

## FDG-PET for management of cervical and ovarian cancer

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Received 25 October 2004

Available online 19 January 2005

### Abstract

**Objective.** To assess the diagnostic performance of Positron Emission Tomography using fluorodeoxyglucose (FDG-PET) in comparison to conventional imaging modalities in the assessment of patients with cervical and ovarian cancer.

**Methods.** Studies published between 1966 and 2003 were identified using an OVID search of the MEDLINE database. Inclusion criteria were use of a dedicated scanner, resolution specified,  $\geq 12$  human subjects, clinical follow-up  $\geq 6$  months or histopathology as reference standard, and sufficient data provided to construct a two-by-two table. Two reviewers independently abstracted data regarding sensitivity and specificity of PET.

**Results.** 25 studies (15 cervical cancer, 10 ovarian cancer) met inclusion criteria for full text review. For cervical cancer, pooled sensitivity and specificity of PET for aortic node metastasis are 0.84 (95% CI 0.68–0.94) and 0.95 (0.89–0.98). Pooled sensitivity and specificity for detection of pelvic node metastasis are: PET, 0.79 (0.65–0.90) and 0.99 (0.96–0.99); MRI, 0.72 (0.53–0.87) and 0.96 (0.92–0.98). Pooled sensitivity for CT is 0.47 (0.21–0.73) (pooled specificity not available). Pooled sensitivity and specificity of PET for recurrent cervical cancer with clinical suspicion are 0.96 (0.87–0.99) and 0.81 (0.58–0.94). For ovarian cancer, pooled sensitivity and specificity to detect recurrence with clinical suspicion are: PET, 0.90 (0.82–0.95) and 0.86 (0.67–0.96); conventional imaging, 0.68 (0.49–0.83) and 0.58 (0.33–0.80); CA-125, 0.81 (0.62–0.92) and 0.83 (0.58–0.96). When conventional imaging and CA-125 are negative, pooled sensitivity and specificity of PET are 0.54 (0.39–0.69) and 0.73 (0.56–0.87), respectively. When CA-125 is rising and conventional imaging is negative, the pooled sensitivity and specificity of PET are 0.96 (0.88–0.99) and 0.80 (0.44–0.97).

**Conclusions.** There is good evidence that PET is useful for the pre-treatment detection of retroperitoneal nodal metastasis in cervical cancer. There is fair evidence that PET is useful for the detection of recurrent cervical cancer. PET is less useful for the detection of microscopic residual ovarian cancer but has fair sensitivity to detect recurrence in the setting of a rising CA-125 and negative conventional imaging studies. Available studies are limited by low numbers of patients and wide confidence intervals.

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**Keywords:** Positron emission tomography; Cervical cancer; Ovarian cancer

### Introduction

Computed tomography (CT) and magnetic resonance (MRI) are anatomic, high-resolution imaging techniques that are commonly used to guide the management of patients with gynecologic cancers. Despite their widespread

use, concerns remain that use of these conventional imaging techniques may result in false negatives due to their inability to resolve small volumes (diameter  $< 1$  cm) of disease and false positives due to their inability to distinguish between viable tumor masses and masses consisting of necrotic or scar tissue [1]. Functional imaging methods such as positron emission tomography (PET) can establish the metabolic or functional parameters of tissue and may aid in these distinctions. Instead of using anatomical deviations to identify areas of abnormality, PET uses positron-emitting

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radioactive tracer that accumulates in abnormal tissue. The most commonly used radioisotope tracer is  $^{18}\text{F}$ -fluoro-deoxy-glucose (FDG), a glucose analog which is preferentially taken up by and retained within malignant cells. Depending on the area or organ under study, baseline glucose metabolism may be low, further establishing the difference between normal background tissue and tumor. Thus, compared to structural imaging techniques, FDG-PET has the potential to be a more accurate technique for diagnosis, staging, and treatment decisions in oncology.

The purpose of this study was to determine via a structured literature review the diagnostic accuracy of FDG-PET in comparison to conventional structural imaging techniques for assessment of the metastatic spread and recurrence of cervical and ovarian cancer. In particular, this study addressed the following questions: (1) How does the diagnostic test performance of FDG-PET compare to conventional imaging (e.g., CT, MRI) in the detection of pre-treatment metastases in newly diagnosed cervical cancer? (2) How does the diagnostic test performance of FDG-PET compare to conventional imaging in detection of residual or recurrent cervical cancer following treatment (surgery, radiation, chemotherapy, or combination therapy)? (3) How does the diagnostic test performance of FDG-PET as an adjunct to conventional imaging (e.g., CT, MRI) compare to conventional imaging alone for ovarian cancer (a) in staging at the time of initial diagnosis, (b) in detecting recurrent disease following treatment (surgery, radiation, chemotherapy, or combination)? (4) Does FDG-PET accurately and reliably detect recurrence in a patient with a history of ovarian cancer who has a rising CA-125 and a negative CT?

