Positron emission tomography alone, positron emission tomography-computed tomography and computed tomography in diagnosing recurrent cervical carcinoma: a systematic review and meta-analysis

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Abstract

Introduction: The aim of the study was to assess systematically the accuracies of positron emission tomography (PET), PET/computed tomography (CT), and CT in diagnosing recurrent cervical cancer.

Material and methods: We searched for articles published from January 1980 to June 2013 using the following inclusion criteria: articles were reported in English; the use of PET, interpreted with or without the use of CT; use of CT to detect recurrent cervical cancer; and histopathologic analysis and/or close clinical and imaging follow-up for at least 6 months. We extracted data to calculate sensitivity, specificity, summary receiver operating characteristic curves, and the area under the receiver operating characteristic curve (AUC) as well as test for heterogeneity.

Results: In 23 included studies, PET had the highest pooled specificity at 92% (95% CI: 90–94), whereas PET/CT had the highest pooled sensitivity at 94% (95% CI: 90–97). The area under the curve (AUC) of PET alone, PET/CT, and CT were 0.9594, 0.9508, and 0.9363, respectively. Results of the pairwise comparison between each modality show that the specificity of PET was higher than that of PET/CT ($p < 0.05$). The difference in the pooled sensitivities and AUC of PET alone and PET/CT showed no statistical significance. No evidence of publication bias was found. However, evidence of heterogeneity was observed.

Conclusions: The PET/CT may be a useful supplement to current surveillance techniques, particularly for patients with negative CT imaging. However, in terms of diagnostic accuracy, interpreted CT images may have limited additional value to PET in detecting recurrent cervical cancer.

Key words: recurrent cervical cancer, positron emission tomography, computed tomography, meta-analysis.

Introduction

Cervical cancer is one of the most common gynecological malignancies worldwide. Approximately 30% of cervical cancers are known to relapse eventually after initial treatment [1]. Most women who recur are not curable. However, early identification of recurrence can alter disease management or treatment-planning options, particularly for those with a central pelvic recurrence and no evidence of metastasis. A large num-

ber of noninvasive imaging methods can be used to identify patients with recurrent cervical cancer. These methods are used in conjunction with physical examination and measurement of squamous cell carcinoma antigen (SCC) levels. Elevated SCC values are established indicators of the active disease and can be used for early detection [2]; however, they do not identify the site of recurrence [2]. Various modalities such as computed tomography (CT) and positron emission tomography (PET) play important roles in the staging of these tumors.

Computed tomography is helpful in determining the radiation portal, site for biopsy, and effect of treatment. Consequently, this modality has been used as a very effective tool in the diagnosis of recurrent uterine cervical cancer. However, with CT, recurrence from postoperative and postradiation fibrosis may be difficult to differentiate, and normal-sized metastatic lymph nodes are hard to detect [3, 4]. Positron emission tomography is an emerging imaging technique that is used to diagnose cancer recurrence and distant metastasis in the preclinical stage before the disease becomes evident in conventional diagnostic imaging modalities. However, PET does not provide anatomic information, and precise localization of any suspicious lesion may be difficult. Early diagnosis of cancer recurrence by PET is also impaired by the presence of increased uptake in physiologic, nonpathologic, or inflammatory states [5, 6].

Squamous cell carcinoma measurements suffer from relatively low sensitivity and specificity for detecting recurrent cervical cancer (76.3% and 70.6%, respectively). The reported sensitivities of imaging methods range from 78% to 93% for CT, 80% to 100% for PET, 83% to 100% for PET/CT imaging, and 86% to 99% for PET using the tracer fluorine 18 (18F)-fluorodeoxyglucose (FDG). No consensus on the most sensitive imaging method for the detection of recurrence in patients treated for cervical cancer is found.

A meta-analysis enables the comparison of various imaging methods through a systematic review of the literature. The process involves combining previously published work and making a summary estimate of the sensitivity and specificity of each imaging modality [7]. The purpose of our present study is to perform a comprehensive systematic review to determine the overall diagnostic performance of PET alone, PET/CT, and CT for the detection of recurrent cervical cancer on a per-patient and a per-lesion basis. To our knowledge, this type of study has not been previously reported.

Material and methods

Literature search

A comprehensive computer literature search of study abstracts involving human subjects was performed to identify articles on the diagnostic performance of PET (interpreted with or without the use of CT) and CT to detect recurrent ovarian cancer. MEDLINE and EMBASE databases were reviewed from January 1980 to June 2013 using the following key words: ("PET" or "positron emission tomography" or "FDG" or "fluorodeoxyglucose" or "CT" or "computed tomography") and ("cervical carcinoma" or "cervical cancer" or "carcinoma of cervix") and ("sensitivity" or "specificity" or "false negative" or "false positive" or "diagnosis" or "detection" or "accuracy"). Other databases, including CancerLit and the Cochrane Library, were also searched for relevant articles. Reference lists of included studies and review articles were manually searched.

