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Diagnostic PET/CT for detecting malignant lymph nodes in patients with cervical cancer Stage IB1

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Summary

Background: After initial diagnosis of cervical cancer, patients are staged and clinically evaluated with PET/CT in order to assess disease extent. Patients with Stage IB1 disease usually undergo definitive surgery. The present authors' objective was to evaluate the diagnostic value of PET/CT in cervical cancer Stage IB1. *Materials and Methods:* By searching the Danish Gynecological Database (DGCD) the authors identified 144 patients treated for cervical cancer Stage IB1 from 2012-2015 at Rigshospitalet, University Hospital Copenhagen, Denmark. Patients who underwent a PET/CT scan and either definitive surgery or diagnostic laparoscopy were included for further analysis. *Results:* One hundred forty patients had a PET/CT scan and results were available for 136 patients, six of which had suspicious lymph nodes; three patients did not have metastases and three patients did. One hundred thirty patients did not have suspicious lymph nodes on PET/CT. Histological results were available for 106 of these patients and 97 of these did not have metastases and nine patients did. Out of all the 12 patients with metastatic lymph nodes, 11 had pelvic, none had para-aortic disease, and data regarding localization was missing for the last patient. Regarding PET/CT detection of pelvic lymph nodes, the sensitivity was 25%, specificity 97%, positive predictive value 50%, and negative predictive value 92%. *Conclusion:* The sensitivity and positive predictive value of PET/CT in cervical cancer Stage IB1 patients were low. PET/CT cannot replace surgical lymphadenectomy and histologic examination in these patients.

Key words: Cervical cancer; Stage Ib1; PET/CT; Sensitivity and positive predictive value of PET/CT.

Introduction

Cervical cancer is the fourth most frequent cancer among women and a common cause of death in the female population [1]. Approximately 30% of patients with cervical cancer develop recurrent disease, most within two years after therapy completion [2].

After the initial diagnosis of cervical cancer, all patients treated at Rigshospitalet, University Hospital Copenhagen, Denmark underwent clinical staging under general anesthesia in accordance with the FIGO classification. Patients with greater than Stage 1A underwent a PET/CT scan to evaluate possible spread to lymph nodes and distant metastatic disease. Patients with Stage IB1 disease were usually surgically treated. If PET-positive lymph nodes were detected, a diagnostic laparoscopy was performed to remove the lymph nodes for histological examination. Nodal status is not included in the FIGO staging system, but was used for treatment guidance [3-5].

In the literature, FDG-PET was superior to conventional imaging methods for detecting metastatic lymph nodes and metastatic disease [6-9]. Tumor volume and lymph node involvement determined by FDG-PET were predictors of overall survival [10]. The presence of metastatic para-aortic lymph nodes was the most important prognostic factor for recurrence and death and generally indicated a poor prognosis. Postsurgical stage was a better indicator of prognosis than clinical FIGO stage [6, 8, 11-13].

PET/CT has been used at Rigshospitalet in cervical cancer for over ten years [14]. A retrospective study evaluated 65 selected cervical cancer (Stage IB-IVA) patients treated there from 2006 to 2011. They all underwent diagnostic laparoscopy due to PET-positive lymph nodes. Thirty-five percent of the patients had false-positive lymph nodes, indicating no sign of malignancy at conclusive histological examination [15]. The reason for false-positive results may be benign tumours (histiocytosis), infection, and inflammation. The female abdomen is difficult to evaluate due to FDG-activity in ovaries, ureters, and intestines [14].

The objective of this study was to evaluate results of initial PET/CT in patients with cervical cancer Stage IB1. The authors hypothesized that the positive predictive value was high, i.e. the rate of false-positive lymph nodes on PET/CT was low. The present authors believed that their skills improved with experience in the assessment of PET/CT.

