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SPECT/CT for SLN dissection in vulvar cancer: Improved SLN detection and dissection by preoperative three-dimensional anatomical localisation

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HIGHLIGHTS

- Exact anatomical and three-dimensional localization of SLN by SPECT/CT.
- Visualization of aberrant lymphatic drainage by SPECT/CT.
- SPECT/CT improves detection rates and facilitates intra-operative SLN detection.

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ABSTRACT

Objective. In this study, we assessed the feasibility and clinical advantages of single photon emission computed tomography with CT (SPECT/CT) for sentinel lymph node (SLN) detection in vulvar cancer.

Methods. This is a unicentric prospective trial. Vulvar cancer patients underwent preoperative SLN marking (10 MBq Technetium (TC)-99 m-nanocolloid) and subsequent planar lymphoscintigraphy (LSG) and SPECT/CT for SLN visualization. Directly before surgery, a patent blue dye was injected. We assessed detection rates of SPECT/CT and those of planar LSG and intraoperative detection. We analyzed the sensitivity, negative predictive value and false negative rate.

Results. At Hannover Medical School, 40 vulvar cancer patients underwent SLN dissection after preoperative LSG and SPECT/CT. The mean diameter of all tumors in final histology was 2.23 (0.1–10.5) cm with a mean tissue infiltration of 3.93 (0.25–11) mm.

In preoperative imaging, SPECT/CT identified significantly more SLNs (mean 8.7 (1–35) LNs per patient) compared to LSG (mean 5.9 (0–22) LNs, $p < 0.01$). In addition, SPECT/CT led to a high spatial resolution and anatomical localization of SLNs. Thus, SPECT/CT identified aberrant lymphatic drainage in 7/40 (17.5%) patients. There were no significant differences, but significant correlation was found between SPECT/CT and intraoperative SLN identification. Regarding inguino-femoral LNs, for all patients who underwent complete groin dissection, sensitivity was 100%, NPV was 100% and false negative rate was 0%.

Conclusion. SPECT/CT leads to higher SLN identification compared to LSG in vulvar cancer. Due to its higher spatial resolution and three-dimensional anatomical localisation of SLNs, SPECT/CT provides the surgeon with important additional information, facilitates intraoperative SLN detection and predicts aberrant lymphatic drainage.

1. Introduction

Vulvar cancer is a relatively rare cancer, but shows increasing incidence rates over the last years [1].

Lymph node (LN) metastasis seems to be the most important prognostic factor [2]. This is indicated by a reduction of the five-year-survival rate from 94.7% to 62% if inguino-femoral LNs are affected [2]. Regarding this, radical vulvectomy combined with bilateral inguino-femoral lymph node dissection (LND) became the recommended surgical treatment for vulvar cancer but is associated with a high rate of complications and comorbidities [3,4].

Since only 25–35% of all patients present with LN metastases at primary surgery and most of them only show ipsilateral LN involvement,

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complete bilateral LND seems to be an overtreatment for the majority of the patients [3,5–7].

Sentinel lymph node (SLN) excision became the gold standard in the surgical treatment of breast cancer and melanoma and is being evaluated for other gynecological cancers like cervical and endometrial cancer [8–11]. Given the fact that the SLN represents the first node in the tumor drainage path, this LN seems to be a perfect predictor for LN metastasis in a designated basin. Since Levenbaeck introduced this surgical approach into the treatment of vulvar cancer, many studies have confirmed its clinical feasibility by reaching a high sensitivity of more than 92% [3,6,12–14]. However, false negative SLNs were reported in several studies which resulted in groin recurrence leading to a high rate of mortality [3]. These facts underline the importance of exact SLN marking and identification. Concerning this, SPECT/CT, allowing for a three-dimensional anatomical localization of SLNs, has proven higher SLN identification rates in several gynecological cancers resulting in higher sensitivity and lower false negative results [10,11,15–17]. Based upon these results, a few groups introduced SPECT/CT for SLN detection in vulvar cancer in small studies with up to 15 patients [18–23]. In theory, SPECT/CT provides higher spatial resolution and results in better identification of the SLN for the surgeon. In this article, we present an even larger study of the role of SPECT/CT for the detection of SLNs in vulvar cancer.

2. Patients and methods

We present a unicentric prospective study. Between 2007 and 2014, patients with histologically confirmed vulvar cancer who were eligible for SLN excision were enrolled and underwent stage adapted resection of the tumor and SLN dissection at Hannover Medical School. Only patients who were expected to have unifocal tumors less than 4 cm in diameter and an invasion depth of more than 1 mm should be included in the study. Before enrolment, informed consent was obtained.

