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Short communications

The influence of depth of marker administration on sentinel node detection in cervical cancer

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Abstract

BACKGROUND: Regional lymph node surgical management is an integral part of cervical cancer therapy. In gynaecological oncology, recent studies have confirmed the utility of the sentinel node concept in vulvar and cervical cancer. The method of the marker's administration is considered to play an important role in sentinel node detection.

MATERIAL AND METHODS: 60 patients with cervical cancer (stage IB–IIA) underwent SLN detection during radical abdominal hysterectomy. The patients were randomly divided into two groups: the first group of 30 patients with 0.5–1cm deep marker injection, the second with sub-epithelial marker injection. Gamma-camera scanning, as well as hand-held probe detection was applied.

RESULTS: All hot nodes visualised on lymphoscintigraphy were "hot" when using the hand-held gamma probe. Deep marker injection revealed a sentinel node in 27 patients (90%) on both sides, in 3 patients (10%) only on one side. Only 40 (67%) sentinel nodes were blue-stained. Sub-epithelial marker administration revealed a sentinel node on both sides in all 30 patients (100%). In 28 patients (93.3%) the sentinel nodes were radioactive and blue-stained, in one case not-blue stained on either side, in one case blue stained only on one side.

CONCLUSIONS: The sentinel node detection rate in cervical cancer is relatively high and depends on the applied technique. The superficial administration of radiocolloid and the blue dye into the cervix provides a higher sentinel node detection rate than deep administration in cervical cancer patients.

Key words: sentinel node, cervical cancer, lymphoscintigraphy

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Introduction

The sentinel lymph node is defined as the first lymph node along the lymphatic channel most likely to contain metastases [1–4]. In order to detect this lymph node a marker substance drained *via* lymphatic channels should be injected around the primary tumour: this can be done by using either a dye substance, or a colloid radiotracer.

Studies in patients with breast cancer and melanoma have shown that the sentinel lymph node concept is useful for predicting regional lymph node metastases. Therefore, complete lymphadenectomy is not performed when the sentinel lymph node is histologically free of metastasis. Although many authors present encouraging results of sentinel node detection in cervical cancer patients [5–12], there are still differences in the technique of marker administration.

The aim of the study was to assess the influence of the depth of marker administration on the sentinel node detection rate in cervical cancer patients.

Material and methods

Patients

60 patients with early cervical cancer (stage IB–IIA) were involved in the study. All patients underwent radical hysterectomy and total pelvic lymphadenectomy. Informed consent was obtained from each patient. We randomly divided patients according to the depth of marker administration into two groups:

— the first group comprising 30 patients, where the ^{99m}Tc-labeled radiocolloid was injected 5–10 mm deep into the cervix;
— the second group comprising 30 patients, where the ^{99m}Tc-labeled radiocolloid was injected in the sub-epithelial way.

Pre-operative lymphoscintigraphy

Pre-operative lymphoscintigraphy was performed more than 18 hours before surgery utilising a single-head gammacamera Diacam (Siemens, Erlangen, Germany) following injection around the tumour ^{99m}Tc-labelled radiocolloid (Amersham, Amersham, England) in a volume of 1.0 ml, dose range 35–70 MBq under the guidance of a speculum-assisted view. The injection was applied using an insulin syringe (22 G) in four sectors around the tumour.

Intra-operative lymphatic mapping

The injection of the radionuclide was repeated on the morning of the procedure, 1 to 6 hours before surgery. The hand-held gamma detector probe (Technical University, Gdansk, Poland), calibrated for a measuring range 130–150 keV, was used to detect the sentinel node.

Blue dye was injected on the day of the operation after the patient had undergone general anaesthesia. 4 ml of blue dye was injected into four sectors around the cervix. In the 1st group, blue dye was administered in the sub-epithelial way into the cervix. In some cases after the blue dye injection a net of lymphatic vessels was visible, which was considered to be proof of correct marker administration. In the 2nd group, blue dye was administered by 5 to 10 mm deep injection the same pattern as the radiocolloid tracer administration.

During the operation the gamma detector probe was positioned along the lymph node regions to detect possible sentinel nodes (SLNs). After the SLNs' detection a conventional lymphadenectomy was performed.

Table 1. Clinical patients and tumour characteristics in both groups

Characteristics	Number of patients	
	Group 1st (deep injection)	Group 2nd (sub-epithelial injection)
Tumour FIGO stage		
IB1	19	18
IB2	6	6
IIA	5	6
Tumour size		
< 4 cm	22	23
> 4 cm	8	7
Prior conisation		
no	28	28
yes	2	2
Squamous	28	29
Adenocarcinoma	1	1
Adenosquamous	1	0

As SLN was defined as a lymph node showing radioactivity higher than 10% of that of the tumour site. The lymph node with the strongest signal measurement was determined to be the sentinel node, those following with a weaker signal were established as post-sentinel nodes. Lymph nodes showing radioactivity identified with the use of the gamma detector probe, as well as blue-stained lymph nodes were removed. If there was more than one blue dye node on one side, the sentinel node was determined to be the blue dye node with the highest radioactive signal.