## Methods

We performed our search as part of a review done for the Centers for Medicare and Medicaid Services [2]. An OVID search of the Medline database was conducted on April 18th, 2003. Filters and limitations were used to eliminate inappropriate publications. General inclusion criteria were applied to maximize the applicability of the search results. The search used applicable MeSH headings and text words with appropriate Boolean operators. The search strategy combined the concepts of “cervical cancer” or “ovarian cancer” and “positron emission tomography”. For PET, we used the Medical Subject Heading (MeSH) term “tomography, emission computed” and text word searches for “PET” and “FDG-PET”. After filtering irrelevant publication types, individual review of the abstracts was performed to identify articles for full review.

Two levels of inclusion criteria were used for accepting studies. The first were general criteria applied during the initial literature search, and were as follows: (1) English language articles reporting primary data and published in a peer review journal (not abstracts); (2) Studies that include

at least 12 human subjects (not animal studies) with cervical or ovarian cancer who underwent FDG-PET scan. A second level of inclusion criteria was applied to all articles identified for full text review based on a review of the abstracts. Prior to full text review, these articles were screened to ensure that they answered at least one of the study questions.

In order to provide a framework for systematically identifying and reviewing relevant studies, we used a classification described by Fryback and Thornbury [3]. Briefly, the categories are: (1) Technical feasibility and optimization, (2) Diagnostic accuracy, (3) Diagnostic thinking impact, (4) Therapeutic choice impact, (5) Patient outcome impact, and (6) Societal impact. For each clinical question, we classified articles into a hierarchy of Categories, from 1 through 6. If an article was solely applicable to Category 1, it was excluded since these studies relate to technologies that are under development rather than those routinely used in clinical practice. For Category 2 articles, a reference standard for diagnosis was required for all patients. For Category 5 and 6 articles, the requirement of 12 human subjects was relaxed if simulation modeling with hypothetical populations was used to calculate survival, quality-adjusted life expectancy, cost-effectiveness, or cost-benefit ratios.

Data on patient population characteristics, PET scanner, conventional imaging modality, criteria for test positivity, and the results of tests including sensitivity, specificity, and prevalence of cancer was abstracted. Assessment of the quality of the study design was based on commonly accepted study design criteria for obtaining unbiased estimates of sensitivity and specificity (Rothman and Greenland, 1998) and included (1) use of a prospective design, (2) matched study design or use of a randomized controlled trial, (3) use of a pre-specified cut-point to determine sensitivity and specificity, and (4) availability of histology or long-term follow-up information on all patients. In addition to the above criteria used to describe an ideal study design, additional criteria for determining the quality of a given study were developed and applied during data abstraction. These criteria were as follows: (1) The study had a representative sample, (2) The setting and selection of the population under investigation were clearly described, (3) The study design minimized differences between patients who received the tests, (4) The scanner model or the type and resolution of the scanner were mentioned, (5) Defined criteria were used for test interpretation, (6) Histopathological or clinical confirmation of disease were mentioned, (7) The test reader and person assigning the reference standard diagnosis were blinded. Each article was reviewed by at least two reviewers. Discrepancies between reviewers were resolved by consensus.

The sensitivity and specificity for each study were calculated along with their corresponding confidence intervals from the true positives, true negatives, false positives, and false negatives abstracted from each article.

Pooled estimates of sensitivity and specificity with 95% confidence intervals were then calculated [4]. A chi-square test was used to test for homogeneity. Funnel plots with the Beggs rank-order correlation test and the Egger regression approach were used to determine the possibility of publication bias (the tendency of published studies to have different results (usually positive findings) from studies rejected from publication or never submitted for review (usually negative findings) at an  $\alpha = 0.1$  level [5,6]. Statistical analyses were performed using STATA 8.0 College Station, TX.

## Results

### Cervical cancer

Thirty-five abstracts were identified of which 20 articles were deemed potentially relevant to the study questions. Fifteen original articles met criteria for full text review and are summarized below. All studies failed to report whether radiologists were blinded to the pathology results, but none were excluded for this reason.

