased during the course of chemoradiation.⁶¹ A group from Taiwan confirmed that gray-level run length encoding/gray-level zone size encoding analyses of textural features within the pretreatment MTV are associated with pelvic failure and worse survival after chemoradiation.⁶² Other groups have attempted to combine multiple PET/CT metrics as well as MRI to assess treatment response.^{63,64}

Finally, a complete radiomics approach to assessing prognosis should include tumor shrinkage kinetics during the treatment of cervical cancer.⁶⁵⁻⁶⁹ Several large retrospective studies have found tumors that shrink 80%-90% after about 5 weeks of external irradiation had optimal disease control,⁷⁰⁻⁷² but only 57% achieved this after external irradiation alone.⁷² Our approach of obtaining weekly planning MRIs for brachytherapy planning could allow for early detection of chemoradiation-resistant tumors, creating an opportunity for dose-escalated brachytherapy boost. This is an area of ongoing investigation in our group (ClinicalTrials.gov ID: NCT02317302).

Prognosis from Post-treatment PET

Current treatment with chemoradiation achieves disease control for 65%-79% of patients,^{32,41} but salvage options are limited for patients that recur and prognosis is poor. Early detection of treatment failure would allow for treatment

escalation with salvage surgical surgery. FDG-PET has been used to assess treatment response in a number of cancer primaries.⁷³ Schwarz et al initially associated the qualitative changes in postradiation FDG-PET with patterns of failure and survival for cervical cancer.^{74,75} A complete metabolic response in all areas of abnormal FDG uptake resulted in a 15% isolated pelvic failure rate and 100% 3-year cause specific survival (CSS). A partial metabolic response had a 58% isolated pelvic failure rate and 51% 3-year CSS. Patients with progressive disease on FDG-PET had a 17% 3-year CSS. In addition, Schwarz et al demonstrated that SUVmax alone could not differentiate persistent tumor from postradiation changes.⁷⁵ The addition of MRI may help differentiate normal postradiation changes from persistent tumor, though more work needs to be done.^{76,77} For patients with persistent FDG uptake 3 months after radiation, we repeat a FDG-PET in 3 months and attempt a biopsy if the abnormal FDG-avidity doesn't resolve.

Role for PET in Further Surveillance

There is still a clinical benefit of further PET surveillance for patients that achieve a complete metabolic response on their 3-month post-treatment scan. Brooks et al prospectively evaluated 103 patients who had a complete metabolic response on their post-treatment PET.⁷⁸ PET detected asymptomatic recurrence in 9/78 (12%) patients a median time of one year after treatment. The majority (8/9) of the patients had isolated locoregional recurrence, and all were treated. Three-year CSS was 19% vs 59% for patients with or without symptoms at the time of PET, respectively. Median time to distant failure after isolated pelvic recurrence was 20 months and median OS for patients salvaged with surgery was 29 months.⁷⁹ Therefore, early detection of recurrence may be critical to prolonging survival. Our current practice, when not limited by insurance coverage, is to obtain a PET/CT every 6 months for 2 years followed by annual scans thereafter.

Future Directions

In addition to on-going investigations mentioned already, alternate radiopharmaceuticals being developed could radically alter the treatment paradigm in cervical cancer. PET tracers that detect hypoxia have the potential to identify radioresistant subvolumes of tumor that could be targeted for dose-escalation.⁸⁰ Recurrent cervical cancers are often treated with bevacizumab (Avastin), an antivascular endothelial growth factor antibody. PET tracers have been developed that could monitor the Avastin-induced neovascular changes within tumors and allow earlier assessment of systemic therapy efficacy.⁸¹ Immune checkpoint inhibitors are now being tested with variable success in multiple solid tumors, and immune checkpoint-labeled PET tracers may allow for selection of patients that would benefit from adjuvant immunotherapy.⁸² The first in-human report of [⁸⁹Zr]-atezolizumab, a radiolabeled-antibody targeted to inhibit programmed cell death ligand-1, found high tumor uptake correlated with

tumor response, progression-free survival, and OS, prompting enthusiasm for further development.⁸³ Molecular imaging has been vital to the staging, treatment, and post-treatment surveillance of cervical cancer. Continued PET tracer development and incorporation into clinical practice will help personalize treatments, increasing tumor control and allowing reduction of unintended toxicities.

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