Selection of studies

Two investigators independently checked the retrieved articles. Disagreements were resolved by consensus. The inclusion criteria were (a) articles were published in English; (b) PET alone, PET/CT, and CT (alone or in combination, but not in sequence) were used to identify and characterize recurrent cervical carcinoma; (c) histopathological analysis and/or close clinical follow-up for at least 6 months were used as reference; (d) for per-patient statistics, sufficient data were presented to calculate the true-positive (TP), false-negative (FN), false-positive (FP), and true-negative (TN) values; (e) 10 or more patients were included; and (f) when data or subsets of data were presented in more than one article, the article with the most detail or the most recent article was chosen. Authors of abstracts and studies that did not report sufficient data were contacted to request additional information.

Data extraction

The same observers independently extracted relevant data on study characteristics and examination results using a standardized form. To resolve disagreements between reviewers, a third reviewer assessed all discrepant items, and the majority opinion was used for analysis.

To ensure accuracy in the analyses, we extracted the following items: description of study population (age); study design (prospective, retrospective, or unknown); patient enrollment (consecutive or not); and interpretation of test results (blinded or not). The following features were also included: for PET alone or PET/CT, the amount of tracer and type of analysis (qualitative, quantitative, or both); and for CT, the section thickness and use or non-use of a contrast agent. The numbers of TP, FN, FP, and TN results in the detection of recurrent cervical cancer were extracted on a per-patient or per-lesion basis.

Statistical analysis

The statistical software "Meta-Disc" version 1.40 was used to analyze separately the 18F-FDG PET, 18F-FDG PET/CT, and CT data. We calculated the pooled sensitivity, specificity, and diagnostic odds ratio (DOR) for each modality. We also calculated the summary receiver operating characteristic curves (SROC) and the *Q index (which is the optimum statistical method for reflecting the diagnostic value). The *Q index is defined by the point at which sensitivity and specificity are equal, which is closest to the ideal top-left corner of the SROC space [8, 9]. The *Z*-test was then performed to determine whether the sensitivity, specificity, DOR, and *Q index of one modality are significantly different from those of the others. The χ^2-test was used to assess the heterogeneity among the studies included in the meta-analysis. A fixed-effect model (FEM) was used when homogeneity existed among different studies, whereas a random-effect model (REM) was used when heterogeneity was found.

Results

Study identification and eligibility

A total of 118 articles in English were initially retrieved from the MEDLINE and EMBASE databases. Twenty-six articles were considered as candidates after a review of titles and abstracts. Two articles were excluded for using CT-magnetic resonance imaging (MRI). Finally, the remaining 23 were included in the study [3, 10–31].

Study description

The characteristics of participants in the 23 eligible studies are outlined in Table I. The mean age of the participants ranged from 41 years to 58 years.

Table I. Main characteristics of the included studies

Author	Year of publication	Age, mean (range)	Patients selection	Blind	Evaluable patients or lesion	Recurrent number *n* (%)	Noninvasive modalities	Study design
Walsh	1981	ND (23–68)	Consecutive	ND	33	29 (88)	CT	Retrospectively
Heron	1988	45 (28–80)	ND	ND	64	26 (41)	CT	ND
William	1989	ND	ND	ND	20	11 (55)	CT	Retrospectively
Park	2000	53 (ND)	ND	ND	36	19 (53)	PET, CT	ND
Sun	2001	ND	ND	ND	20	18 (90)	PET	Retrospectively
Belhocine	2002	52 (38–66)	ND	ND	60	28 (47)	PET	Retrospectively
Nakamoto	2002	52 (26–82)	ND	ND	20	5 (25)	PET	Retrospectively
Ryu	2003	51 (31–78)	ND	ND	249	31 (12)	PET	Retrospectively
Havrilesky	2003	42 (28–69)	ND	ND	29	22 (76)	PET	Retrospectively
Lai	2004	51 (25–87)	Consecutive	ND	400	67 (17)	PET	Retrospectively
Yen	2004	51 (25–86)	ND	ND	550	94 (17)	PET	Prospective
Chang	2004	54 (35–76)	Consecutive	ND	27	18 (67)	PET	ND
Grisaru	2004	56 (20–85)	Consecutive	Yes	12	10 (83)	PET/CT	ND
Sakurai	2006	56 (27–80)	Consecutive	ND	54	87%	PET	ND
Amit	2006	50 (31–71)	ND	ND	28	7 (25)	PET/CT	ND
Sironi	2007	28–69	Consecutive	Yes	12	5 (42)	PET/CT	Retrospectively
Chung	2007	53 (32–77)	ND	ND	32	28 (88)	PET/CT	Retrospectively
van der Veldt	2008	41 (27–61)	ND	ND	39	25 (64)	PET	Retrospectively
Kitajima	2008	58 (37–78)	Consecutive	Yes	52	25 (48)	PET/CT, PET	ND
Mittra	2009	50 (28–87)	ND	ND	30	24 (80)	PET/CT	Retrospectively
Pallardy	2010	46 (35–81)	ND	ND	40	33 (83)	PET/CT	Retrospectively
Cetrina	2011	47	ND	ND	16	12 (75)	PET/CT	Retrospectively
Lee	2011	ND	ND	ND	51	37 (73)	PET/CT	Retrospectively