### Newly diagnosed cervical cancer

Thirteen studies addressed the diagnostic accuracy of PET in the radiographic assessment of patients with newly diagnosed cervical cancer. Four prospective studies addressed the diagnostic accuracy of PET for diagnosis of aortic node metastasis using histology after aortic lymphadenectomy as the gold standard [7–10]. The pooled sensitivity of PET for the detection of aortic node metastasis is 0.84 (95% CI 0.68–0.94) and pooled specificity is 0.95 (95% CI 0.89–0.98). Results of the individual studies are summarized in Table 1 and Fig. 1. In three of these studies, the accuracy of conventional imaging could not be calculated because inclusion criteria for study entry was a negative CT or MRI of the abdomen [8–10]. Reinhardt et al. did not require a negative abdominal imaging study prior to surgery. Among 12 patients who underwent aortic node

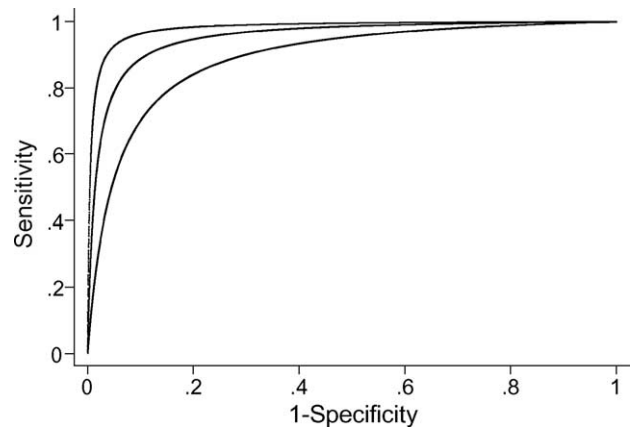


Fig. 1. ROC curve for PET to detect aortic nodal metastasis in newly diagnosed cervical cancer, with 95% confidence intervals (Area under curve = 0.952).

sampling, the sensitivity and specificity of MRI for aortic node metastasis are 0.67 and 1.00 [7]. There was no evidence of publication bias in these studies using Begg's test and Egger's test.

Four studies addressed the diagnostic accuracy of PET for diagnosis of pelvic node metastasis (Table 2, Fig. 2) [7,8,11,12]. Two of these used histology after lymphadenectomy as the gold standard [7,8], while two used either histology or clinical follow-up for confirmation [11,12]. The pooled sensitivity of PET for detection of pelvic node metastasis is 0.79 (95% CI 0.65–0.90), while pooled specificity is 0.99 (95% CI 0.96–0.99). Two studies each compared PET to MRI and CT. MRI had pooled sensitivity of 0.72 (95% CI 0.53–0.87) and pooled specificity 0.96 (95% CI 0.92–0.98), while CT had pooled sensitivity of 0.47 (95% CI 0.21–0.73) and not enough data to calculate a pooled specificity. All four studies concluded that PET has utility for predicting pelvic nodal disease. Sugarawa et al. reported the results of patients with both newly diagnosed and recurrent cancer and included patients in whom the final diagnosis was not confirmed [11]. For the purposes of this review, results were calculated from the published raw data excluding patients with recurrent disease, those without a confirmed diagnosis, and those in whom studies were read

Table 1  
Sensitivity and specificity of FDG-PET for detection of aortic node metastasis in newly diagnosed cervical cancer

| Author (year)  | N  | PET              |                  | MRI                                |                  | CT                                |             |
|----------------|----|------------------|------------------|------------------------------------|------------------|-----------------------------------|-------------|
|                |    | SN (95% CI)      | SP (95% CI)      | SN (95% CI)                        | SP (95% CI)      | SN (95% CI)                       | SP (95% CI) |
| Reinhardt 2001 | 12 | 1.00 (0.29–1.00) | 1.00 (0.66–1.00) | 0.67 (0.09–0.99)                   | 1.00 (0.66–1.00) |                                   |             |
| Rose 1999      | 32 | 0.75 (0.35–0.97) | 0.92 (0.73–0.99) |                                    |                  | 0 (All had negative abdominal CT) |             |
| Lin 2003       | 50 | 0.86 (0.57–0.98) | 0.94 (0.75–0.99) |                                    |                  | 0 (All had negative abdominal CT) |             |
| Yeh 2002       | 42 | 0.83 (0.52–0.98) | 0.97 (0.32–1.00) | 0 (All had negative abdominal MRI) |                  |                                   |             |

SN = sensitivity.

