Positron emission tomography-computed tomography has a clinical impact for patients with cervical cancer

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ABSTRACT

INTRODUCTION: Many studies have found that positron emission tomography-computed tomography (PET-CT) has a high sensitivity and specificity in the identification of metastasis in cervical cancer. Herlev Hospital, Denmark, has been performing PET-CTs in stage I-IV cervical cancer since 1 May 2006. The present study investigates the positive (PPV) and negative predictive value (NPV) of PET-CT in stage I disease and the clinical impact of the scan results in all disease stages.

MATERIAL AND METHODS: In this retrospective study, 83 consecutive patients with cervical cancer were included between 1 May 2006 and 1 November 2007. Data were collected from patient records and PET-CT reports.

RESULTS: Among 47 stage I patients, four had PET-positive findings on the scan in addition to cervical cancer. Only one was a true positive finding. Pelvic lymphadenectomy was performed in 36 stage Ia2-Ib1 patients. Histology from stage I patients revealed a PPV of 25% and a NPV of 88%. Among a total of 36 stage II-IV patients, 14 had PET-positive findings. Five patients had a biopsy performed. Three of these patients were true positives and two were true negatives. Taking of biopsies in the remaining patients was clinically irrelevant. Five patients (6%), all in stage ≥ IIb, were offered an alternative treatment owing to the additional information obtained from the PET-CT.

CONCLUSION: PET-CT is useful in the identification of metastatic disease in cervical cancer and it may assist optimal treatment planning; especially in International Federation of Gynecologists & Obstetricians (FIGO) stage > I cancers. Histological verification of PET-positive findings is necessary. The clinical value of PET-CT in early stage cervical cancer may be questioned.

Denmark sees approximately 400 new cases of cervical cancer per year, corresponding to an incidence of 11/100,000. The prognosis is favourable in early-stage disease, but decreases dramatically with advancing tumour stage. Lymph node metastases are the most important prognostic factor for survival in patients with cervical cancer [1-3]. To improve survival and to reduce the treatment morbidity, knowledge about lymph node status is crucial in treatment planning. A Danish study using combined positron emission tomography (PET) and computed tomography (CT) in cervical cancer stage ≥ Ib showed metastatic disease in 37% of patients at the time of diagnosis; 22% of these cases of metastasis were outside the pelvic radiation field [4]. Several authors have studied the usefulness of PET and PET-CT to identify lymph node metastases in cervical cancer [4-11] and have found a high sensitivity, specificity, positive (PPV) and negative predictive value (NPV) [12-14]. The Danish Gynaecological Cancer Group (DGCG) therefore recommends that cervical cancer patients undergo PET-CT before radiation and chemotherapy [15]. In the present retrospective study, we evaluated whether PET-CT compared with clinical staging contributes with additional information about metastatic disease.

Cervical cancer is staged according to the International Federation of Gynecologists & Obstetricians (FIGO) staging system (**Table 1**) [16]. The system is based on clinical examination and incorporates only tumour size and tumour extension. Findings from other diagnostics, e.g. PET-CT or surgery, do not change the stage. The FIGO staging was revised 01.01.2009 [17]. The previous/unrevised FIGO staging system was used in the present study.

MATERIAL AND METHODS

From 1 May 2006 to 1 November 2007, a total of 117 consecutive patients with newly diagnosed cervical cancer stage I-IV were included. Due to limited capacity, 34 patients with early-stage disease did not have a PET-CT performed and were excluded from the study, leaving 83 evaluable patients. The patients were randomly chosen, depending on the time of admittance to the hospital and the capacity at the PET-CT scanners. With a view to staging, all patients underwent gynaecological examination, and cysto- and proctoscopy in general anaesthesia. Vaginal and transabdominal ultrasound of the pelvis and the abdomen were also performed. All patients were referred to routine PET-CT after clinical staging to identify any metastatic disease. Either a Gemini (92%) or a Gemini–TF (8%) PET-CT scanner (Philips Medical) was used. The Gemini whole-body PET scanner uses gadolinium-oxyorthosilicate crystals and has dual-slice CT system (slice thickness 6.5 mm, 5 mm overlap, rotation time 0.75 s/rotation, 2 × 5 mm collimation). Gemini-TF uses lutetium-yttrium oxyorthosilicate crys-

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TABLE 1

FIGO staging system for cervical cancer.

