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Intraoperative lymph node evaluation using ^{18}F-FDG and a hand-held gamma probe in endometrial cancer surgery - a pilot study

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Summary

Purpose: The purpose of this pilot study was to assess feasibility, safety, and accuracy of detection of metastatic nodes intraoperatively with a hand-held gamma (PET) probe after administration of ^{18}F-FDG in patients with high risk endometrial cancer (EC). *Materials and Methods:* This is a prospective, cohort study. Twenty-two patients with clinical Stage I or II EC with high-risk histologic subtypes who were candidates for open surgical intervention were screened for the study. After screening, there were seven study patients (mean age: 64; range: 53−77) who were eligible for the study. In the entire cohort, there were 61 nodal stations that were assessed with a gamma counter intraoperatively, in vivo and again after removal of the node. All adverse events were recorded and operating room staff was monitored for radiation exposure. Resected nodes underwent histological assessment as per routine clinical practice. *Results:* Range of maximal counts per second recorded in vivo and ex vivo were 0−86 and 0−17, respectively. Of all the nodes examined, one node was positive for metastatic disease; however, intraoperatively the lymph node readings were not higher than other lymph node basins assessed in same patient. No adverse events were recorded. The surgeons recorded the maximum average radiation exposure of all healthcare personnel with an average exposure of 0.08 mSV per case (range, 0.06−0.15). *Conclusion:* Use of hand-held gamma probe for intraoperative staging of patients with high risk EC is feasible, safe, and radiation exposure levels for all members of the healthcare team were within radiation safety guidelines. However, its use for detection of lymph node metastases needs further evaluation.

Key words: Lymph nodes; ^{18}F-FDG; Endometrial cancer; Gamma probe.

Introduction

Endometrial cancer (EC) is the most common gynecologic malignancy with an estimated yearly incidence of 50,000 cases in the US alone [1]. Although the majority of cases are low grade and have a favorable prognosis, high grade histologic subtypes have high rates of metastases (up to 30%), high rates of recurrence and mortality rates of 40% at five years in some cases [2]. The predominant spread pattern in endometrial cancer is lymphatic mediated and the most common sites of recurrence for high grade cancers are distant sites within the body.

The surgical management of "high-risk" histologic endometrial cancer usually involves hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymph node dissection unless there is evidence of extrauterine disease at the time of surgery. To date the incorporation of lymphadenectomy at the time of surgery has not been proven to be therapeutic but is more commonly used to guide adjuvant treatment. The extent of surgery and inclusion of lymph node dissection in the surgical staging is a balance between ensuring adequate histopathologic information while minimizing unnecessary patient morbidity.

To deal with this balance, some disease sites have moved toward sentinel lymph node assessment. Removal of only the sentinel lymph node is standard of care for melanoma, breast, and vulvar cancers [3-5]. It is also being studied in cervical cancer [6]. In this strategy ^{99}Tc-sulfur colloid (radiolabelled colloid) injected into the tumor site is drained via lymphatic channels and identifies the first node of potential metastatic spread. If negative, no other lymph nodes need to be removed.

Groups around the world have attempted to identify the sentinel lymph node for EC. Abu-Rusteem *et al.* have reported on the use of the cervix as the sole site of injection for sentinel lymph node identification in EC [7]; however, to date no robust technique has proven to be adequate to use in standard practice [8-10].

^{18}F-FDG PET/CT imaging is increasingly being used to identify sites of metastatic disease for cancer. However, the sensitivity of FDG-PET for detecting lymph node metastases in patients with EC is only moderate. A recently published meta-analysis including 16 studies and 807 patients reports a sensitivity of approximately 72.3% (range: 63.8%−79.8%), although specificity is high (92.9%) [11].

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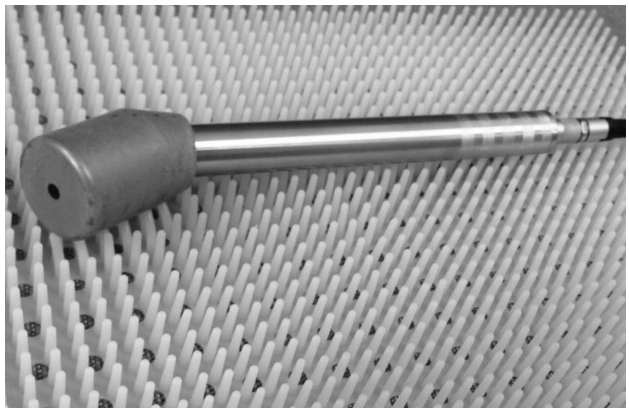

Figure 1. — Hand held gamma probe.