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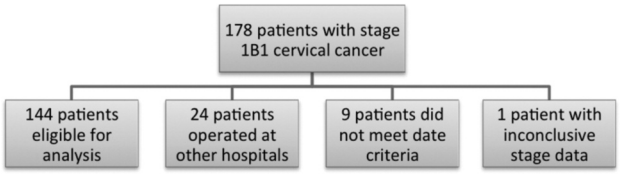

Figure 1. — Patient selection. *Source: DGCD [1].*

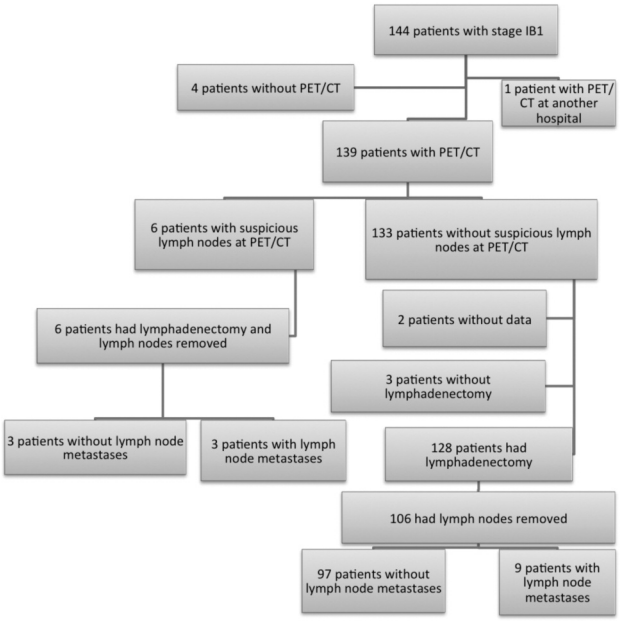

Figure 2. — Patients with Stage IB1 included in the study. *Source: DGCD [1].*

Materials and Methods

The authors searched the Danish Gynecological Database (DGCD)[16] for data on patients treated for cervical cancer at Rigshospitalet, University Hospital Copenhagen, Denmark, from January 1st, 2012 to December 31st, 2015. Patients with cervical cancer Stage IB1, who underwent a PET/CT scan and either definitive surgery or diagnostic laparoscopy, thereby yielding histologic lymph node status, were included. Patients were excluded from further analysis if data on clinical stage and/or lymph node status were not available in DGCD [16].

The diagnostic value of initial PET/CT scan was evaluated by calculating the sensitivity, specificity, positive predictive value, and negative predictive value. Sensitivity was calculated as the number of patients with true PET-positive lymph nodes divided by the number of patients with nodal disease. Specificity as the number of patients with true PET-negative lymph nodes were divided by the number without nodal disease. Positive predictive value as patients with true PET-positive lymph nodes were divided by total number of patients with nodal disease. Negative predictive value as patients with true PET-negative lymph nodes were divided by number of patients without nodal disease [17].

Table 1. — *Patients per year.*

Year	Number of patients
2012	17
2013	35
2014	53
2015	39
Total	144

Source: DGCD [1].

Table 2. — *Patient characteristics.*

	Number of patients
Performance status	
Performance status 0	114
Performance status 1	21
Performance status 2	3
Performance status 3	1
Unknown	5
Smoking status	
Smoker	37
Non-smoker	56
Ex-smoker	49
Unknown	2
Menopause	
Pre-menopausal	95
Post-menopausal	44
Prior hysterectomy	2
Unknown	3
HPV status	
HPV-vaccinated	15
Not HPV-vaccinated	94
Unknown	35

Source: DGCD [1].

Table 3. — *Dominating cervical histology.*

	Number of patients
Squamous carcinoma	95
Adenocarcinoma	24
Adenosquamous carcinoma	1
Sarcoma	1
Other malignant morphology	3
No tumor remnants in surgical specimen	7
Unknown	13
Total	144

Source: DGCD [1].

Results

One hundred seventy-eight patients with Stage IB1 cervical cancer from 2012 to 2015 were identified by searching DGCD [16] (Figure 1). Hereof 34 patients were omitted from further analysis; nine patients did not meet date criteria, 24 were operated at other hospitals (one at Bornholm Sygehus and 23 at Herlev Hospital), and one patient had inconclusive final stage data.