Of the 23 studies, 1 [19] enrolled patients prospectively, whereas 15 [3, 11, 13–18, 24–26, 28–31] were retrospective database reviews. The status of the remaining 7 studies was not defined [10, 12, 20–23, 31]. Seven studies [13, 22, 24–26, 28, 31] enrolled patients in a consecutive manner, including three studies [21, 24, 27] in which the operator was blinded to prior test results. The TP, FN, FP, and TN results, as well as some features of each modality, are shown in Tables II–IV.

Summary estimates of the sensitivity, specificity, and diagnostic odds ratio

The pooled sensitivities for 18F-FDG PET, FDG-PET/CT, and CT were 91% (95% CI: 88–94), 94% (95% CI: 90–97), and 89% (95% CI: 81–95), respectively. No statistically significant difference was found among the three noninvasive modalities ($p > 0.05$). In addition, the pooled specificities for the three modalities were 92% (95% CI:

Table II. TP, FP, FN, TN and other features of PET alone

Author	18F-FDG dose	TP	FP	FN	TN
Park	2.5 MBq/kg	18	1	0	17
Sun	ND	16	0	2	2
Nakamoto	370 MBq	5	6	0	9
Belhocine	164.28–249.38 MBq	25	3	0	10
Ryu	370–555 MBq	28	52	3	166
Havrilesky	0.14 mCi/kg	12	2	2	13
Lai	370 MBq	61	6	6	327
Yen	ND	84	8	10	448
Chang	370 MBq	17	2	1	7
Sakurai	200–400 MBq	43	3	4	4
Kitajima	4.0 MBq/kg	20	6	5	21
van der Veldt	370 MBq	23	1	2	13

Table III. TP, FP, FN, TN and other features of PET-CT

Author	18F-FDG dose	TP	FP	FN	TN
Grisaru	370–666 MBq	10	0	0	2
Chung	555–740 MBq	28	4	3	17
Amit	370–555 MBq	6	0	1	4
Sironi	370 MBq	5	0	1	6
Kitajima	4.0 MBq/kg	23	2	2	25
Mittra	400–555	22	2	1	5
Pallardy	6 MBq/kg	31	1	2	6
Cetina	ND	12	2	0	2
Lee	370–555 MBq	36	4	1	10

Table IV. TP, FP, FN, TN and other features of CT

Author	Method	Section [mm]	TP	FP	FN	TN
Wlash	Not enhanced	ND	27	2	2	0
Heron	Not enhanced	8	24	2	2	36
William	Not enhanced	ND	10	2	1	7
Park	Not enhanced	10	14	3	4	15

Table V. Summary estimates of sensitivity, specificity, DOR, *Q index and AUC for PET, PE/CT and CT

Modality	Pooled sensitivity (95% CI)	Pooled specificity (95%CI)	DOR	*Q	AUC
PET	91% (88–94%)	92% (90–94%)	74.15 (27.04–203.32)	0.9037	0.9594
PET/CT	94% (90–97%)	84% (75–91%)	62.74 (27.82–141.47)	0.8915	0.9508
CT	89% (81–95%)	87% (76–94%)	29.31 (5.46–157.31)	0.8728	0.9363

90–94), 84% (95% CI: 75–91), and 87% (95% CI: 76–94), respectively. Therefore, for the specificity estimates, PET had a higher pooled sensitivity ($p < 0.05$) compared with PET/CT. No statistical difference was found between PET/CT and CT in terms of their pooled specificities ($p > 0.05$). The forest plots for the sensitivities and specificities of 18F-FDG PET, FDG-PET/CT, and CT are shown in Figures 1–3.