Ia	*Invasive cancer identified only microscopically*
Ia1	Measured stromal invasion of ≤ 3 mm and extension of ≤ 7 mm
Ia2	Measured stromal invasion of > 3 mm and not > 5 mm with an extension of not > 7 mm
Ib	*Clinical lesions confined to the cervix or preclinical lesions greater than stage Ia*
Ib1	Clinical lesions ≤ 4 cm in size
Ib2	Clinical lesions > 4 cm in size
II	*Extends beyond the cervix, but not onto the pelvic wall*
IIa	No obvious parametrial involvement. Involvement of as much as the upper two thirds of the vagina
IIb	Obvious parametrial involvement, but not onto the pelvic sidewall
III	*Extends to the pelvic wall and/or to the lower thirds of the vagina. All cases with hydronephrosis or nonfunctional kidney should be included, unless known to be due to other causes*
IIIa	Tumour involves the lower third of the vagina with no extension to the pelvic wall
IIIb	Extension to the pelvic wall or hydronephrosis or non-functioning kidney
IV	*Extends beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum*
IVa	Spread of tumour to adjacent pelvic organs
IVb	Spread to distant organs

FIGO = International Federation of Gynecology and Obstetrics.

tals and time-of-flight mode for the PET component, and has a 16-slice CT scanner (with a slice thickness of 3.0 mm, 1.5 mm overlap, rotation time 0.75 s/rotation, 16 × 1.5 mm collimation). The acquisition time for the PET-scanning was two minutes per bed position for both scanners. A fixed dose of 370 MBq ^{18}F-fluorodeoxyglucose (^{18}F-FDG) was given intravenously (IV). Oral contrast was given after 30 minutes rest. Data acquisition started 60 min post injection and included the region from the mid femoral level to the base of the skull. For the CT part, IV contrast was given routinely. Data were reconstructed iteratively using 3D row-action maximum-likelihood algorithm (RAMLA). For viewing, scanner-specific software was used (Syntegra or Brilliance Workspace). Specialists in nuclear medicine interpreted the PET part and oncoradiologists the CT part. The specialists undertook a final common consensus interpretation and a written report was made. A focus was considered PET-positive by visual analysis when it was clearly focal with activity higher than the soft tissue background level. No cut-off values were used. For the CT part, any lymph node larger than 1 cm on the shortest axis was reported as being suspect for cancer.

Biopsies of suspicious findings were taken if it was of clinical relevance. Thus, biopsies of lymph nodes were not taken if they were included in the planned radiation- or surgery field or if palliative treatment was planned due to stage IVb disease and/or poor general health.

Treatment was offered in accordance with current national guidelines issued by the DGCG.

Data collection was carried out retrospectively. Since radical pelvic lymphadenectomy (PL) is still regarded the true confirmation of PET-positive findings and due to the biopsy criteria given above, PPV and NPV was only calculated for patients with stage Ia2 and Ib who had PL.

Trial registration: not relevant

TABLE 2

Demographic data (n = 83).

	n	%
Stage		
Ia	11	13
Ib	36	43
IIb	20	24
IIIb	11	13
Iva	2	2
IVb	3	4
Histological types		
Squamous cell carcinoma	62	75
Adenocarcinoma	14	17
Adenosquamous carcinoma	5	6
Others, e.g. small cell carcinoma	2	2

RESULTS

Demographic data

The tumour stage distribution is given in **Table 2**. The patients' mean age was 50 years (range 26-90 years). The distribution of histological types was in accordance with Danish and international data [4, 7, 13, 14, 18].

Treatment

Among 11 stage Ia patients, four were treated with conization, five with simple hysterectomy (SH) and two with radical hysterectomy (RH) and PL. A total of 34 stage Ib patients were treated with RH and PL. One stage Ib1 patient with a body mass index (BMI) of 40 was not deemed suitable for surgery due to obesity and hence received chemo-radiation. One patient primarily operated at another hospital with SH for presumed stage Ia disease had stage Ib1 disease on final histological assessment and therefore received adjuvant external radiation and chemotherapy. Fifteen of the stage Ib patients also received adjuvant chemo-radiation due to histologically negative prognostic factors.

Among the 36 stage IIb-IVb patients, 26 received primary chemo-radiation (external beam radiation to the pelvis, brachytherapy, and six series of cisplatin). Three patients received radiotherapy only; one patient refused chemotherapy, a second patient had renal insufficiency, and nephrotoxic cisplatin was therefore not applicable. The final patient was considered too old for chemotherapy. Six patients received palliative radiation and/or chemotherapy and one patient died before treatment was started.

Positron emission tomography-computed tomography compared with histological examination

PET-positive findings apart from the known cervical cancer were identified in 18 of 83 patients (22%), of which 14/18 (78%) were identified in patients with more than stage I disease. Eight patients (10%) had PET-positive findings in the pelvis only. PET-positive foci outside of the pelvis were detected in ten patients (12%). The PET-CT scans revealed metastatic disease in lymph nodes and organs throughout the pelvis, abdomen, thorax and neck.

