Sentinel node identification and intraoperative lymphatic mapping. First results of a pilot study in patients with endometrial cancer

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Summary

Introduction: To minimize the surgical morbidity after lymphadenectomy, sentinel node biopsy (SLNB) has become fundamental in the management of different malignancies. We decided to evaluate sentinel lymph node (SNL) biopsies also in patients with endometrial cancer undergoing hysterectomy with lymphadenectomy.

Methods: In the setting of a prospective study we developed a technique for sentinel node biopsy of ten patients with histologically confirmed endometrial cancer. Prior to surgery 99m Tc Nanocol® was injected in the peritumoral region by hysteroscopy. Six hours later lymphoscintigraphy was performed to identify the draining lymph nodes. During surgery we first detected the sentinel lymph node by a hand-held gamma tracer and then removed it. Surgery was completed by the standard therapy of total hysterectomy, bilateral salpingo-oophorectomy and pelvic and/or para-aortic lymphadenectomy.

Results: Scintigraphic identification was possible in eight out of ten patients. Intraoperative identification of sentinel lymph nodes was possible in seven out of eight patients. In five patients we found the sentinel lymph nodes in the pelvic region while the other two patients had bilateral sentinel nodes in the pelvic and para-aortic region. Histologically confirmed microscopic tumor metastases of the SLNs and para-aortic lymph nodes were only found in one case. The sentinel lymph nodes from the other six patients were free of tumor and accurately reflected the pathological status.

Conclusion: The identification of sentinel lymph nodes in endometrial cancer is a practical and safe method. In order to improve this technique as a standard procedure for staging of endometrial cancer further studies with a larger number of patients have to be done.

Key words: Sentinel lymph node; Endometrial cancer; Lymphatic mapping; Lymphoscitigraphy.

Introduction

Endometrial cancer is the most common cancer in gynaecology. Its incidence has increased over the past few years. Every year there are approximately 9,600 new cases [1]. Two-thirds of all patients are postmenopausal and the average age at the time of diagnosis is between 65 and 70 years. Over 70% of all endometrial cancers are diagnosed as FIGO Stage I [2].

Surgery with total hysterectomy, bilateral salpingo-oophorectomy and pelvic and/or para-aortic lymphadenectomy is today the gold standard of staging and therapy [3]. The old clinical FIGO classification has been replaced by a system of surgical staging that specifically addresses the depth of myometrial invasion. The key aspects for prognosis and therapeutic planning are: depth of myometrial invasion, tumor grade, peritoneal cytology and the likelihood of lymphatic spread [4-6].

The decision for lymphadenectomy is based on different prognostic factors such as the overall condition of the patient, clinical tumor stage, histological grading as well as histological types others than endometroid adenocarcinoma. Despite these selective criteria, cancer is only detected in 15-20% [7-9].

Although the therapeutic benefit of lymphadenectomy is controversial and it is of limited benefit for the large majority of patients, lymphadenectomy is recommended as a guide for therapy. The histological evaluation of the lymph node status has been shown to be superior to all other visual prognostic methods [4, 5].

Consequently it is very important to improve predictors of lymphatic spread which preserve the high degree of accuracy and at the same time would allow a reduction of surgical morbidity associated with lymphadenectomy. Sentinel node biopsy is such a method, and has been evaluated in different solid tumors and shown to provide accurate and sufficient information about the lymphatic status [9-12]. Specifically the experience with breast cancer serves as a guide for a similar approach in patients with endometrial cancer.

Material and Methods

In a prospectively designed clinical study a sentinel node biopsy protocol was established for patients with endometrial cancer [14].

In patients with histologically confirmed endometrial cancer, hysteroscopy was performed 24 hours prior to laparotomy. Using a 5 mm operative hysteroscope, the neoplastic process was identified in the uterine cavity; 1 ml of the tracer 99m Tc-Nanocoll (40-100 MBq) was injected in the peritumoral areas (Figure 1).