Diagnostic odds ratio expresses the odds of having the disease for people with a positive test result compared with those with a negative test result. The pooled DOR for PET alone was 74.15 (95% CI: 27.04–203.32), with the heterogeneity χ^2 at 71.08 ($p = 0.0001$). The pooled DOR for PET/CT was 62.74 (95% CI: 27.82–141.47), with the heterogeneity χ^2 at 0.00 ($p = 0.9911$). Meanwhile, the DOR for CT was 29.31 (95% CI: 5.46–157.31), with

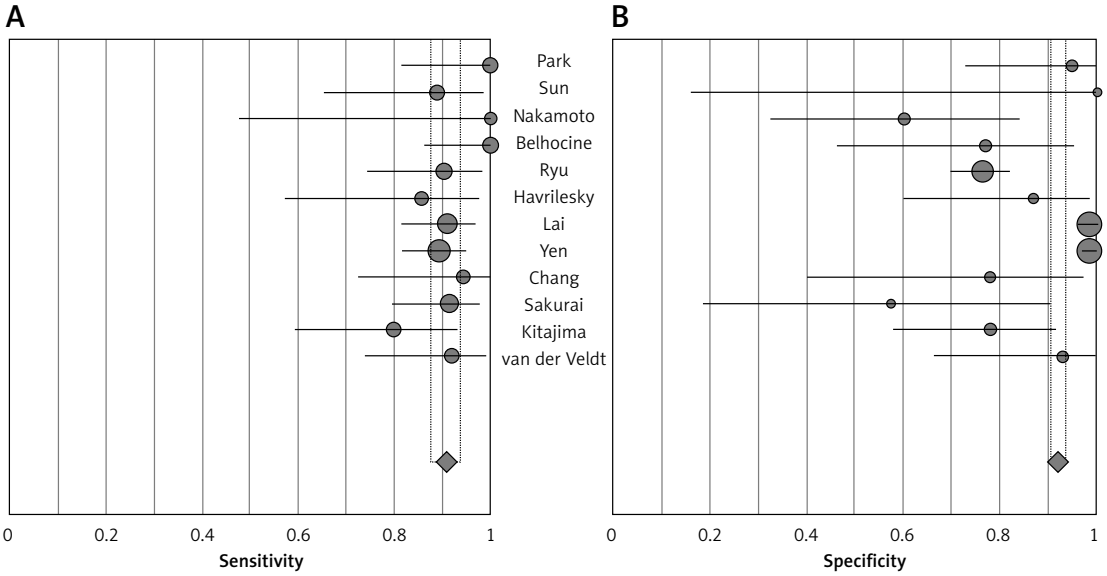


Figure 1. Sensitivity (**A**) and specificity (**B**) of PET alone

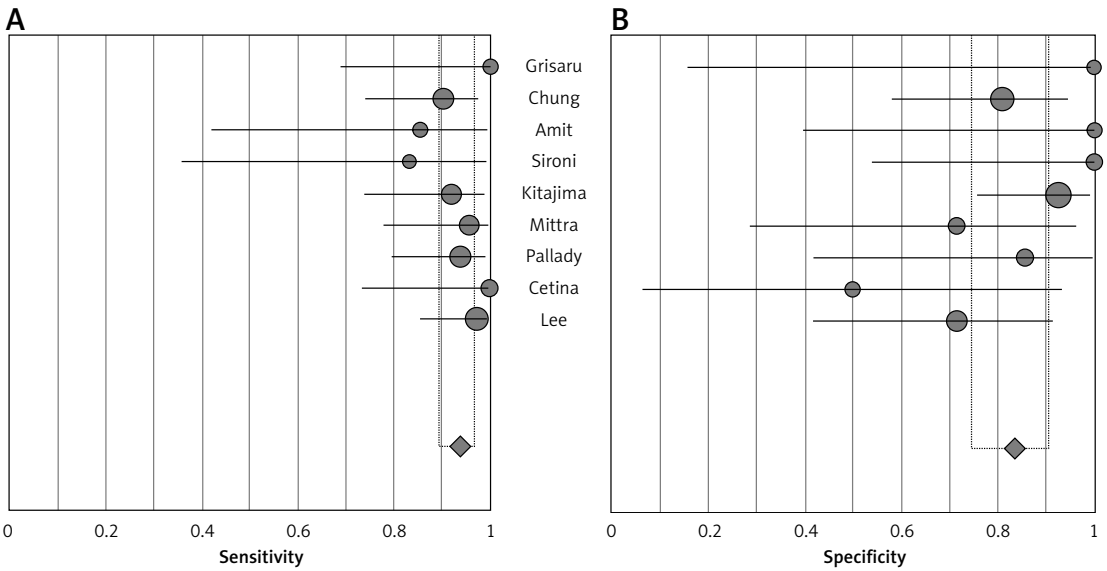


Figure 2. Sensitivity (**A**) and specificity (**B**) of PET/CT

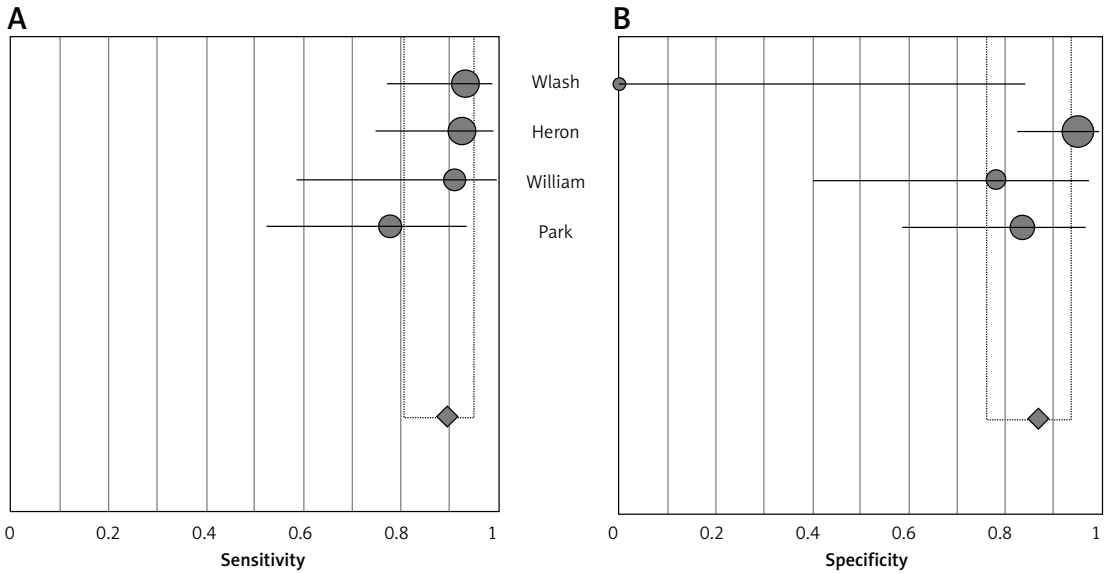


Figure 3. Sensitivity (**A**) and specificity (**B**) of CT

the heterogeneity χ^2 at 53.5 (p = 0.0916). The results are also shown in Figure 4 (Table V).

Publication bias and heterogeneity

Begg's funnel plot and Egger's test were performed to determine the publication bias of the literature. The shapes of the funnel plots do not reveal any evidence of obvious asymmetry (Figure 5). Accordingly, Egger's test was used to provide statistical evidence of the observed funnel