The limited sensitivity is thought to be due to inadequate detection of small volume metastatic disease by current PET technology, as detection rate for metastatic nodes below five mm has been reported to be only 16.7% [12]. Recently, researchers have used intra-operative hand-held gamma probes to better localize metastatic disease for various cancer types including metastatic ovarian cancer [13-15]. Hand-held intraoperative PET probes may have higher sensitivity in detecting small volumes of tumor, due to proximity of detector to the examined field. The purpose of the current pilot study is to assess feasibility, safety, and accuracy of detection of metastatic nodes in patients with high risk EC.

Materials and Methods

This prospective cohort study received institutional research ethics approval and conducted in accordance to ICH/GCP guidelines. Informed consent was obtained from all patients accrued. Patients recruited had newly diagnosed clinical Stage I or II EC with high-risk histologic subtypes (high grade endometrioid, serous, clear cell, and carcinosarcoma) who were candidates for "open" (non-laparoscopic) surgical intervention. The probe was not laparoscopic compatible and necessitated a laparotomy for its use (Figure 1).

Exclusion criteria included previous history of pelvic or abdominal radiation, patient receiving neoadjuvant chemotherapy and/or radiation therapy, or lymphadenopathy (> 2 cm) on preoperative staging CT. Relevant clinical and demographic date including age, disease stage, histologic subtype, and tumor grade were abstracted from clinical charts.

Over a one-year period (March 2012−March 2013) 22 women were screened and 12 women agreed to participate in the study. Of the 12 consented women, three were withdrawn due to positive lymph nodes identified on preoperative imaging, one due to late arrival of FDG on the day of surgery, and one because preoperative high grade histology could not be confirmed. This left seven study patients that were analyzed.

^{18}F-FDG PET/CT

Participants underwent ^{18}F-FDG PET/CT imaging on the morning of surgery. Whole-body PET/CT scan were acquired from the skull base to the upper thighs. Patients were asked to fast for at least six hours before undergoing the examination. Data was acquired 60–90 minutes after an IV injection of approximately five MBq/kg body weight of FDG (up to 550 MBq). For attenuation correction and anatomic land marking, helical CT scans from the neck to the pelvis were obtained with the following parameters: 130 kVp; 105 mAs; scan width, five mm; feed per rotation, 8.4 mm. Immediately after completion of CT, PET scans of the same area was acquired for three minutes per bed position, five to seven bed positions per patient.

The radiologist interpreted the scan prior to surgery. Positive nodes on PET were nodes measuring ≥ 1.5 cm in diameter with FDG uptake above background liver uptake or any node < 1.5 cm in diameter with uptake above background. The location of lymph nodes was categorized according to laterality as external iliac, internal iliac, common iliac, presacral, or para-aortic. A verbal report regarding findings on preoperative PET/CT performed on the morning of surgery was provided to the surgeon prior to start of surgery.

Intraoperative identification of metastatic disease with hand-held gamma probe

Surgery commenced approximately four hours after intravenous injection of FDG (range: 3.87−4.82 hours; median, 4.48 hours). The hand-held gamma counter was covered with a sterile sleeve and was used to help localize "hot" (^{18}F-FDG laden) lymph nodes. Maximal counts per second (cpsMax) and counts over a ten-second period (cps10s) were recorded for all examined nodal basins. Three sigma criteria were used to determine the threshold for positivity of tissue for the gamma probe. The three sigma criteria define the threshold for positivity of tissue as the average background activity in normal tissue plus three times the square root of the average background activity. After the removal of an affected node, it was confirmed that this node is "hot" using the gamma counter. This was done off the surgical field away from background counts of the primary site and cpsMax was recorded. In the case of multiple "hot" lymph nodes, they were separated and sent separately in different containers. Following completion of the lymphadenectomy, the lymph node basins were examined with the gamma probe to ensure there were no other "hot" nodes. The location of the "hot" lymph node was recorded on a data collection form. Furthermore, background readings were recorded from the operating room (cpsMax and cps10s), from the background pelvis, bladder, and kidneys.