SP = specificity.

CI = confidence intervals.

Table 2

Sensitivity and specificity of FDG-PET for detection of pelvic node metastasis in newly diagnosed cervical cancer

| Author (year)  | N  | PET              |                  | MRI              |                  | CT               |                  |
|----------------|----|------------------|------------------|------------------|------------------|------------------|------------------|
|                |    | SN (95% CI)      | SP (95% CI)      | SN (95% CI)      | SP (95% CI)      | SN (95% CI)      | SP (95% CI)      |
| Reinhardt 2001 | 35 | 0.91 (0.59–1.00) | 1.00 (0.86–1.00) | 0.73 (0.39–0.94) | 0.83 (0.63–0.95) |                  |                  |
| Sugarawa 1999  | 13 | 1.00 (0.40–1.00) | 1.00 (0.66–1.00) |                  |                  | 0.50 (0.07–0.93) | 1.00 (0.66–1.00) |
| Rose 1999      | 32 | 1.00 (0.71–1.00) | 1.00 (0.54–1.00) |                  |                  | 0.45 (0.17–0.77) |                  |
| Belhocine 2002 | 22 | 0.56 (0.31–0.78) | 0.98 (0.95–1.00) | 0.72 (0.46–0.90) | 0.97 (0.94–0.99) |                  |                  |

SN = sensitivity.

SP = specificity.

CI = confidence intervals.

as “equivocal”. Belhocine et al. reported results on a “per lymph node” as opposed to a “per patient” basis, which may contribute to bias (by allowing patients with true positive or true negative findings to be counted multiple times) [12]. The sensitivity and specificity for detection of pelvic node metastasis from the Belhocine study as presented here were calculated using the raw data presented in the paper. There was no evidence of publication bias or heterogeneity in these four studies.

Two studies addressed the prognostic significance of PET in newly diagnosed cervical cancer [13,14]. Both studies are from the same institution and report on patients treated consecutively during overlapping time periods; it is unclear whether they represent overlapping patient subsets. Grigsby et al. retrospectively studied pre-treatment lymph node staging using PET and CT in 101 consecutive patients with newly diagnosed stage I–IV cervical cancer prior to primary radiotherapy [13]. Radiologists were not blinded and no criteria were given for PET interpretation. The primary outcome studied was progression-free survival. Patients with PET-positive and CT-negative aortic lymph nodes had a 2-year progression-free survival of 18%, compared to 64% for PET-negative and CT-negative aortic nodes and 14% for PET-positive, CT-positive aortic nodes. There were no patients with negative PET and positive CT findings. In multivariate analysis, PET-positive aortic lymph

node status was the only significant variable predicting lower progression-free survival ( $P = 0.025$ ); lymph node status by CT assessment was not prognostic. However, there was a difference in treatment between the two groups: aortic radiation was given to 7 of 7 patients with positive nodes by CT, but only to 4 of 14 of those with positive nodes only on PET, and exposure to aortic external radiation was not included in the survival models. Controlling for treatment effects is needed to assess whether differences in treatment contributed to the observed differences in survival.

Miller et al. retrospectively analyzed survival among 47 patients who underwent PET prior to primary radiotherapy for stage I–IV cervical cancer [14]. PET results were read in a blinded fashion by 3 radiologists (inter-observer variability was low); scoring criteria for PET interpretation were given. Patients with PET-negative lymph nodes had better overall ( $P = 0.04$ ) and progression-free ( $P = 0.03$ ) survival using Kaplan-Meier analysis at 2 1/2 years than patients whose lymph nodes were assessed as positive by PET. When lymph node status was included in a prognostic scoring system which included primary tumor size and shape, and heterogeneity of uptake as well as node status, discrimination was excellent: disease-free survival was 88% in good prognosis patients and 25% in bad prognosis patients. Both studies support the prognostic significance of pre-treatment lymph node staging using PET.

