The prognostic value of FDG-PET/CT in diagnostic of patients with vulva cancer: comparison with MR, SN and FDG-PET/CT.

Background
Vulva cancer is a relatively rare disease with approximately 100 cases per year in Denmark. The disease is more common in women with a median age of 60 years [1, 2]. The incidence is rising, which can presumably be associated with the HPV-virus [3, 4]. The vast majority of vulvar cancer, approximately 90%, is caused by squamous cell carcinoma. Of prognostic value are, besides tumor size, lymph node involvement and invasions of vessels [4-8]. Of these, lymph node metastases are the most important factor in survival. Patients with lymph node metastases have a 5-year survival rate of about 90 %, whereas patients who have been radically operated with lymph node metastases have a significantly lower survival rate of about 50 % [9-11]. Thus early diagnosis is imperative.

In the case of lymph node metastases survival is dependent on the number of involved lymph nodes, which are detected in 20-30 % of the patients when diagnosed [10, 12]. The risk of lymph node metastases is increased according to invasions depth, tumor size and localization of the tumor [2, 10, 13].

The cancer cells are mainly spreading from the primary tumor to the inguinal lymph nodes followed by the iliac lymph nodes. In case of midline tumor bilateral spreading to the inguinal lymph nodes is common.

Hematogenous spread is relatively rare. About 30 % of the treated patients develop recurrence [14]. In 50 % of these cases the metastases are local, whereas the rest are distant metastases with a worse prognosis [2].

The treatment of vulva cancer is individual and depends both on the stage and localization of the disease. Most often the treatment is operation, but in advanced disease stages a combination of both radiation– and chemotherapy has proven advantageous with local control of the tumor and a long-term survival rate with an acceptable level of side effects [1, 15-17].

Localization of the primary tumor and the stage of metastases are decisive for the choice of treatment. Thus the treatment of an estimated local tumor with an invasion depth more than 1 mm is operation and unilateral radical lymphadenectomy. On the contrary, the treatment of midline tumors is bilateral.

Because only 20 % of the patients have lymph node metastases there is in fact an overtreatment of 80 %. Previous studies have shown that radical lymphadenectomy is associated with a higher morbidity [4, 18, 19], mostly lymph edema. In order to avoid the above-described problem it is of great importance to investigate a method able to detect any lymph node metastasis.

Non-invasive methods as ultra sound, MRI and CT have all been tested, but none proved suitable as a diagnostic tool to detect lymph node metastases [18].

Vulva cancer has a spreading pattern, which makes it suitable for the sentinel node method. This procedure has shown great results in e.g. breast cancer [7, 8]. It is an
invasive procedure which therefore can lead to discomfort in the patients [20], but is without serious side effects.
A recent study has shown a surprisingly high number of false negative lymph nodes [21, 22]. This indeed emphasizes one of the big pit falls of the sentinel node procedure, and can be attributed to the presence of metastases in the ingino-femoral lymph nodes that obstruct the lymph system, and therefore prevent the uptake of the radioactive tracer.
The absence findings will lead to an under treatment of the patients. Again this elucidates the importance in finding a procedure that is able to detect the metastases and has a high specificity as well as sensitivity.
The use of MR-scanning is wide spread and is very efficient in discriminating tumor tissue from the normal surrounding tissue. In detection of lymph node metastases however it is less precise [23]. Only a few studies have so far been able to describe the use in case of vulva cancer.

PET scanning is a non-invasive nuclear medicine technique that utilizes a radioactive tracer. Predominately $^{18}$FDG is used as a tracer. This compound has a flour isotope bound to the sugar molecule, deoxyglucose. The cancer cells have an increased metabolism and therefore will have a faster cellular uptake than normal cells. As a result tumors and metastases will be visible at the PET-scanner. In combination with a diagnostic CT scanning, the exact anatomic localization of metastases can be determined.
Numerous studies of breast cancer, cervical cancer, ovarian cancer[24] and malignant melanoma[25] have proven PET-CT scanning to be very efficient in detecting metastases and thus it is superior to MR-scanning[26].
No studies so far have shown whether PET-CT could be suitable in the treatment of vulva cancer. Especially for the detection and assessment of metastases the method is thought to be useful. Likewise there are yet no records that describe the application of this method in the recurrence diagnoses of vulva cancer.

**Purposes**
- Prospectively evaluate PET-CT diagnostic value in stage classification of vulva cancer and furthermore evaluate the application in recurrence.
- Comparison of PET-CT with MR and Sentinel Node. Evaluate whether PET-CT scanning gives additional information by comparing the results from Sentinel Node and MRI.

**Method**
Patients who have been newly diagnosed with vulva cancer will be examined with Sentinel Node, MR-scanning and PET-CT scanning. Subsequently a histological verification of the PET positive findings differing from Sentinel Node and the biopsy of suspect metastases from MRI will be performed.
In addition all patients with suspected recurrence will be examined with both MRI and PET-CT, where the positive findings from these examinations will be biopsied or
removed by surgery. The histological findings from the operation and biopsy are the accurate value in the method evaluation. It is estimated that about 50 patients will be examined within 2 years.

**Datacollection (appendix)**
- Tumor size
- Lymph node metastases
- Stage classification
- Tumor histology
- Sentinel Node

**Inclusions criteria**
- Patients with newly diagnosed vulva – or vaginal cancer and recidive will be referred to the Gynecologic-Oncological department Aarhus University Hospital, Skejby

**Exclusions criteria**
- Patients, who because of either age or other diseases, do not get curative intended treatment when diagnosed
- Patients who do not seem able to participate in the examinations
- Pregnancy
- Any other malignant disease.

**Ethical aspects**
This study is a method validation project and therefore is not obliged to report to the ethics committee. No patients will be exposed to interventions that exacerbate the given disease when the current guidelines will be followed in all aspects. PET-examinations are used routinely in clinical oncology and are associated with only a minimal increased radiation.

**Time frame**
01.07-2011-01.07.2012
The results will continuously be reported.

**Data acquisition**
Will be reported to Datatilsynet.

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References