Adverse events

All intraoperative adverse events attributable to the use of hand-held gamma probe were recorded.

Radiation safety

The isotope used in this study is ^{18}F-FDG (fluorodeoxyglucose). Clinical studies have shown that the radioactivity of ^{18}F-FDG partitions into two major fractions. About 75% of the fluorine-18 activity remains in tissues and is eliminated with a half-life of 110 minutes and another fraction representing about 20% of the total fluorine-18 activity of an injection is eliminated renally by two hours after a dose of ^{18}F-FDG, with a rapid half-life of about 16 minutes. The amount of radiopharmaceutical administered is equivalent to that of a standard PET scan (usually 300−450 MBq). The study design was reviewed by the Institution's Radiation Safety Office. All involved operating room personnel underwent radiation safety training. Radiation dosimeter badges were provided to record radiation exposure and to ensure radiation dose limits are not exceeded (20 mSv/year).

Table 1. — *Demographic, surgery, and pathology data.*

Study ID	Age (median, 64)	Clinical Stage	Histology	Nodes on PET/CT	# of nodes resected	Pathology stage
1001	53	I	CS	N0	10	pT1a, pN0
1003	64	I	HGSC	N1	43	pT1b pN1
1005	75	I	CS	N0	13	pT1b pN0
1006	59	I	MIXED	N0	48	pT1a pN0
1007	77	I	CS	N0	12	pT1a pN0
1009	59	I	HGE	N0	37	pT1a pN0
1012	75	I	CS	N0	17	pT1a pN0

CS = carcinosarcoma: HGSC = high grade serous carcinoma;
HGE = high grade endometrioid carcinoma;
Mixed: one case of mixed histology: 40% serous, 30% clear cell, and 30% high grade tumor.

Results

Demographic, surgery and pathology data of the seven women analyzed is summarized in Table 1. Only one of seven of the patients had a histologically proven metastatic node. Using hand held gamma probe, background readings (cpsMax and cps10s) were recorded and were as follows: in operating room: 0−2 and 0−26, respectively; in pelvis: 25−79 and 195−709, respectively; in bladder 50−172 and 575−1639, respectively; and in kidney: 24−531 and 247−1681, respectively.

In all seven patients there were 61 nodal stations assessed with the hand-held gamma probe and these included external iliac (n=14), internal iliac (n=6), obturator (n=12), common iliac (n=11), presacral (n=6), and para-aortic (n=12) nodes. The cpsMax, cps10s for nodes in vivo and cpsMax for excised nodes (ex vivo) are presented in Table 2. The case with a positive right external iliac lymph node, the node was identified accurately with preoperative PET/CT; however intraoperatively the lymph node readings were not higher than other lymph node basins assessed in same patient (281 *vs.* 357, 301, 339, 347, 331, 333, and 295). Ex vivo, the cpsMax and cps10s were 0 and 8, respectively; compared to 0, 1 for other nodes resected in same patient.

There were no intraoperative adverse events, and no postoperative event attributable to the use of the probe. The radiation exposure of all operating room staff was recorded. The surgeons recorded the maximum average exposure of all healthcare personnel with an average exposure of 0.08 mSV per case (range, 0.06−0.15). The fellow, resident, scrub nurse, circulating nurse, and anesthesiologist had exposure of 0.03 (range, 0−0.11), 0.04 (range 0−0.09), 0.03 (0−0.07), 0.02 (0−0.03), and 0.01 (0−0.03), respectively.

Discussion

Stage of disease remains the most important prognostic indicator in the management of EC and has been the fundamental reason why comprehensive surgical staging needs to be performed. To date, no preoperative assessment has proven to be sufficiently accurate to eliminate surgical staging as part of the surgical management for EC.

There exist a number of problems with the current management strategy of EC. First, the majority of women, even in cases with high grade histology, will not have positive lymph nodes at the time of surgery. Second, the extent of lymphadenectomy is based on anatomical landmarks; however, variation exists to the extent of the lymph node tissue that has been removed. Chen *et al.* published data using the SEER database outlining the likelihood of identifying a positive lymph node based on the number of lymph nodes removed [16]. The likelihood of finding a positive node increased exponentially until one removed 20 lymph nodes at which point the curve flattened. Therefore, the current surgical strategy for EC results in an unnecessary procedure for the majority of patients and for those "adequately treated" it is unclear whether the appropriate lymph nodes have been removed.