plot symmetry. The results still do not suggest any evidence of a publication bias (p, PET = 0.681; p, PET/CT = 0.677 and p, CT = 0.497). Regarding the limited number of data points for CT imaging, current results do not show evidence of any publication bias.

For the PET and CT studies, the specificity (heterogeneity χ^2: 138.75 and 11.44; $p < 0.001$ and 0.0096, respectively) was highly heterogeneous and affected the diagnostic value of PET and CT in diagnosing patients with current cervical cancer. Thus, the REMs were selected. No significant heterogeneity was found among the PET/CT studies.

Summary of the receiver operating characteristic curves and area under the curve

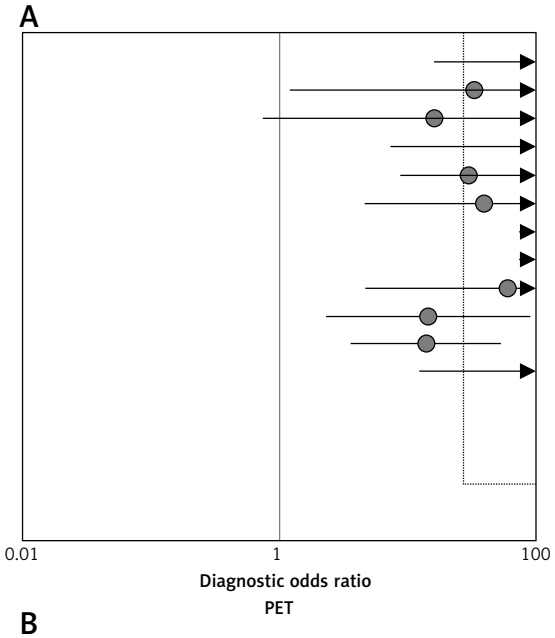
We used SROC analysis to compare the noninvasive modalities. The SROC curves for 18F-FDG PET, PET/CT, and CT are shown in Figure 6. Given the heterogeneity, we chose REM to synthesize the ROC curves for 18F-FDG PET and CT, whereas FEM was used for PET/CT. The AUC values of 18F-FDG PET, PET/CT, and CT were 0.9594, 0.9508, and 0.9363, respectively (Figure 6). However, no significant difference was found among the three imaging modalities ($p > 0.05$).

