PREOPERATIVE AND INTRAOPERATIVE DETECTION OF SENTINEL LYMPH NODES IN PATIENTS WITH CERVICAL CANCER UNDERGOING RADICAL SURGERY

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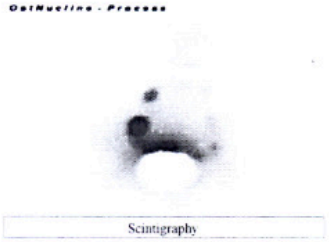
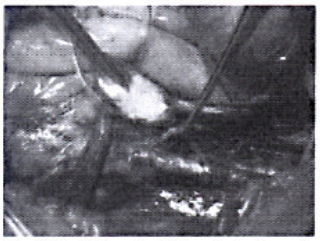
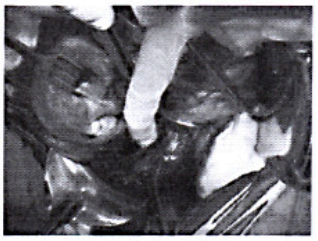


Scintigraphy

Introduction: Lymphatic spreading and the lymphonodes status is the most significant negative prognostic factor of the cervical cancer (CC). There is no suitable non invasive imaging method of the involvement of the regional lymphonodes and radical hysterectomy with systematic pelvic lymphadenectomy remains a golden standard of the treatment currently employed to detect lymph node involvement. Morbidity rate accompanying radical surgery is not low and morbidity rate of combined treatment is higher than for either of treatment methods alone.



Blue SLN with blue stained efferent lymphatic vessels



Detection of SLN by using hand-held detection probe

Backgroung and aims: The aim of the study was to analyse the feasibility and accuracy of preoperative and intraoperative SLN detection using combined radioisotopic lymphatic mapping with technecium^{99m} labeled coloid and blue dye lymphatic mapping in patients undergoing radical surgery for treatment of early stage CC.

Table 2. – 4.

FIGO stage	side detection rate %			
	Scintigraphy	BD	Tc99	BD+Tc99
IA2-IB1 < 2 cm	64,3	70,1	79,2	86,6
IB1 > 2 cm	63,6	73,9	80,4	89,1
IB2	50,0	36,8	57,9	68,4
Total	**62,2**	**66,8**	**76,6**	**83,8**

Methods	PDR	SDR	Bilateral detection	FNR
Scinti	82,3%	62,2%	51,7%	
BD	78,1%	66,8%	71,0%	6,9%
Tc99	86,1%	76,6%	77,9%	6,9%
BD+Tc99	**94,2%**	**83,8%**	**79,1%**	6,9%

	Scintigraphy	BD	Tc99	BD+Tc99
Sensitivity	93,4	92,3	93,8	94,5
Specificity	27,8	100	100	100
PPV	67	100	100	100
NPV	73,2	98,1	98,3	98,3
Accuracy	67,5	98,5	98,6	98,6

BD –Blue dye **Tc99** – Technecium-99-labeled nanocolloid **FNR**– False negative rate
PDR – Patient detection rate **SDR** - Side detection rate **PPV** – Positive predictive value
NPV – Negative predictive value

Patients and methods: In the time period from May 2004 to December 2007 137 patients were enrolled in this study of combined lymphatic mapping with SLN detection. Patients with a tumor measuring more than 40 mm in largest diameter were treated primary with a dose densitity neoadjuvant chemotherapy. (3 courses of 75 mg/m2 DDP + 2g/m2 IFO in 10 day interval).

Clinical and histopathological characteristics of the study population are depicted in Table 1.

In the beginning of the study two days protocol with aplication 80-100 MBq of the tracer NANOCOL 14-16 hours before surgery and static lymphoscintigraphy was used. From May 2005 one day protocol with aplication 50 MBq of SENTISCINT one hour before scintigraphy and two hours before surgery was introduced. Four injections, each with 0, 2 ml of the tracer, were administered with a 25-gauge spinal needle injection under direct visual control peritumorally into the tumor bed at 2, 4, 8 and 10 oclock position . Static images were obtained using a double - head gamma camera fitted with a low – energy and high – resolution collimator. The first appearing persistent focal accumulation was considered to be a SLN and localisation of the SLN was marked on corresponding skin topography with indelible ink to guide the surgeon. After induction of general anesthesia and after visualisation of the abdominal cavity blue dye was injected at the same locations as the tracer. Blue lymphatics were followed to their ending in a blue lymph node. Then the peritoneal cavity was scanned with a handheld gamma – ray detection probe to localize the hot spots marked by the lymphoscintigraphy. If the counts were at least ten – fold above background radiation levels or if the node were blue coloured, it was classified as sentinel and removed separatelly. All SLN were recorded by their relative position to the major pelvic vessels and labeled hot (radioactive) positive, blue positive or hot and blue positive. Subsequently, a complete pelvic lymphadenectomy and Piver type II – III radical hysterectomy were performed.

SLN were cut perpendicularly to the long axis into 2 mm thick sections that were submitted for paraffin embedding. Serial step sections 100 um apart and 5 um thick were stained with hematoxylin – eosin and with immunohistochemistry using a monoclonal antibody directed against cytokeratins AE1 – AE3 (DAKO, Carpinteria, CA Denmark). Whole SLN were evaluated at multiple levels.

Table 1.

	N	%
IA2 – IB1< 2cm	72	52,5
IB1 > 2cm	46	33,6
IB2	19	13,9
Squamous	113	82,5
Adenocarcinoma	19	13,9
Other	5	3,6
Grade 1	63	46,0
Grade 2	48	35,0
Grade 3	26	19,0
LVSI yes	103	75,2
LVSI no	34	24,8
LEEP yes	50	24,5
LEEP no	87	63,5

Results: In total 175 SLN were detected by lymphoscintigraphy (1,3 nodes per patient), 439 SLN were detected intraoperatively (3,2 nodes per patient). Preoperatively and intraoperatively SLN detection rate per patient and detection rate per side (SDR) are depicted in the table 2. 43 patients (31,4%) had lymph node metastases, false negative rate for single methods, sensitivity, specificity, predictive value and accuracy are depicted in the table 2-4.

Discussion: Review of the present literature and also results of our study make clear that the combined use of radioactive isotope and blue-dye injection is the optimal procedure for lymphatic mapping in patients with CC and it is superior to methods using the blue dye or tracer alone. SLN based on dual labelling with radiocoloid and patent blue provides a high SLN identification rate and low false negative rate. FIGO stage and tumor size are the important factors negatively influencing the detection rate. A satisfactory SLN mapping study is one where at least one SLN is identified on each side. Detection of SLN is considered per side rather than per patient. In future, to rely on SLN status to avoid a complete lymphadenectomy, the SDR will have to be higher. If not, too many patients will have to undergo at least unilateral complete lymphadenctomy, which may reduce the benefit of lymphatic mapping in the avoidance of overtreatment and prevention of the morbidity.

SLN techniques may reduce morbidity without affecting survival by allowing omission of parametrectomy and complete lymphadenectomy in patients with negative SLN and by ommission of surgical treatement and indication of primary chemoradiotherapy in patients with positive SLN. Recent data support tailoring of the radicality of surgery to LN status.

Conclusions: Lymphatic mapping with detection and histological ultramicrostaging evaluation of SLN is a promising strategy for the assessment of nodal status in early stage CC. The combined intraoperative detection techniques are feasible and accurate methods to detect lymphatic spreading and potentially identify patients in whom radical surgical treatment could be avoided.