

# Detection of sentinel lymph nodes in cervical cancer. A comparison of two protocols

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## Abstract

**BACKGROUND:** The aim of this study was lymphatic mapping to identify SLN in cervical cancer (CaCerv) with radioactive colloids, intraoperative detection with patent blue dye (PBD) and gamma probe (GP) and biopsy and comparison of two protocols.

**MATERIAL AND METHODS:** In 54 patients with CaCerv before hysterectomy and lymph nodes dissection (LND) we performed preoperative lymphoscintigraphy utilizing <sup>99m</sup>Tc-colloid (Nanocoll, SentiScint or Nanocis), activity 40 MBq, on the operation day (30 women) or the day before operation (24 women). Gynaecologists injected 4 peritumoural injections of colloid into the cervix around the tumour. Scintigraphy followed 25–50 minutes (one-day protocol) or 12–19 hours (two-day protocol) after injection. Gynaecologists also injected 4 peritumoural injections of PBD into the cervix around the tumour. All women underwent SLN biopsy and LND (in average 35 lymph nodes were taken) and hysterectomy. SLNs (active and/or blue lymph nodes) were examined by a pathologist [histopathology and immunohistochemistry (IH) with detection of cytokeratine]. No SLN was examined without IH.

**RESULTS:** The gynaecologists withdrew 123 SLNs (on average 2.27/1 patient) and in total 1898 lymph nodes (on average 35/1 patient). In 1 woman the tumour was inoperable. Two-day protocol, which involved scintigraphy, PBD and GP detected SLNs on both sides (45 SLNs) in 17 women (70.8%), SLNs on the one side (6 SLNs) in 3 patients (12.5%) and no SLNs were found in 4 women (16.7%). One-day protocol detected SLNs on both sides in 23 patients (74.1%) — 63 SLNs, in 7 women on one side (25.9%) — 9 SLNs. Metastases in SLNs (with or without metastases in other LN) were found in 21 patients (38.9%) — in 1 woman of stage FIGO IB1, in 1 woman of stage FIGO IB2, in 1 patient of stage FIGO IIIA and in all 18 patients of stage FIGO IIIB. False negative SLN detection was 0%.

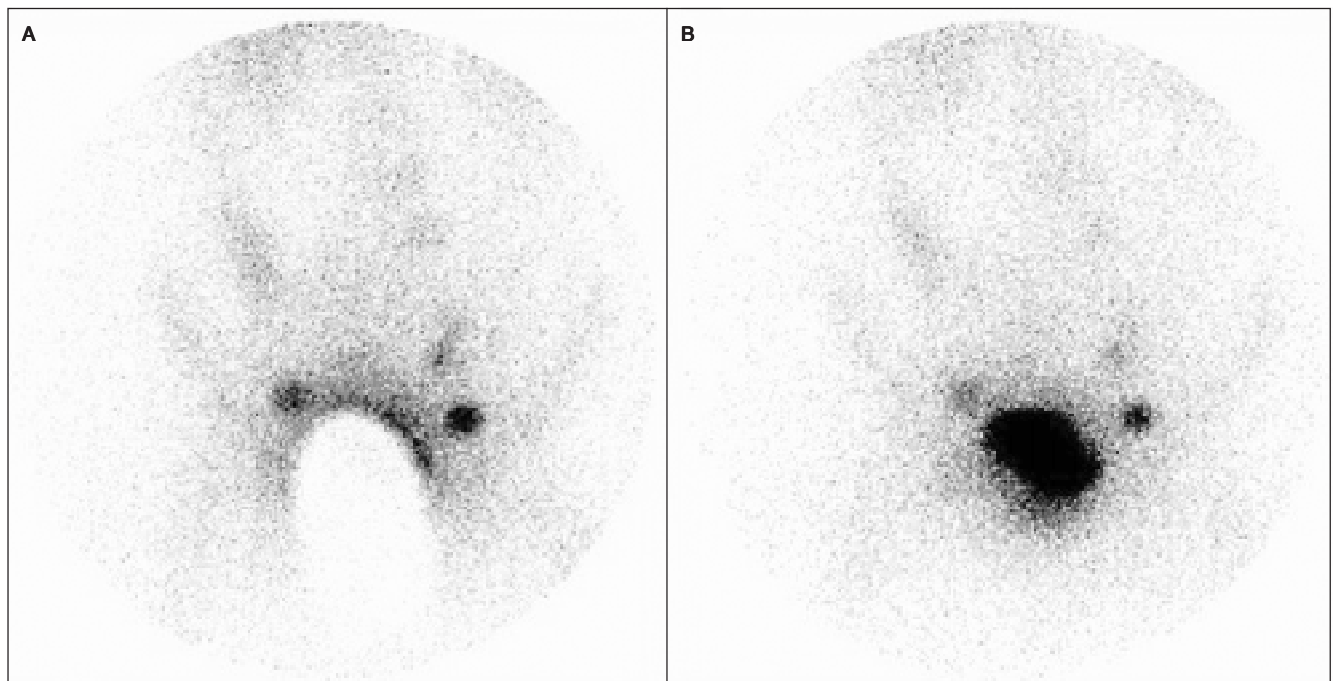
**CONCLUSIONS:** In SLN detection in patients with CaCerv, all 3 methods — scintigraphy, PBD and GP — should be used, and the success rate of SLN detection increases, although scintigraphy has lower significance than in SLN detection in malignant melanoma and breast cancer. One-day protocol had a better detection rate of SLN than two-day protocol. The method is promising but its results are not as unequivocal and optimistic as in breast cancer and malignant melanoma, and it is still experimental. Additional experience is necessary.