One hundred forty-four patients treated for Stage IB1 cervical cancer at Rigshospitalet from 2012-2015 were included in the following analysis (Tables 1-3). One hundred

forty of these patients had a PET/CT scan, hereof six patients had suspicious lymph nodes, 130 did not, and four patients' results were unknown (Figure 2). In total 12 patients had metastases at histologic examination; 11 of them had pelvic metastatic lymph nodes and none had para-aortic disease. Data regarding localization of lymph nodes were missing for one patient. All six patients with suspicious lymph nodes underwent lymphadenectomy and had lymph nodes removed. The numbers of harvested lymph nodes were 1, 2, 5, 15, 26, and 31, respectively. Histological examination demonstrated three patients without metastases and three with metastases; two patients had one metastases and one had two metastases.

Among the 130 patients without suspicious lymph nodes; 125 patients underwent lymphadenectomy and three patients did not. Results on removed lymph nodes were only available for 106 patients in DGCD [16]. Hereof 97 patients did not have metastases and nine patients did. Five patients had one metastases and one had respectively 2, 4, 5, and 10 metastases at histologic examination. The number of harvested lymph nodes varied between one and 75.

Based on data from the 112 patients with complete lymph node status on PET/CT and histologic examination, the authors calculated the sensitivity of 25%, specificity of 97%, positive predictive value of 50%, and negative predictive value of92%.

Discussion

In a previous study by Loft *et al.* [14] 28 patients had Stage IB1 disease. Twenty-seven patients underwent radical surgery after PET/CT including histological examination of removed pelvic lymph nodes. Four patients had pelvic PET-positive lymph nodes; hereof one had no sign of malignancy on histological evaluation and three patients did. For pelvic nodal disease, the sensitivity was 75%, specificity 96%, positive predictive value 25%, and negative predictive value 96%. PET/CT was useful for biopsy guidance and treatment planning, but histological verification was necessary [14]. The PET/CT scans in this study and in Loft *et al.* study were evaluated at the Department of Clinical Physiology, Nuclear Medicine, and PET at Rigshospitalet. It was surprising, that the present recent results were inferior to results from Loft *et al.* in 2007 [14]. A plausible explanation for the false positive results was presence of inflammation in lymph nodes in cervical cancer patients.

Fifty-nine patients (Stages IA-IIA) underwent PET scans prior to surgery. Pelvic lymph node metastases were present in 19 patients, and para-aortic in four patients. For pelvic disease, the sensitivity was 53%, specificity 90%, positive predictive value 71%, and negative predictive value 80%. For para-aortic disease the sensitivity was 25%, specificity 98%, positive predictive value 50%, and negative predictive value 93%. Pre-surgical PET lacked the sensitivity and positive predictive value needed to replace surgical lymphadenectomy [18]. This was in accordance with various other studies [14, 19-22], including the present, which found that PET/CT could not replace lymphadenectomy in early cervical cancer due to low accuracy of predicting pelvic nodal status.

PET/CT demonstrated limited sensitivity (41.2%) and high specificity (94.1%) for the detection of metastatic pelvic lymph nodes in 34 patients (Stages IA2-IIB), who underwent PET/CT before radical hysterectomy and pelvic lymphadenectomy. Fifty percent had pelvic nodal metastases [23]. In a study of 181 patients (Stages IB2-IVA) para-aortic pathology was present in 20% in FIGO Stage 1, 17% in Stage 2, and 32% in Stage 3 [24]. Among the present 144 patients, 11% demonstrated pelvic nodal metastases on final histology and none had para-aortic disease. This was likely attributable to the low stage of the present patients. Dong *et al.* [25] studied 59 patients (Stages IA-IIA) who underwent PET/CT and pelvic lymph node dissection; they found that positive lymph node invasion on PET/CT did not show a correlation with clinical stage in their study [25].

FDG-PET had little value in primary staging of patients (Stages IA2-IIA) who were lymph node negative on MRI. For FDG-PET detection of pelvic lymph nodes, the sensitivity was 10%, specificity 94%, positive predictive value 25%, and negative predictive value 84% [26]. The diagnostic accuracy of FDG-PET *vs.* MRI for detecting metastatic lymph nodes was investigated in 35 patients (Stages IB-IIA). The corresponding values were sensitivity 91% *vs.* 73 %, specificity 100% *vs.* 83%, positive predictive value 100% *vs.* 67%, and negative predictive value 96% *vs.* 87%. There was a tendency towards higher FDG-PET values, but it was not significant [7].