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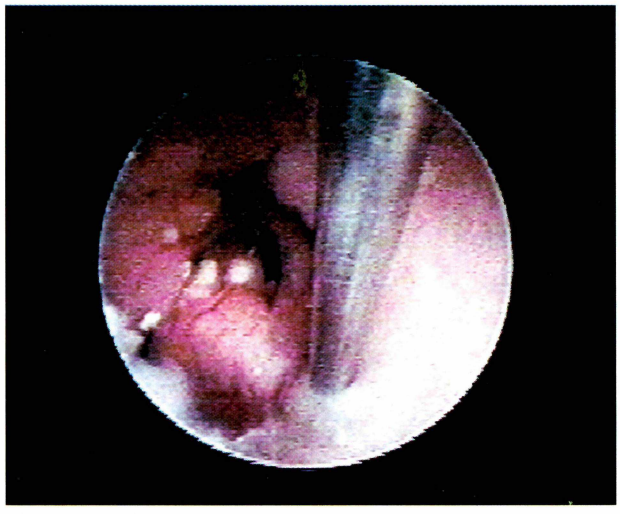

Figure 1. — Hysteroscopic application of 1 ml of 99m Tc- Nannocoll (40 MBq) in the peritumoral area to visualize the lymph node draining system.

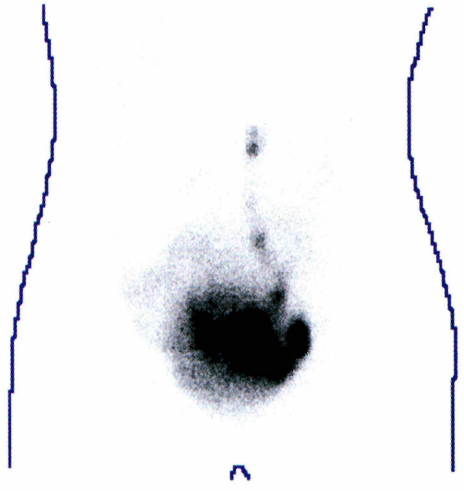

Figure 2. — After hysteroscopic application of the tracer lymphoscintigraphy was performed for lymphatic mapping. Schematic representation of the pelvic lymph nodes (inter-iliac, lateral common iliac, and aortic).

Lymphoscintigraphy was performed six hours later, showing good accumulation of tracer in the draining lymph nodes (Figure 2).

At the time of laparotomy, intraoperative location of the sentinel lymph nodes was performed by the hand held gamma-tracer (Navigator®GPS-System, Autosuture Healthcare Germany). After surgical removal of the "hot spots" of the lymph nodes complete pelvic and – when indicated – also para-aortic lymphadenectomy was done to determine the predictive value of the technique.

Patients characteristics

Patients with clinical Stage > Ib or histological grade G 2-3 of endometrial cancer underwent abdominal hysterectomy, bilateral salpingo-oophorectomy as well as pelvic and/or para-aortic lymph node sampling. All patients gave prior informed consent to this study approved by the Ethics Committee of the University of Tuebingen. Patient characteristics are summarized in Table 1.

Table 1. — Clinical patient and tumor characteristics.

Number	10
Age	60 (44-75)
Type of Surgery	
LAVH* with lymphadenectomy	2
Laparotomy	8
Histology	
Endometroid adenocarcinoma	7
Clear cell adenocarcinoma	1
Tubulo-papillary carcinoma	2
Grading	
1	2
2	7
3	1
Cytology	
Negative	9
Positive	1
Lymph node status	
Negative	9
Positive	1

*Laparoscopically assisted vaginal hysterectomy.

Results

Ten Patients with histologically diagnosed endometrial cancer agreed to participate in this study and underwent explorative laparotomy for a planned radical hysterectomy. The mean age of the cohort was 60 years (range: 44-77 years).

Eight patients were diagnosed with endometroid adenocarcinoma, one patient with clear cell carcinoma and one patient with papillary carcinoma. Deep myometrial invasion appeared in five patients. Peritoneal cytology obtained at the time of surgery was negative for all patients.

After the hysteroscopic application of the radioactive tracer lymphoscintigraphy was performed. In eight patients the draining lymph system was visualized. Scintigraphic hot spots were seen in different locations (Figure 2). In seven patients distribution of the tracer was detected in two or more lymph nodes. Five patients had bilateral SLNs and in two patients pelvic as well as para-aortic lymph nodes could be shown.