**Key words:** cervical cancer, sentinel lymph node, lymphoscintigraphy, patent blue dye, surgical gamma probe

## Introduction

In many tumours, lymph node staging is performed using various nuclear medicine procedures, especially sentinel lymph node (SLN) biopsy. SLN biopsy has an established role in malignant melanoma and breast cancer [1, 2]. A group of patients who might benefit from a SLN biopsy are those with cancer of the uterine cervix and other gynaecological malignancies. In gynaecologic malignancies, regional lymph node status is a major prognostic factor and a decision criterion for adjuvant therapy [3]. Current FIGO staging is unreliable. The reliability of staging can be improved by laparoscopic staging and new imaging techniques such as PET. These techniques still have to be refined [4].

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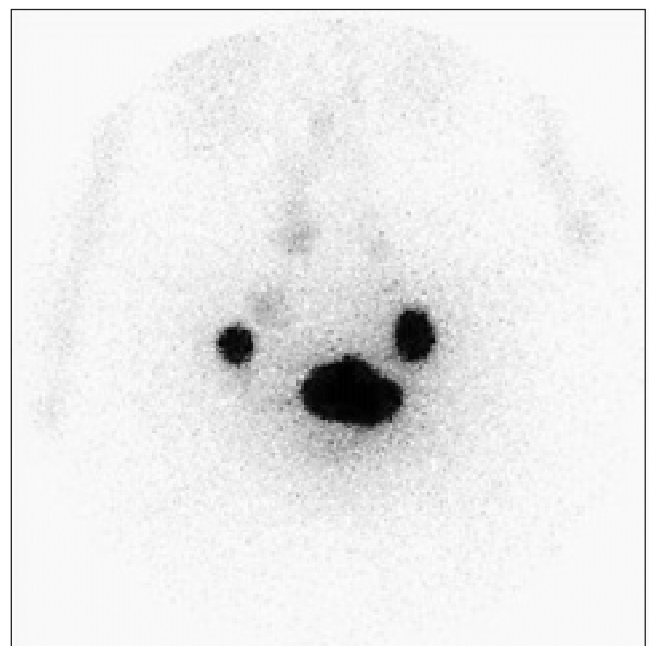
**Figure 1.** Scintigraphic detection of SLN in cervical cancer — anterior projection. **A.** Image with the lead plate covering injection sites; **B.** Without the lead plate.

## Material and methods

Gynaecologists injected 4 peritumoural injections of radiocolloid, activity 40 MBq (in volume  $4 \times 0.5$  ml) into the cervix, around the tumour. Scintigraphy followed 25–50 minutes (one-day protocol) or 12–19 hours (two-day protocol) after injection. 54 patients (age range 25–76 yrs; average age 48.3 yrs) with CaCerv were studied and operated on.

Staging of CaCerv in our patients was: FIGO IA1 in 1 patient, IA2 in 2 patients, IB1 in 30 patients, IB2 in 2 patients, IIIA in 1 patient, IIIB in 18 patients.