All patients received marker administration, SLN imaging and surgery on the same day (Hannover one day low dose protocol). For marker administration, a peritumoral, subepithelial injection of Tc-99 m nanocolloid (10 MBq; 0.5 (range 0.25–0.85) ml each) was performed before surgery. To verify correct SLN marking, LSG and SPECT/CT were carried out directly after injection of the tracer. In addition to the radioactive marker administration, a patent blue dye (4 ml) was injected subepithelially around the tumor directly before surgery. During surgery, SLNs were identified by blue staining and the use of a handheld gamma-probe (Neoprobe Corporation, Dublin, USA). All LNs, which showed a radioactive count of more than 10% of the most radioactive LN or blue staining, were dissected and called SLNs. On behalf of easier and more specific SLN identification, SPECT/CT results were considered intraoperatively to facilitate targeted SLN excision. Especially in adipose patients, incisions were performed according to distances from the illiac spine or symphysis which were determined in preoperative SPECT/CT imaging.

The higher risk of LN recurrence by sole SLN dissection was explained to all patients. Patients who agreed to sole SLN dissection underwent complete LND if metastatic SLNs or suspect groin LNs were detected during surgery or in final histology. Only unilateral SLN excision or LND were performed if the tumor was located more than 2 cm away from midline. In addition, pelvic LNs were dissected if more than three inguino-femoral LNs were affected, extracapsular growth was detected or the diameter of metastasis was more than 10 mm.

2.1. Preoperative imaging

At least 30 min after marker injection, LSG was performed in primary. For detection we used a dual-headed gamma camera with high resolution low energy parallel-hole collimator (LEHR) in conjunction with a two-slice spiral CT (Symbia T, Siemens Medical Solutions, Erlangen, Germany). With a field of view of 53.3 cm × 38.7 cm we took a static image (matrix size 512 × 512) of the pelvis and abdomen of the patient.

Next we performed a SPECT/CT emission transmission study (matrix size 128 × 128, angular increments of 2.813°, 180° rotation, 30 s time frames, 128 views). The CT consisted of a dual-detector helical X-ray CT-scanner with a minimal gantry rotation-time of 800 ms. We used the following scan parameters: 130 kV, 17 mAs, rotation time 20.9 s, delay 3 s, collimation 2 × 4.0 mm. After correction of the attenuation, the images were reconstructed by means of the ordered-subset expectation maximization technique (OSEM 3D) using 4 iterations and 8 subsets. Data were reconstructed to 61 images of 5 mm slice thickness with a reconstruction increment (pitch) of 1.5 mm. Finally, after fusion of SPECT and CT data, the images were analyzed by a specialist in nuclear medicine resulting in essential screenshots that were demonstrable immediately clinic wide.

2.2. Pathology

The preparation regimen of the SLN depended on the LN size, but no frozen sections were performed routinely. All SLNs were routinely fixed in formalin and paraffin embedded. All excised SLNs smaller than 0.5 cm in diameter were fully embedded without preparation, whereas SLNs between 0.5 cm and 1 cm in diameter were bisected along the longitudinal axis. Larger SLNs were sectioned perpendicularly to their long axis at 0.3 cm intervals and submitted totally for routine paraffin embedding. Eight step sections (3 μm thick) were taken at 250 μm intervals from each block and HE stained. Additional immunohistochemistry was performed for all SLNs which were negative on routine examination. This was done according to a standard protocol on Ventana BenchMark Ultra automated stainer (Ventana Medical Systems, Tucson, AZ, USA). Antigen retrieval was performed with CC1 buffer (Cell Conditioning 1; citrate buffer pH 6.0, Ventana). As primary antibody CK5/6 (D5/16B4, Dako, 1:200 dilution) was used. In compliance with the UICC nomenclature, macrometastases were defined as tumor deposits >0.2 cm in size; micrometastases were defined as deposits of 0.02–0.2 cm in size; and isolated tumor cells (ITC) were defined as deposits smaller than 0.02 cm, including the presence of single non-cohesive cytokeratin-positive tumor cells.

2.3. Statistics

This study was approved by the ethics committee of Hannover Medical School. For statistical evaluation, all data were collected from clinical records and stored in a database. In detail, the paired t-test was used for the calculation of p-values of continuous data and 95% confidence intervals (CI 95%) were calculated for determining rate differences of dichotomous data. A p-value below 0.05 was called significant. Correlation was calculated using Pearson's correlation coefficient. Additionally, sensitivity was calculated by dividing the number of patients or LN basins with affected SLNs by all patients or LN basins with affected LNs. For the evaluation of the NPV, the number of non-affected patients or LN basins was divided by the number of patients or LN basins which showed a non-affected SLN. The rate of patients with non-affected SLNs which showed metastatic LNs in final histology divided by all patients was called false negative. Contingency tables were used for the calculation of sensitivity, NPV and the false negative rate.

3. Results

Between 2007 and 2014, 144 patients with vulvar malignancies underwent surgery at the Hannover Medical School. 40 patients with vulvar cancer were included in this study.

The mean age of the patients was 65.9 (32–93) years. Keratinizing squamous cell carcinoma was identified as the most frequent histologic type in (30/40, 75%) patients. Moreover, 31/40 (77.5%) patients showed