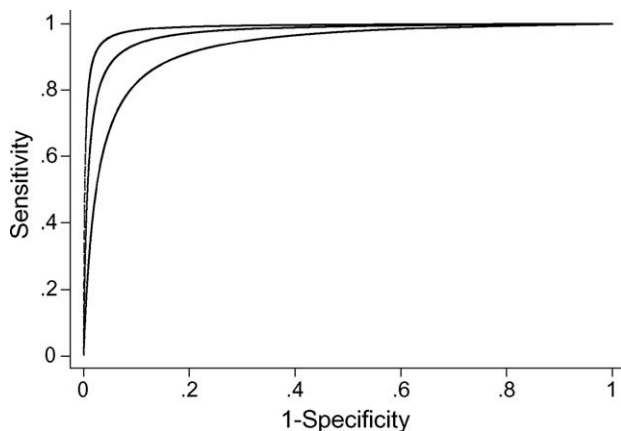


Fig. 2. ROC curve for PET to detect pelvic nodal metastasis in newly diagnosed cervical cancer, with 95% confidence intervals (Area under curve = 0.970).

#### Recurrent cervical cancer

Six retrospective studies addressed the use of PET for diagnosis of recurrent cervical cancer [12,15–19]. Confirmation of radiologic findings was either by histology or clinical follow-up of 6 months or more in all cases. Three studies included only patients in whom recurrent cancer was suspected clinically, with pooled sensitivity of PET 0.96 (95% CI 0.87–0.99) and pooled specificity 0.81 (95% CI 0.58–0.94) [15,18,19]. Chang et al. calculated sensitivity and specificity on a “per lesion” as opposed to a “per patient” basis, which may contribute to bias (by allowing patients with true positive or true negative findings to be counted multiple times) [19]. Results reported here are analyzed by individual patient (each patient, not each lesion, is assigned as “true positive” or “false negative” based on confirmation of PET results). Two of these studies had a



limited ability to calculate specificity since only 1 patient out of 20 in each study was without recurrence [18,19]. Begg's test indicates no evidence of publication bias.

Two studies reported the results of surveillance PET performed without clinical suspicion for recurrence, with pooled sensitivity of 0.92 (95% CI 0.77–0.98) and pooled specificity of 0.75 (95% CI 0.69–0.80) [16,17]. Neither study reported a comparison to conventional imaging studies, although a prior negative CT or MRI was part of the inclusion criteria used by Ryu. In a retrospective study, Belhocine et al. performed PET scans on 38 patients with a history of cervical cancer. The authors did not separately analyze PET scans performed for surveillance and those performed due to clinical suspicion, but reported that PET had sensitivity and specificity of 1.0 and 0.77 to detect recurrence, compared to 0.48 and 0.85 for conventional imaging [12].

The diagnostic accuracy of surveillance PET following primary treatment was also addressed by Grigsby et al., who retrospectively reviewed 76 patients undergoing a post-treatment surveillance PET within 10.4 months of completion of primary radiotherapy for stage I–IV cervical cancer [20]. Criteria for PET interpretation were not given. Two-year progression-free survival was 40% among patients with persistent PET abnormalities following treatment, compared to 86% for patients without abnormalities. In a multivariate analysis, post-treatment abnormal PET was a significant predictor of death ( $P < 0.0001$ ). The authors concluded that post-treatment surveillance PET is predictive of progression-free survival in patients with a history of cervical cancer. No data was provided on whether salvage therapies differed by PET status.

Two studies addressed the possible impact of PET on therapeutic choices for recurrent cervical cancer [12,21]. In a retrospective study, Belhocine et al. performed PET scans on 38 patients with a history of cervical cancer. PET results contributed to a change in treatment plan in 13/25 (52%) patients with confirmed recurrences who had an equivocal result by conventional imaging, suggesting that the addition of PET to conventional imaging may impact therapeutic choices for recurrent cervical cancer. Lai et al. [21] addressed the impact of PET on treatment planning and clinical outcome in a prospective study of 40 patients with biopsy-confirmed recurrent or persistent cervical cancer. Patients underwent PET as well as CT or MRI prior to salvage treatment planning. The authors found that the treatment plan was altered by the PET results in 22/40 (55%) of patients. In two-thirds of cases in which treatment planning was changed by PET, the treatment objective was changed from curative to palliative intent. The authors compared the survival of patients who underwent PET prior to surgery to the survival of a group of historical controls with recurrent cervical cancer who underwent surgery without prior PET. Surgically managed patients who had PET scans prior to treatment planning had a significantly better 2-year overall survival following surgery compared to

the historical control group managed surgically without PET (HR 0.21, 95% CI 0.05–0.83).