Before hysterectomy and lymph nodes dissection (LND) we carried out preoperative lymphoscintigraphy (Figure 1, Figure 2) with the following  $^{99m}\text{Tc}$  colloids: 1. Two-day protocol: in one patient Nanocis —  $^{99m}\text{Tc}$ -colloid rhenium sulphide — nanocolloid (Cis bio International, Gif-sur-Yvette Cedex, France), in 17 patients Nanocoll —  $^{99m}\text{Tc}$ -nanocolloid of human serum albumin (Nycomed Amersham Sorin, Saluggia, Italy), in 6 patients SentiScint —  $^{99m}\text{Tc}$ -human serum albumin colloid (FJC National Research Institute for Radiobiology and Radiohygiene, Budapest, Hungary); 2. one-day protocol: in 29 patients SentiScint and in 1 patient Nanocoll. Lymphoscintigraphy was carried out on the operation day (30 women) or the day before operation (24 women) in the anterior projection on a planar gamma-camera MB 9200 (Gamma, Budapest, Hungary) with a high-resolution collimator focusing on the area of interest. Acquisition time was 10 minutes. If the sentinel lymph node was displayed, to facilitate the surgical resection a reference mark was placed on the skin, corresponding to the position of the SLN visualised by lymphoscintigraphy with the help of the  $^{57}\text{Co}$  mark (before this the occurrence spot was marked with self-adhesive label on the computer monitor — for better orientation



**Figure 2.** Scintigraphic detection of SLN in cervical cancer — anterior projection.

upon marking). The skin surface, under which the lymph node was located, was marked by felt-tip pen cross first and subsequently with dye.

Surgery followed 1.5–4 hours (one-day protocol) or 14–20 hours (two-day protocol) after radiocolloid injections. Gynaecologists

injected 4 peritumoural injections of 4 ml PBD (Patent Blue V or Blue Patenté V, Laboratoire Guebert, Aulnay-sous-Bois, France) into the cervix around the tumour and they intra-operatively detected blue-stained SLNs (or lymph vessels) and radioactive SLN by means of surgical gamma probe DI SURPO (DeLong Instruments, Brno, Czech Republic). All women underwent LND and radical surgery — hysterectomy according Wertheim-Meigs with radicalism PIVER II, III. Radioactive and/or blue-stained lymph nodes (SLN) were examined by the pathologist histopathology — formol fixation, parafin embedding, serial sectioning, hematoxylin and eosin, PAS staining and immunostaining with a monoclonal mouse anti-human cytokeratin/Clone AE1 (AE3 antibody DAKO). No SLNs were examined without immunohistochemistry.

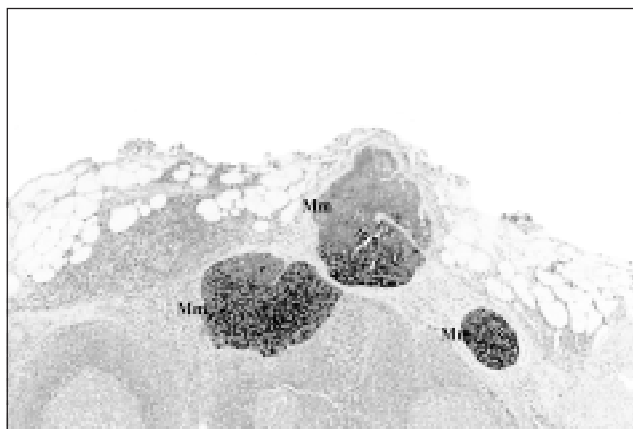
### Results

The gynaecologists withdrew 123 SLNs (in average 2.27/1 patient), in total 1898 lymph nodes (on average 35 lymph nodes were taken in each patient). In 1 woman the tumour was inoperable. Two-day protocol: scintigraphy, PBD and GP detected SLN on both sides (45 SLN) in 17 women (70.8%), SLN on the one side (6 SLN) in 3 patients (12.5%) and SLN were not found in 4 women (16.7%). Detection rate of SLN was 83.7%. These 4 women without SLN detection had CaCerv of these stages: 2 × FIGO 1B1 in 2 patients, FIGO IB2 in 1 patient and FIGO IIIB in 1 patient. In 3 patients with unsuccessful SLN detection we used Nanocoll and in one woman SentiScint. One-day protocol results were: SLN was detected on both sides in 23 patients (74.1%) — 63 SLNs, and in 7 women on one side (25.9%) — 9 SLNs. Detection rate of SLN was 100%. Tables 1 and 2 show detection rates of SLNs.