Discussion

Cancer of the uterine cervix (cervical cancer) is among the top three leading diagnoses among gynecological malignancies worldwide. This disease has a relatively high 5-year mortality and recurrence rate (28%). Hence, enhanced staging, therapy, and evaluation of recurrence are essential to improve the prognosis for cervical cancer patients [32]. The current meta-analysis focused on evaluating the diagnostic efficiency of PET, PET/CT, and PET in the diagnosis of recurrent cervical cancer.

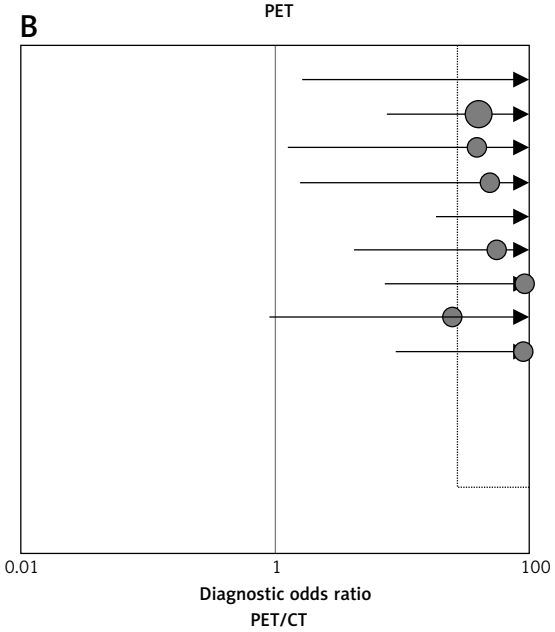
Positron emission tomography and positron emission tomography/computed tomography

Positron emission tomography using FDG has been successfully used to diagnose cancer recurrence and distant metastasis in the preclinical stage before the disease becomes evident by conventional imaging modalities. Positron emission tomography provides anatomical image resolutions from 4 mm to 6 mm, which are significantly better than those of conventional gamma cameras but inferior to the 1 mm to 2 mm resolution of CT or MRI. Our results confirm that FDG-PET may be a useful modality in detecting the recurrence of cervical cancer, exhibiting high sensitivity at 91% and high specificity at 92%. Ryu *et al.* [16] reported that the sensitivity and specificity of 18F-FDG PET were 90.3% and 76.1%, respectively, for the detection of early recurrence in 249 patients with no evidence of the disease on physical examination and had negative tumor markers, chest radiography, and annual pelvic CT or MRI. Sugawara *et al.* [33] reported that 18F-FDG PET can detect lymph node metastasis more accurately than CT or MRI



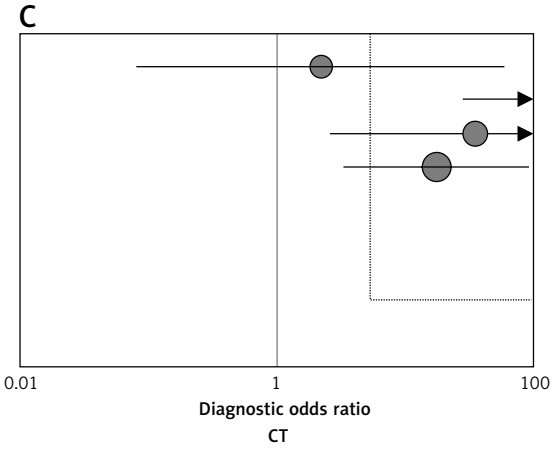
	Diagnostic OR (95% CI)
Park	431.67 (16.46–11,319.94)
Sun	33.00 (1.20–908.20)
Nalkamoto	16.08 (0.75–343.62)
Belhocine	153.00 (7.25–3,227.75)
Ryu	29.79 (8.70–102.01)
Havrilesky	39.00 (4.72–322.06)
Lai	554.08 (172.98–1,774.82)
Yen	470.40 (180.39–1,226.65)
Chang	59.50 (4.61–767.18)
Sakurai	14.33 (2.34–87.93)
Kitajima	14.00 (3.68–53.23)
Van der Veldt	149.50 (12.33–1,812.10)