### *Ovarian cancer*

The literature search identified 36 abstracts. Review of the abstracts identified 19 articles for full text review. Of the 19 articles, 10 met the criteria for full text review; these are discussed below and classified by pre-imaging clinical scenario. There were 3 prospective studies [22–24]. All of the articles meeting criteria for review addressed the detection of recurrent or persistent ovarian cancer; none addressed detection of metastasis at the time of initial staging. None of the studies addressed whether radiologists were blinded to the pathology results.

Five studies addressed the use of surveillance PET to detect recurrent or persistent ovarian cancer in the absence of clinical suspicion [22,24–27]. Three of these studies included at least 12 patients and required both negative serum CA-125 and negative conventional imaging studies for classification as “no clinical suspicion” prior to PET imaging [22,24,25]. The pooled sensitivity of PET in these 3 studies is 0.54 (95% CI 0.39–0.69) and pooled specificity is 0.73 (95% CI 0.56–0.87). There is no evidence of publication bias using Begg's test and Egger's test. In a prospective study, Rose et al. required a negative abdominal and pelvic CT and normal CA-125 prior to entry and performed a second look laparotomy with biopsies on all patients following the PET scan [22]. The authors reported that PET has a relatively low sensitivity (0.18) and specificity (0.45) and concluded that PET is not sensitive for detection of small volume disease. In a fourth study, Karlan performed PET on 6 patients who were clinically free of disease prior to laparotomy. PET failed to detect microscopic disease in 5 out of 6 patients [27]. In a fifth study, Cho performed secondary surgery on 31 patients following primary treatment for ovarian cancer but did not report pre-operative CA-125 levels and did not require negative conventional imaging studies [26]. Among 21 evaluable patients, the sensitivity and specificity of PET were 0.82 and 0.90 compared to 1.0 and 0.90 for CT. The authors concluded that PET did not improve the diagnostic accuracy of CT in this setting.

Three studies addressed the use of PET to detect recurrent ovarian cancer in the setting of a rising CA-125 and negative or equivocal conventional imaging studies [25,28,29]. The pooled sensitivity of PET is 0.96 (95% CI 0.88–0.99) and pooled specificity 0.80 (95% CI 0.44–0.97). Two studies were limited by lack of specified minimum clinical follow-up to confirm PET results [25,29].

Six studies addressed the use of PET to detect recurrent ovarian cancer when clinical suspicion exists; those including at least 12 patients in this category are summarized in Table 3 and Fig. 3 [23–25,27,30,31]. Pooled PET sensitivity is 0.90 (95% CI 0.82–0.95) and specificity 0.86 (95% CI 0.67–0.96). Two studies compared PET to the results of CA-

Table 3

Sensitivity and specificity of FDG-PET, conventional imaging, and CA-125 for detection of recurrent ovarian cancer in the presence of clinical suspicion

| Author (year) | N  | PET              |                  | MRI/CT           |                  | CA-125           |                  |
|---------------|----|------------------|------------------|------------------|------------------|------------------|------------------|
|               |    | SN (95% CI)      | SP (95% CI)      | SN (95% CI)      | SP (95% CI)      | SN (95% CI)      | SP (95% CI)      |
| Torizuka 2002 | 25 | 0.80 (0.56–0.94) | 0.83 (0.36–1.00) | 0.55 (0.31–0.77) | 0.83 (0.36–1.00) | 0.75 (0.51–0.91) | 1.00 (0.48–1.00) |
| Nakamoto 2001 | 12 | 0.80 (0.44–0.97) | 0.50 (0.01–0.99) |                  |                  |                  |                  |
| Zimny 2001    | 58 | 0.94 (0.85–0.99) | 0.75 (0.19–0.99) |                  |                  |                  |                  |
| Yen 2001      | 24 | 0.91 (0.59–1.00) | 0.92 (0.64–1.00) | 0.91 (0.59–1.00) | 0.46 (0.19–0.75) | 0.91 (0.59–1.00) | 0.77 (0.46–0.95) |
| Hubner 1993   | 14 | 0.91 (0.59–1.00) | 1.00 (0.29–1.00) |                  |                  |                  |                  |

SN = sensitivity.

SP = specificity.

CI = confidence intervals.