None of the stage I patients who underwent conization or SH (ten patients) had PET-positive findings; neither had the obese stage Ib1 patient. In total, 36 patients (43%) in stage Ia2-Ib1 underwent RH and PL. Three of the patients with stage Ib1 disease also had a biopsy taken from suspicious findings outside the pelvis: One had a synchronous breast cancer and two had negative extra pelvic lymph node biopsies – one true negative (TN) (several enlarged lymph nodes at the neck) and one false positive (FP) (lymph nodes in the pelvis, behind the clavicle and in the armpit – biopsy showed systemic lupus erythematosus (LED)).

The distribution of PET-positive scans compared with the histology is provided in **Table 3**. There were four false negative (FN) scans; all in patients with stage Ib disease who had one or more histologically confirmed pelvic lymph node metastases. Three stage Ib patients had FP scans (one with a lymph node in the pelvis, one with two small foci in the lungs and no metastases in the pelvis, and one with LED as described above) and one patient had true positive (TP) pelvic lymph nodes and a synchronous breast cancer.

Among the 14 PET-positive stage II-IV scans, six foci were localised in the pelvis and eight outside of the pelvis. Three of these cases had a biopsy taken and all three were diagnosed with metastatic disease (TP). One patient with a PET-positive paravertebral lymph node had a fine needle biopsy taken. It showed no cancer cells, but was not considered valid to preclude metastases and the patient was regarded as having a metastasis. As we do not have a valid histological examination of the lymph node, the patient was counted as if she had received no further examination, and we therefore cannot conclude whether the PET-CT scan was TP or FP. Two stage IIb patients with suspicious, but PET-negative scans had biopsies performed.

One patient had a 32 mm × 13 mm lymph node close to the porta hepatis and several small, but visible retroperitoneal lymph nodes. The other patient had several pathologically enlarged lymph nodes in the pelvis and a focus in the liver – biopsy-confirmed TN scans. One patient with PET-positive findings outside of the pelvis had stage IVb disease and died immediately after hospitalisation.

TABLE 3

Positron emission tomography-computed tomography (PET-CT) compared with the histological examination of lymph nodes and biopsies of suspicious findings (n = 83).

Histology	PET-CT negative (n = 65)	PET-CT positive (n = 18)
Non-malignant	30	3[c]
Malignant	4[b]	4[d]
Not examined[a]	31	10

a) Histological verification of positron emission tomography positive findings was only instituted in case of clinical impact on the treatment (see text).
b) False negatives: all stage Ib with pelvic lymph node metastases.
c) False positives: all stage Ib, one with a falsely positive pelvic lymph node, one with lupus erythematosus, 1 with false positive foci in the lung.
d) True positives: 1 Ib patient with four true positive lymph nodes and a truly positive mamma cancer, and 3 patients at stages > I with distant metastases.

In all, histology from lymphadenectomy and biopsy was performed in 36 stage I patients, and biopsies were drawn from five stage IIb-IVb patients. TP, FP, TN and FN scans could thus be calculated for 41 of the 83 scans performed. In total, we found four FN, three FP, four TP and 30 TN scans. Due to the study design, PPV and NPV could only be calculated for those 36 patients who had undergone PL. This yields a PPV of 25% and an NPV of 88% (**Table 4**). Follow-up on all patients would have enabled more precise PPV and NPV calculations.

Seven patients were scanned on a Gemini-TF PET-CT scanner. One was FN, one TP, three TN and two had no histological examination performed. We found no a priory indication of differences between the two scanners, and the material is too small for any conclusion in this regard.

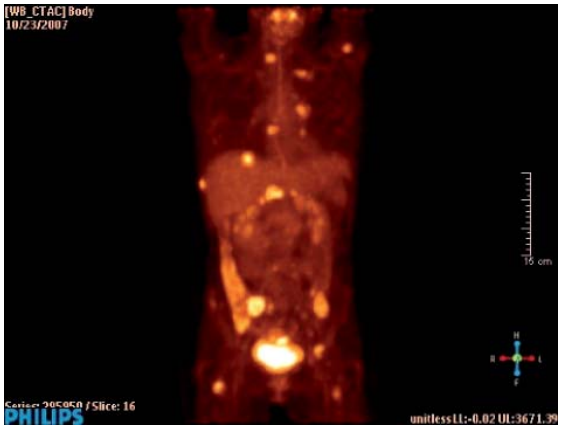
The clinical impact of Positron emission tomography-computed tomography findings in relation to treatment.