Random effects model
Polled diagnostic odds ratio = 74.15 (27.04–203.32)
Cochran-Q = 39.07; d*f* = 11 (*p* = 0.0001)
Inconsistency (I^2) = 71.8%
τ^2 = 1.9991



	Diagnostic OR (95% CI)
Grisaru	105.00 (1.65–6,697.46)
Chung	39.67 (7.90–199.18)
Amit	39.00 (1.28–1,190.85)
Sironi	47.67 (1.60–1,422.71)
Kitajima	143.75 (18.69–1,105.68)
Mittra	55.00 (4.13–732.72)
Pallardy	93.00 (7.23–1,196.65)
Cetina	25.00 (0.90–695.80)
Lee	90.00 (9.02–898.21)

Fixed effects model
Polled diagnostic odds ratio = 62.74 (27.82–141.47)
Cochran-Q = 1.59; d*f* = 8 (*p* = 0.9911)
Inconsistency (I^2) = 0.0%



	Diagnostic OR (95% CI)
Wlash	2.20 (0.08–59.70)
Heron	216.00 (28.46–1,639.52)
William	35.00 (2.63–465.38)
Park	17.50 (3.31–92.48)

Random effects model
Polled diagnostic odds ratio = 29.31 (5.46–157.31)
Cochran-Q = 6.45; d*f* = 3 (*p* = 0.0916)
Inconsistency (I^2) = 53.5%
τ^2 = 1.5357

Figure 4. DOR of PET (**A**) alone, PET/CT (**B**), and CT (**C**)

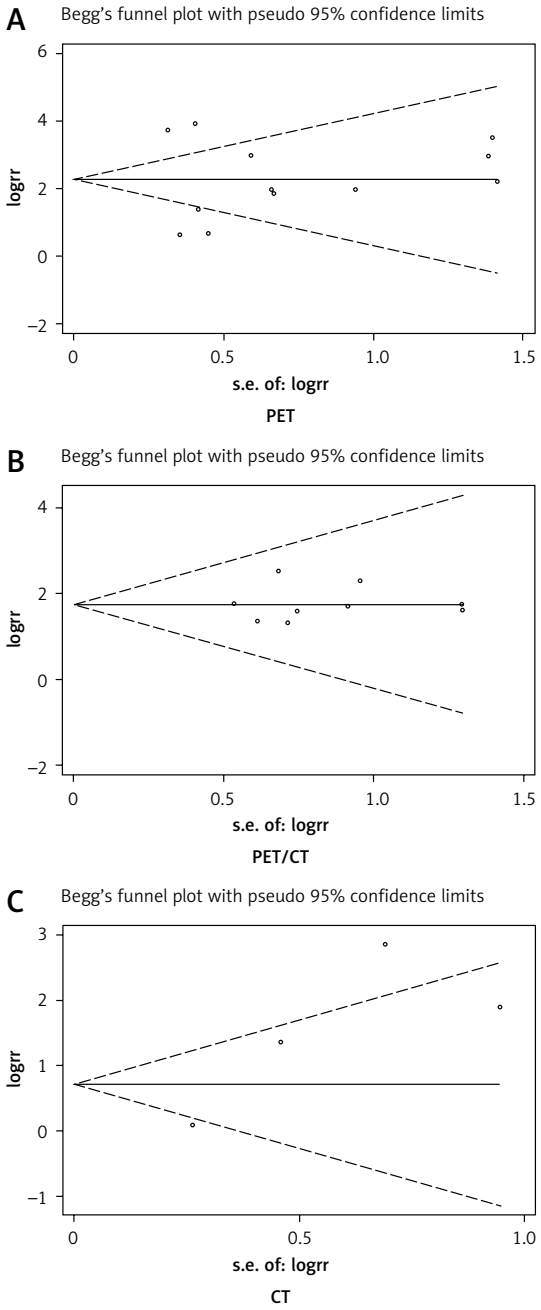


Figure 5. Begg's funnel plots for assessing the publication bias risk of PET (**A**), PET/CT (**B**) and CT (**C**)

in patients with cervical cancer. 18F-FDG PET can detect recurrences in small lesions (< 1 cm) and in the retrovesical area, which are frequently obscured by postradiation fibrosis. Chung *et al.* [25] found that the sensitivity and specificity of FDG-PET for detecting recurrence in patients who had elevated serum SCC-Ag levels and negative conventional imaging findings were 94% and 78%, respectively. Therefore, PET alone may be useful in the early diagnosis of recurrence, particularly when SCC levels are increasing and conventional imaging (e.g., CT or MR imaging) is inconclusive or negative. However, PET does not provide sufficient structural information for direct topographical