125 and conventional imaging using MRI or CT [23,30]. The pooled sensitivity of conventional imaging is 0.68 (95% CI 0.49–0.83), while pooled specificity is 0.58 (95% CI 0.33–0.80). The pooled sensitivity of CA-125 is 0.81 (95% CI 0.62–0.92), and pooled specificity is 0.83 (95% CI 0.58–0.96). There was no evidence of publication bias for the PET results; there were not enough studies reporting on CA-125 and conventional imaging to report on publication bias. All authors concluded that PET may be useful in the detection of recurrent ovarian cancer. Nakamoto also reported on the possible therapeutic impact of PET imaging, noting that management of patients changed in 5/12 (42%) of patients undergoing PET who were initially suspected of having recurrent disease [24].

## Discussion

### Cervical cancer

#### Detection of pre-treatment metastases

Cervical cancer spreads by direct extension and via lymphatics, with pelvic node metastasis preceding aortic node metastasis in almost all cases. Sensitive and specific radiologic imaging modalities that identify occult lymph

node metastasis may allow avoidance of morbid surgical procedures and facilitate the planning of such novel, tailored treatments as intensity-modulated radiation therapy, which allows a substantial radiation dose to the lymph nodes with sparing of normal structures [32]. CT and MRI are fairly inaccurate for the detection of retroperitoneal nodal metastasis; calculated sensitivities range from 24% to 34% for CT and from 24% to 62% for MRI in studies which include more than 20 patients [33–35]. Using a meta-analysis of studies on cervical cancer [36], the pooled sensitivities of CT and MRI for detecting lymph node metastasis are 47% and 54%, respectively. Any imaging modality which improves the accuracy of pre-treatment staging of cervical cancer has the potential to positively impact survival from this disease. In this systematic review of the literature, we found fair evidence that PET is more sensitive than CT or MRI for detection of retroperitoneal nodal metastasis in patients with newly diagnosed cervical cancer. Several prospective studies using pathology report as a gold standard [7–10] reported that PET has sensitivity superior to that of conventional imaging in this setting, with comparable specificities; however, the studies are all limited by small sample sizes and resulting large confidence intervals in the estimates of sensitivity and specificity of both modalities. In addition, two retrospective studies from the same institution [13,14] demonstrated that pre-treatment PET findings are predictive of progression-free survival and possibly overall survival; however, neither study controlled for potential differences in treatment based on radiology findings.

It is possible that the addition of PET to the oncologist's imaging armamentarium may ultimately improve both outcomes and costs by altering primary management strategies. For example, a pre-treatment diagnosis of aortic nodal metastasis changes the patient's prognosis and has the potential to change the primary treatment modality from radical surgery to chemo-radiation, which results in a different set of expected morbidities. For patients diagnosed with aortic nodal metastasis, ongoing improvements in techniques such as intensity-modulated radiation therapy may result in reduced morbidity [32]. We conclude that FDG-PET has the potential to have a substantial impact on treatment choices for newly diagnosed cervical cancer. This

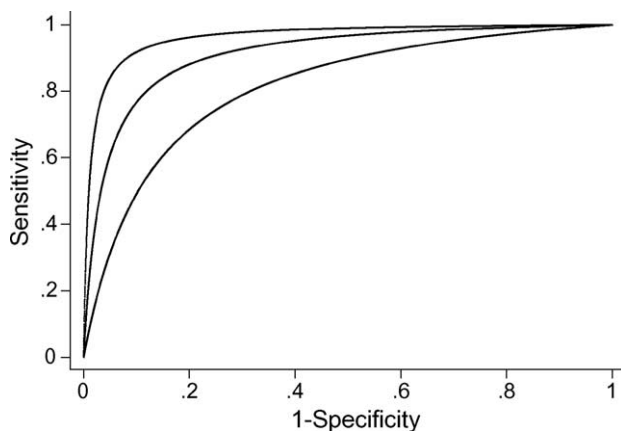


Fig. 3. ROC curve for PET to detect recurrent ovarian cancer in the presence of clinical suspicion, with 95% confidence intervals (Area under curve = 0.912).

potential should be confirmed by performance of properly designed randomized clinical trials comparing PET to conventional imaging modalities with treatment based on PET results.

#### *Persistent and recurrent disease*

Earlier detection of recurrent cervical cancer has the potential to improve survival, since some patients may be salvaged using radiotherapy or radical surgery [37–39]. Locally recurrent disease is often difficult to detect by pelvic examination due to thickening of the soft tissue structures following radiation and/or surgery. Detection of recurrent disease in the pelvis using MRI and CT is problematic in this setting because the cancer often grows by infiltration of tissues which causes only subtle changes in architecture. Cervical cancer recurrences at the pelvic sidewall or in pelvic or aortic nodes are unlikely to be cured, but new treatment modalities such as radical resection in combination with intraoperative high-dose-rate brachytherapy have afforded prolonged local control in preliminary reports [40,41]. As the available treatments for cervical cancer recurrence improve, the improvement of imaging modalities to identify recurrences early becomes more important.