TABLE 4

Result of positron emission tomography-computed tomography (PET-CT) examination of lymph nodes status in the pelvis compared with the histological diagnosis in patients with stage I disease who underwent pelvic lymphadenectomy. The values are number of patients.

	Histology of pelvic lymph nodes		
PET-CT	positive	negative	total
Positive	1	3	4
Negative	4	28	32
Total	5	31	36

The positive predictive value of positron emission tomography-computed tomography to identify lymph node metastases = 25%; negative predictive value = 88%.



Philips Gemini TF, 60 minuts after injection of 370 MBq (10 mCi) ^{18}F-fluorodeoxyglucose showing focal increased uptake in the cervical cancer extending into the corpus uteri. Metastases are visualised in two foci in the liver, both adrenal glands and in multiple foci in the skeleton – particularly the seventh and the twelfth thoracic vertebrae and the pelvic bones.

Five patients (6%) had their treatment changed as a consequence of the PET-CT scan. One patient had the radiation field extended to include the para-aortic lymph nodes. In four cases the treatment strategy was changed from intended curative chemo-irradiation to palliative care.

Three patients with PET-positive findings outside the pelvis had already been scheduled for palliation due to advanced disease and poor general condition.

DISCUSSION

The diagnostic value of PET and PET-CT in detecting lymph node and distant metastases has been discussed in the literature. At present, PET-CT seems to outperform magnetic resonance imaging and stand-alone CT as the best non-invasive method for the identification of suspicious lymph nodes [4-11]. However, none of these modalities can identify micro-metastases [7, 10, 12-14], and lymphadenectomy with histological examination remains the gold standard for evaluation of the true lymph node status [13, 18].

The literature is not unanimous on the sensitivity and specificity of PET and PET-CT for the detection of lymph node metastases. Sensitivity varies from 25% [13] to 100% [4] and specificity from 55% to 99% [8]. Most studies have found high NPV (73-100%) and PPV (91-100%), [4, 6, 7, 10, 18]. However, one study has demonstrated a PPV of 50% for para-aortic lymph node metastases [13].

In the present study, we evaluated PET-CT in 83 patients of whom 18 proved to have PET-positive foci. Among these patients, 14 were beyond stage I. One of four PET-positive foci visualized in stage I patients turned out to be true positive.

The PPV was low and the NPV was 88%. These numbers probably reflect the inclusion of a large group of early-stage cervical cancer (80% ≤ stage IIb) with low risk of metastases.

PET-CT is sensitive in evaluation of extra-pelvic lymph nodes, which was seen in eight patients in this study. Presently, there is no evidence-based diagnostic strategy in these cases, and it is unclear whether PET-positive extra-pelvic findings should always be confirmed by lymphadenectomy or whether fine-needle biopsy is adequate in selected cases. In general, a negative fine-needle biopsy in PET-positive findings should always give rise to further diagnostic evaluation as PET-positive extra-pelvic disease is associated with recurrence and poor survival [19, 20].

Our retrospective study was performed 1.5 years after the introduction of PET-CT to assess the clinical impact of this new diagnostic instrument. In total, 57% of the subjects were stage I patients, and for these patients it is essential to evaluate potential metastatic disease before the final decision on treatment modality is made. The status of para-aortic lymph nodes is particularly important since para-aortic lymph nodes would not per se be included in a pelvic radiation field. In case of distant metastases, palliative care rather than treatment with a curative intent is considered to avoid increased morbidity.

The retrospective design of our study prevents us from drawing any definitive conclusions. However, our results emphasize the importance of histological confirmatory biopsies or lymph node excision and further indicate that PET-CT may be more advantageous than any other treatment modality in patients with advanced cervical cancer.

In the present study, five out of 36 stage IIb-IVb patients (14%) had their treatment modified because of findings on the PET-CT scan. Clinically, this has a great implication for those patients who are offered combined chemo-radiation with curative intent after clinical staging. This treatment is extensive with a comparatively high rate of morbidity and should always be held up against its benefits.

CONCLUSION

The present study supports the usefulness of PET-CT for the detection of lymph node metastases and distant metastases in patients with cervical cancer, although the study had a relatively low PPV in patients with early stage disease. Histological verification of PET-positive findings is necessary, particularly in stage ≤ Ib. No positive scans were detected in patients with stage Ia1 and due to the low sensitivity, we have ceased to offer PET-CT scans to these patients. Five patients (6%), all ≥ stage IIb, had their treatment changed as a result of the PET-CT scan.

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