The SLN and post-SLN were separately sent for pathologic evaluation, fixed in buffered 4% formaldehyde solution, then stained with hematoxillin/eosin (HE).

Results

The median age of the 1st group cohort was 46.7 ± 12.3 years (range 27–76 years), the median age in the 2nd group 48.2 ± 12.8 years (range 28–76 years). The characteristics of patients in both groups are given in Table 1.

Pre-operative lymphoscintigraphy results

Pre-operative lymphoscintigraphy was performed before the surgery in 15 patients in group 1 and in 15 in group 2. All 30 patients had at least one sentinel node localized on lymphoscintigraphy. In one case from the 1st group, a para-aortic sentinel node was localized. It was also a positive node on routine HE processing.

Intra-operative lymphatic mapping results

All nodes visualised on lymphoscintigraphy were "hot" when using the hand-held gamma probe.

A total of 117 lymph nodes were identified as sentinel nodes and 132 as post-sentinel nodes based on hand-held gamma probe detection. 202 nodes were blue-stained: 134 (67%) in group 1 and 68 (33%) in group 2. The characteristics of sentinel nodes identified in both groups are summarised in Table 2.

In the 1st group, in 27 patients the sentinel nodes were radioactive on both sides. In 3 patients radioactivity was confirmed only on one side. The sentinel nodes were blue-stained only in 40 (67%) patients from this group.

In the 2nd group, all the 30 patients' sentinel nodes were radioactive on both sides. In 28 (93.3%) patients the sentinel nodes showed radiation and were blue-stained. In 1 case sentinel nodes were not-blue stained on either side, in one case only on one side. Altogether, in 28 patients, 57 sentinel nodes became blue-dye visible.

No patients experienced anaphylaxis during the injection of either blue dye or technetium-99 radiocolloid. Some patients complained that the radionuclide injection was painful. The discomfort was very brief and spontaneously disappeared after 1–2 minutes.

Table 2. Sentinel node blue/hot characteristics in analyzed groups

	Hot		Not hot	
	Group 1st (deep injection) n = 30	Group 2nd (sub-epithelial injection) n = 30	Group 1st (deep injection) n = 30	Group 2nd (sub-epithelial injection) n = 30
Blue-stained	40	57	3	0
Not blue-stained	17	3	0	0
Total	57	60	3	0

Discussion

Regional lymph node status is being evaluated in all women with cervical cancer undergoing surgery. Lymphadenectomy of pelvic, parametrial, and para-aortic nodes causes increased intra-operative and post-operative morbidity with bleeding, nerve lesions, lymphoedema, and serocele formation. Lymphadenectomy of tumour-negative nodes can potentially have a negative influence on the immune system. More than 90% of the lymph nodes resected are without nodal metastasis [5]. Therefore, extensive lymphadenectomy may be unnecessary in the majority of patients. The most important factor in the sentinel procedure is the standardisation of the technique. Some authors performed sub-epithelial injections into the cervix [6–8], while others reported the 5–10 mm depth of the marker administrations [9–10]. There is also a group of authors who do not mention anything about this aspect [11–13].

In a discussion of the results given above, two questions emerge:

— first — regarding the mutual relation of radiocolloid and blue-dye sentinel node identification techniques;
— second — regarding the influence of the injection technique on the sensitivity of both methods.

Regarding the first issue, it seems that radiocolloid technique is slightly superior to blue-dye method, but the best results are achieved when these two techniques are applied simultaneously. Malur and co-workers reported a cohort of 50 patients studied with blue dye and/or radioactively labelled albumin techniques [7]. The detection rate using blue dye, radioactively labelled albumin or both substances was respectively 55.5%, 76.2% and 90%. The overall detection rate was 78%, sensitivity 83.3%, predictive value 97.1%. The sensitivity and negative predictive value were 100% when both techniques were combined. Similar results were reported by Verheijen et al. [14].

Regarding the second issue, we have compared two ways of the marker administration. The use of the sub-epithelial method gave higher sentinel node detection rates, both in the radiocolloid method and the blue dye method. The difference between both techniques is visible especially with the blue dye application. We achieved a 93% identification rate applying the sub-epithelial injection technique and a 67% identification rate was achieved with deep blue dye injection.

The authors are not aware of the comparative studies on the influence of the injection site on the sensitivity of the lymphoscintigraphy/blue dye technique in cervical cancer.

The better results obtained with superficial marker administration may be attributed to the anatomical structure of the cervical lymphatic system. Within the vaginal part of the cervix there is a well developed net of capillary lymph vessels located just under the cervical epithelium. The lymph from this part is drained to the larger lymphatic vessels of the superficial layer of the cervical muscular membrane. On the other hand the muscular membrane has its own vessels net, which has its greatest density close to the cervical mucosa. Therefore, superficial tracer administration allows more a efficient absorption of the tracer than a deeper injection, when the marker is placed in the part of the cervix with a relatively smaller density of lymphatic capillary vessels [15].

Conclusions

Superficial administration into the cervix of radioisotope-labelled colloid and blue dye has a higher sentinel node detection rate than deep marker administration in cervical cancer patients.

Lymphoscintigraphy has a higher sentinel node detection rate than blue dye injection, but the best results have been achieved using these two methods together.

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