We found fair evidence that PET is useful for the diagnosis of recurrent cervical cancer. One retrospective study reported that PET was superior to CT in the presence of clinical suspicion of recurrence, but small numbers resulted in wide confidence intervals [15]. Two retrospective studies found that in the post-treatment surveillance setting, PET has acceptable sensitivity and specificity but the authors did not directly compare PET to conventional imaging [16,17]. A fourth retrospective study [20] demonstrated that abnormalities on post-treatment surveillance PET predict lower progression-free survival, while the appearance of new abnormalities on surveillance PET predicts poor overall survival. Taken together these data suggest that PET is a useful adjunct to conventional imaging and may have the potential to hasten the diagnosis of recurrent cervical cancer.

If PET is able to improve the detection of recurrent cervical cancer, there are two potential means of benefit: improved survival and reduced morbidity. If PET detects local recurrence earlier and curative salvage therapy is possible, survival may be improved. If the detection of metastatic disease by PET leads to the deferral of radical salvage surgery in favor of palliative measures, unnecessary morbidity is avoided. Two recent analyses, one prospective [12,21], suggest that the addition of PET to conventional imaging to detect recurrent cervical cancer influences treatment choice in over 50% of cases. In one study, a comparison to historical controls suggests that patients who have PET performed prior to surgical salvage have improved survival [21]. We conclude that PET is a potentially useful tool for the management of patients with a history of cervical cancer; again, confirmatory prospective

trials with a direct comparison between PET and conventional imaging modalities are needed.

#### *Ovarian cancer*

##### *Recurrence following treatment*

Although recurrent ovarian cancer is almost never curable, early detection of recurrence theoretically affords a better chance that salvage treatment will result in prolonged remission and sustained quality of life. Although CA-125 elevation is often useful in detecting recurrence, it is not helpful in localizing the disease. Knowledge of the location of recurrence could guide tailored salvage treatment. For example, a patient with a localized pelvic recurrence is a candidate for secondary cytoreductive surgery, while one with miliary peritoneal carcinomatosis might be better served by treatment with salvage chemotherapy. Conventional imaging modalities often give non-specific results and are suboptimal for the reliable detection of peritoneal recurrence of ovarian cancer [42–44]. The identification of more accurate imaging modalities should improve management decisions for patients with recurrent ovarian cancer.

Two studies of patients undergoing second look laparotomy without clinical evidence of recurrence demonstrate that PET is not sensitive for the detection of microscopic residual disease [22,27]. In addition, two studies using histology or clinical follow-up as a standard report that PET has variable sensitivity for detection of recurrence when clinical suspicion for recurrence is low [24,25]. When clinical suspicion for recurrence exists, two studies [23,30] report that PET has similar sensitivity and specificity to conventional imaging modalities. Other retrospective studies [24,25,31] demonstrate that PET has good sensitivity and specificity in the detection of recurrent ovarian cancer when there is a clinical suspicion of recurrence. Confidence intervals are wide due to low numbers. Three studies [25, 28,29] give evidence that PET is helpful for detecting recurrence when CA-125 is elevated despite negative conventional imaging.

There is one prospective study demonstrating a change in treatment plan in 25% of cases when PET was added to conventional imaging for detection of ovarian cancer recurrence [17]. Most of the impact was among patients suspected of recurrence based on conventional imaging or CA-125 prior to PET scan. Evidence that the change in therapy had any impact on patient outcomes is lacking.

We conclude that PET does not appear to be useful in the routine surveillance of patients with a history of ovarian cancer, nor is it likely to improve the sensitivity of conventional modalities to detect microscopic intraperitoneal disease. There is fair evidence to support the use of PET for the detection of recurrent ovarian cancer when the CA-125 is elevated and conventional imaging is negative or equivocal, although whether this results in improved patient outcomes is unclear. A worthwhile prospective study would

investigate the addition of PET to conventional imaging for asymptomatic patients with a rising CA-125, with biopsy confirmation required for diagnosis. Newer technologies which combine metabolic and anatomic imaging such as combination PET/CT may have the potential to improve the accuracy of individual imaging modalities for recurrent ovarian cancer [45,46].

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