Intraoperative sentinel lymph node assessment for EC has been promising in diminishing the need for full lymphadenectomy but inherent limitations in this technique exist [6-8]. The use of the cervix as the sole site of injection for sentinel lymph node identification in EC is described. This methodology uses the principle that the majority of lymphatic drainage from the endometrium follows the same path as the cervix. This does not account for other drainage patterns from the uterus. Injection sites including the fundus, endometrium proper through the use of hysteroscopy, or a combination of sites have all been investigated [7, 17, 18]. If no clear site of injection is practically feasible, it may be that the sentinel node for EC in the traditional sense is not obtainable and therefore strategies independent of injection site may be necessary.

No study has shown a survival benefit to lymphadenectomy in EC. Survival benefit through lymphadenectomy could arise from either appropriate diagnosis of advanced

Table 2. — *Counts measured in each nodal station assessed.*

	EI		*II*		*Obt*		*CI*		*PSac*		*PA*	
	cpsMax	Cps10s	cpsMax	Cps10s	cpsMax	Cps10s	cpsMax	Cps10s	cpsMax	Cps10s	cpsMax	Cps10s
In vivo	0-75	0-671	0-64	0-595	0-86	0-681	0-57	0-593	0-72	0-566	0-68	0-649
Ex vivo	0-4	0-38	0-0	0-13	0-3	0-17	0-4	0-13	0-0	0-0	0-1	0-7

EI = external iliac; II = internal iliac; Obt = obturator; CI = common iliac; PSac = presacral; PA = para-aortic;
"In vivo" = counts measured before surgical resection at time of surgery; "Ex vivo" = counts measured in nodes after surgical resection.

stage disease and administration of adjuvant treatment or potentially removing affected lymph nodes thereby eliminating or "debulking" disease. If identifying a solitary positive lymph node in order that adjuvant chemotherapy or radiation may be administered, then sentinel lymph node strategies may be sufficient, however if one is aiming to remove affected lymph nodes, then novel strategies of metastatic lymph node identification as the one attempted in this study, will be necessary.

In this study the authors describe a novel technique using FDG PET/CT followed by intraoperative lymph node assessment using a hand-held gamma probe to identify metastatic nodes in patients with high risk EC. Although high specificity has been reported with FDG PET/CT in lymph node staging of EC, sensitivity is only moderate, limiting its clinical utility in lieu of surgical lymph node staging patients with high risk EC. The present authors' hypothesis was that the use of a hand-held intraoperative device shown in other studies to increase rate of intraoperative identification of disease sites for various malignancies would improve the sensitivity of this method and obviate the need for full lymph node dissection for accurate staging [13-15].

This pilot study has shown that this technique is feasible logistically and radiation exposure levels for all members of the healthcare team were within radiation safety guidelines. However, the hand-held gamma probe failed to identify a case of metastatic node seen preoperatively on PET/CT. One explanation may be the high level background activity identified intraoperatively. The kidneys, ureters, and bladder may have high level of radiation as FDG undergoes renal excretion. Furthermore, loops of bowel have variable FDG uptake, and at times physiological uptake of FDG in bowel may be high, further contributing to high level background activity [19]. This may explain why many of the nodal basins examined had high background activity in vivo but not when examined ex vivo. Another limitation may be detector technology, as the single node identified on preoperative PET and confirmed on pathology had only minimally higher ex vivo cps10s than other nodes resected in same patient. Given these limitations, and as most patients in the authors' department currently undergo staging through minimally invasive approaches (laparoscopic and robotic) and not through laparotomy, this pilot study was prematurely terminated.

In conclusion, use of hand-held gamma probe for intraoperative staging of patients with high risk EC is feasible and safe. However, its use for detection of lymph node metastases needs further evaluation. High level background radiation in the abdomen and pelvis from physiological structures, may limit its use for detection of lymph node metastases, especially for small volume metastatic disease. The technique requires further development if it were to be incorporated into clinical practice. Improved collimation to minimize background activity, and most importantly development of a gamma probe that can be compatible with minimally invasive procedures would be needed.

Use of hand-held gamma probe for intraoperative staging of patients with high risk EC is feasible, safe, and radiation exposure levels for all members of the healthcare team were within radiation safety guidelines. However, its use for detection of lymph node metastases needs further evaluation.

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