Successful intraoperative mapping was possible in seven patients. In five patients the identification was easy. In two patients the lymph nodes were located bilaterally in the inter-iliac lymphatic channels, two other patients had SLNs in the anterior parametrial tissue and in one patient the sentinel node was observed in the para-aortic area.

However in the two remaining patients sentinel lymph nodes could only be identified after bilateral lymphadenectomy (pelvic and para-aortal).The removed tissue showed "hot spots" after the excision and therefore five sentinel lymph nodes could be identified retrospectively.

In general high uterine background activity made it difficult to identify the lymph nodes in the pelvic space. In one patient no hot spot could be observed during or after sampling of the lymph nodes.

A total of 20 SLNs (range 0-7 per nodal basin) were identified. Only one of the eight patients had micrometastases. The metastases were found in the sentinel lymph node in the para-aortic area and around the iliac vessels. In the other six patients the sentinel lymph nodes were negative for micrometastases and no metastatic tumor was identified in the remaining lymphatic tissue. The intraoperative SLN identification reflects the pathological status of all lymph nodes. This means, if a SLN was identified with tumor, there was no overall false-negative result in the study.

Discussion

Lymphatic mapping procedures have been increasingly applied in the treatment of a variety of solid tumors [12-17]. Sentinel lymphadenectomy has been successful in treating melanoma and breast cancer patients and decreased morbidity by allowing omission of complete lymphadenectomy in particular patients [14-16]. Successful implementation of this innovative approach depends on surgical skills as well as tumor specific factors such as tumor size, location, prediction of the regional lymphatic drainage pattern and its possible access.

In this pilot study we analysed the feasibility of lymphatic mapping in patients with endometrial cancer. All patients underwent radical hysterectomy and complete lymphadenectomy (pelvic and/or para-aortic). During the study the following facts about lymphatic mapping were observed:

First, the hysteroscopic application of 1 ml 99m Tc-Nannocoll (40 MBq) was sufficient for subsequent lymphoscintigraphic visualization of the draining system. Moreover the application to the peritumoral area within the uterine cavity proved to be best for exophytic tumors. Lymphoscintigraphy should be done after four to six hours and a simple a. p. view seems to be valid.

Secondly, the lymphatic mapping procedure was well tolerated. However retention of radioactive tracer in the uterus was occasionally a problem as the uterine background radiation made scintigraphic identification of the pelvic lymph nodes difficult. In eight patients we found "hot spots" in the lymphatic drainage system but only in five patients could this be done intraoperatively by successful determination of the SLN.

Plentl *et al.* described a predictable pattern of lymphatic drainage with stepwise progression from the uterine stroma and serosal lymphatics to successive nodal groups in the parametrial, pelvic lymphatics and para-aortic nodes, although significant variations exist [18]. In our study the location of SLNs was variable but mostly in the expected area of drainage. Multiple sentinel lymph nodes were found in the majority of patients and lymphatic mapping was successful in five of ten patients. Parametrial lymph nodes were found in all five patients. Two patients had para-aortic nodes and three bilateral SLN identification.

At the moment it is unclear why multiple sentinel lymph nodes were found. Maybe it is a result of delayed node excision or of multiple independent lymphatic pathways. Studies of other gynecological cancers also noted this phenomenon of multiple SLNs and described a very low identification rate [18-20]. It has been shown that these limitations can be reduced by injecting larger amounts of tracer or by combining the radioactive tracer with dye injection [16, 19]. We are currently evaluating the role of concomitant lymphoscintigraphy and blue dye in endometrial cancer patients undergoing radical hysterectomy.

Lymphatic mapping in patients with an early stage of endometrial cancer is technically feasible. However the detection rate with the current approach is low and warrants further improvement. The identification of SLNs was best in patients with exophytic tumors. In only one case nodal metastases were found in the sentinel node, accurately reflecting the overall pathological status of the involved basin. This study showed that there was no false-negative result, if representative SLNs were diagnosed with tumor.

Our preliminary results indicate that in endometrial cancer the properly identified and excised sentinel nodes are representative of the actual lymph node status as established by complete lymphadenectomy. In future studies we have to use the combined technique (lymphoscintigraphy and blue dye) to evaluate the validity of this innovative approach.

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