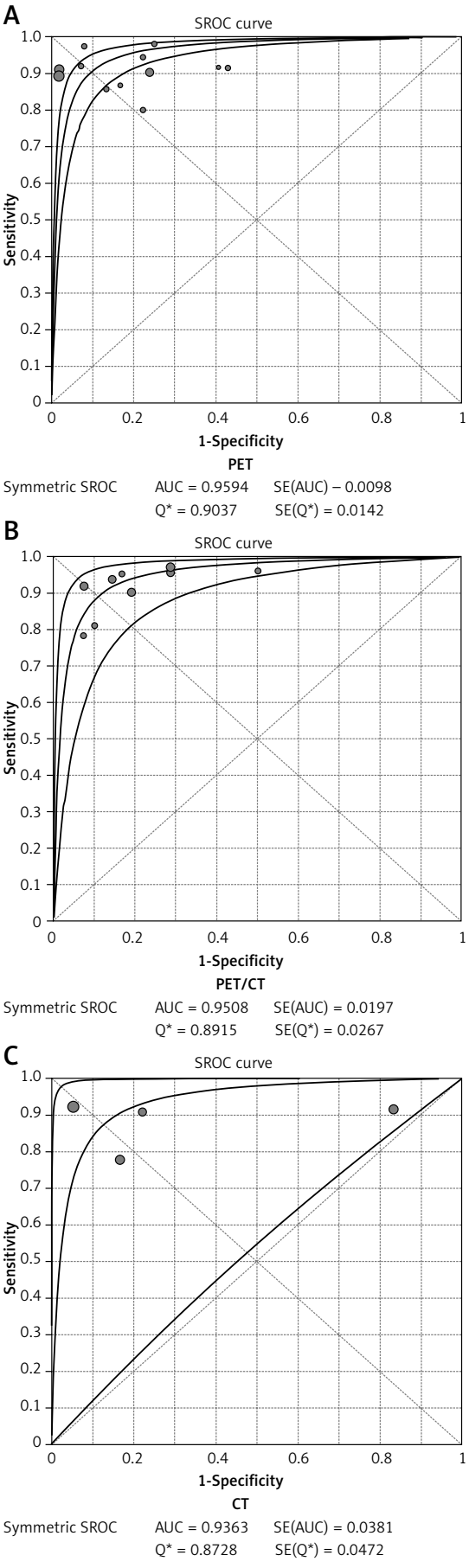


Figure 6. SROC curves of PET (**A**), PET/CT (**B**) and CT (**C**) for detecting recurrent cervical cancer

evaluation. Thus, image analysis has to be based on additional anatomical information [34]. An integrated PET/CT system, in which a dedicated PET ring and a multidetector helical CT are combined, has recently facilitated the acquisition of both metabolic and anatomical imaging data using a single device in a single diagnostic session. This integrated system provides precise anatomical localization of suspicious areas with increased FDG uptake and rules out false-positive PET findings [35]. The use of combined PET/CT in detecting recurrent cervical cancer was first described by Grisaru *et al.* in 2004. They reported that the sensitivity and specificity of PET/CT for detecting recurrent cervical cancer were both 100%. A limitation of this pilot study is that the number of enrolled suspected recurrent cervical cancer patients was not sufficient for a powerful statistical analysis. In our meta-analysis, we found no significant difference between PET alone and PET/CT ($p > 0.05$). A possible explanation for this discrepancy is that the accuracy of PET/CT may have been compromised by inflammatory lesions induced by recent surgery or radiotherapy. However, the use of PET/CT can help identify biopsy sites, avoiding the interpretation problems resulting from poor anatomic localization of PET alone. A further CT scan may be based on a positive FDG PET scan.

Computed tomography

Computed tomography is often used in postoperative, follow-up examinations of patients after cervical cancer surgery. Choi *et al.* [36] performed a meta-analysis to assess the diagnostic performances of CT and PET or PET/CT for the detection of metastatic lymph nodes in patients with cervical cancer. Computed tomography was reported to show pooled sensitivity and specificity of 50% and 92%, respectively, whereas PET or PET/CT showed 82% and 95%, respectively. Park *et al.* [12] also reported that PET is superior to CT in terms of sensitivity and specificity. Walsh *et al.* [3] found that CT has difficulty in differentiating recurrence from postoperative and postradiation fibrosis and in detecting normal-sized metastatic lymph nodes. These findings suggest that PET may be crucial in detecting recurrent cervical cancer when CT results are negative.

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