Metastases in SLNs (with or without metastases in other LN) were found in 21 patients (in 38.9%) — in 1 woman of stage FIGO IB1, in 1 woman of stage FIGO IB2, in 1 patient of stage FIGO IIIA and in all 18 patients of stage FIGO IIIB (Figure 3 — IH detection of cytokeratine in SLN metastases). False negative rate of SLN detection was 0.

### Discussion

In the Czech Republic, cervical cancer is the third most common gynaecological malignant tumour with incidence



**Figure 3.** Immunohistochemistry (IH) detection of cytokeratine in SLN metastases of cervical cancer.

of 20 cases per 100 thousand women, which is the highest in Europe.

The main factors which have influence on the prognosis are: disease stage, type, size and differentiation of tumour. The most important prognostic factor is the state of the lymph nodes. The treatment of choice in clinically node-negative early stage cervical cancer (up to stage IIa) is radical hysterectomy and pelvic lymph node dissection [5], in higher stages (the frontier is affliction of parametrium) the primary treatment is radiotherapy. Radical surgery according Wertheim-Meigs with radicalism PIVER II, III consists of withdrawal of the uterus, adnexa, parametria, proximal part of vagina and pelvic lymph nodes. Complications resulted from extensive radicalism of surgery are lymphocyst formation, lymph drainage blockade with lymphoedema formation of lower extremities. Affliction of the lymphatic system is in the stage FIGO I up to 15%, in the stage FIGO II 25–30 %. There is not suitable pre-surgery examination procedure of detection of impacted lymph nodes. SLN biopsy can be feasible in cervical cancer and may result in custom-designed treatment strategies with a reduction in morbidity. The most important benefits of the SLN procedure for the patients with cervical cancer are avoidance of over treatment and prevention of morbidity [6].

**Table 1. Sentinel lymph node detection — one-day protocol**

SLN detection	Scintigraphy	Gamma probe	Patent blue dye	Perioperative-combination
Number of patients	30	29	29	30
Successful detection	23	28	23	30
Percentage of SLN detection	76.7	96.6	79.3	100

SLN — sentinel lymph node

**Table 2. Sentinel lymph node detection — two-day protocol**

SLN detection	Scintigraphy	Gamma probe	Patent blue dye	Perioperative-combination
Number of patients	24	23	22	24
Successful detection	22	17	18	20
Percentage of SLN detection	91.7	73.9	81.8	83.3

SLN — sentinel lymph node

Detection rate of SLN can be negatively influenced by the FIGO stage and primary cervical tumour size [7]. We had small amount of patients and we could not confirm this connection. We had a lower scintigraphic SLN detection than gamma probe detection by Wydra et al. [8]. The injected tracer amount is another factor that can influence SLN visualization [9]. Particle size of radiocolloid can be also significant. We had a small amount of patients in Nanocoll and SentiScint subgroups and it is not possible to draw conclusions about influence of particle colloid size. Namkoong et al [10] recommend  $^{99m}\text{Tc}$ -antimony sulphide colloids with the size of particles ranging 1 to 15 nm. We think that this size is too small with a high possibility for second echelon lymph node visualization. The sentinel lymph node concept is valid in patients with cervical cancer [11]. However, sensitivity and negative predictive value have to be improved before the concept can be integrated into clinical practice [4], and large and multi-institutional trials are required in order to define the implementation of SLN biopsy in clinical practice with the objective of achieving safer and more conservative surgery [12]. However, some authors have proven high and unacceptable false negative rates of SLN in cervical cancer. This high false-negative rate associated with sentinel lymph node biopsy raises questions regarding the validity of the sentinel lymph node concept in cervical carcinoma [13]. In recent studies, the usefulness of SLN biopsy in the early stages of cervical cancer with highly negative predictive value was proven [14, 15].

## Conclusions

In SLN detection in patients with CaCerv, all 3 methods — scintigraphy, PBD and GP - should be used and the success rate of SLN detection increases, although scintigraphy has a lower significance than in SLN detection in malignant melanoma and breast cancer. One-day protocol has better detection rate of SLN than two-day protocol. The method is promising but its results are not as unequivocal and optimistic as in breast cancer and malignant melanoma, and it is still experimental. Additional experience is necessary (learning curve). Sentinel lymph node concept is valid in patients with cervical cancer. However, sensitivity and negative predictive values have to be improved before the concept can be integrated into clinical practice.

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