FDG-PET could not reliably detect microscopic pelvic lymph node metastases and 80% of FDG-PET false-negative lymph nodes contained micrometastases [6]. A strength in this study was that histologic confirmation was performed, which decreased the risk of overlooking micrometastatic disease.

The prognosis in cervical cancer depended on the presence of pelvic and para-aortic lymph nodes. The disease-free survival and overall survival were lower in patients with metastatic lymph nodes, than in patients without nodal metastases [12, 27, 28]. Para-aortic lymph node metastases were a significant negative prognostic factor for overall survival [29]. The lymph node status determined by FDG-PET was a significant predictor of time to recurrence, progression-free survival, disease-specific survival, and overall survival. Disease-specific survival decreased progressively with the most distant level of lymph node involvement [2, 8, 30]. Survival was poor with para-aortic lymph node metastases over 5 mm [29]. The survival of patients, with para-aortic metastases of 5 mm or smaller, treated with extended field chemoradiation, was similar to survival of patients without para-aortic nodal involvement. This

suggested that laparoscopic surgical staging had an important therapeutic effect for micrometastatic nodal involvement, which could be overlooked by PET/CT staging [24, 29]. For patients without post-therapy FDG uptake, the five-year disease-specific survival rate was 80%. With persistent FDG uptake, it was 32%, and with new sites of uptake it was 0% [31].

Improved surgical outcome, i.e. increasing number of acquired pelvic nodes, and decreased complication rates were seen with greater experience in laparoscopic staging and treatment of cervical cancer [32, 33]. The complication rate of laparoscopic lymphadenectomy was 0-7 % [9, 34-37], and included adhesions, lymphocysts/lymphedema, vessel damage, infections, port-site metastases, and ureter lesions. Staging surgery had potential treatment and survival benefits, as the histology results could lead to expansion of radiation field to include the para-aortic area. However extended field radiation treatment resulted in increased toxicity/morbidity [9]. Three hundred forty-three patients (Stages IB-IIA) were randomized for either radiotherapy or radical hysterectomy and pelvic lymph node dissection. Overall survival was 83% in both arms, and a significant difference in toxicity was observed in favor of radiation treatment (28% *vs.* 12%). A significant number of surgical patients (54% in Stage IB1 and 84% in Stage IB2) required adjuvant radiation treatment due to adverse prognostic factors [38].

Correct pretreatment staging was important, as the correct treatment modality could be initiated up front. Multimodality treatment increased the risk of toxicity and complications [38, 39]. The rate of false-negative PET/CT scans had to be weighed against the complication rate of para-aortic lymphadenectomy [37]. A Cochrane review failed to establish clear recommendations on surgical para-aortic lymph node assessment in locally advanced cervical cancer due to the lack of controlled randomized studies. Survival data were conflicting and individualized treatment plans recommended. If surgery was performed, it should have been laparoscopic [40].

Limitations of the present study were in part incomplete data registration in DGCD [16], especially in 2012-2013. The authors did not gain permission from The Danish Patient Safety Authority to access patients' electronic journals. Both factors contributed to partly incomplete data, thereby decreasing the number of patients eligible for full evaluation. The authors identified a relatively small number (12 patients) with nodal metastases, which also contributes to insecurity of the present results.

Conclusion

One hundred twelve patients demonstrated complete lymph node status on PET/CT and histological examination. Hereof 12 patients had pelvic lymph node metastases and none had para-aortic disease. For PET/CT detection of pelvic lymph node disease, the authors found low sensitivity (25%) and positive predictive value (50%). PET/CT could not replace lymphadenectomy in early cervical cancer, due to low accuracy of predicting pelvic nodal status. PET/CT was a valuable complement to clinical FIGO staging, as para-aortic lymphadenectomy or extended field radiation could be omitted in patients without suspicious lymph nodes.

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