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The sentinel node in gynaecological malignancies

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Abstract

As lymph node metastasis is one of the earliest features of tumour cell spread in most human cancers, assessment of the regional lymph nodes is required for tumour staging, determining prognosis and planning adjuvant therapeutic strategies. However, complete lymph node dissections are frequently associated with significant complications. Conjugating the diagnostic advantages with decreased morbidity, the sentinel node concept represents one of the most recent advances in surgical oncology. In this review we briefly highlight the historical background of the development of the sentinel node concept, the anatomical evidence for applying the sentinel node concept in pelvic gynaecological cancers and the technical aspects of sentinel node detection. We discuss recent studies in vulval, cervical and endometrial cancer.

Keywords: Sentinel node; lymphatic mapping; cervical cancer; vulval cancer; endometrial cancer.

Introduction

During the past two decades the operative management of cancer has changed to a large extent. In breast cancer, the Rotter–Halstedt radical surgical procedure has been replaced more and more by a breast-conserving treatment combined with adjuvant local (radiotherapy) and systemic (hormonal and/or chemotherapy) treatment. The less ablative surgical management has resulted in a significant decrease in morbidity whilst retaining a similar survival rate.

As lymph node metastasis is one of the earliest features of tumour cell spread in most human cancers, assessment of the regional lymph nodes is required for tumour staging, determining prognosis and planning adjuvant therapeutic strategies. In most solid tumours, dissection of all regional lymph nodes is part of the surgical procedure; however, in breast cancer and cutaneous malignant melanoma this has been replaced by dissection of the sentinel lymph node(s) only. The sentinel node (SN) is defined as the very first lymph node or group of nodes that drain the anatomical region or primary tumour[1,2]. The status of the SN should represent the whole lymphatic area, i.e. if the SN is negative the non-sentinel lymph nodes should also be negative. The application of the SN dissection (SND) in breast cancer has resulted in a further decrease in morbidity, especially the formation of lymphoedema, by avoiding a complete axillary lymph node dissection[3–5].

The SN concept is based on the detection of SN(s) using both dye-based and gammaprobe-guided methods (radioimmunoscintigraphy), and removal of the identified SN(s) with subsequent histological analysis. The detection rate of small clusters of (micro)metastases in SN(s) can be increased when the nodes are subjected to serial sectioning and the use of immunohistochemistry, i.e. antibodies against epithelial markers[6].

In this review we briefly highlight the historical background of the development of the SN concept, the anatomical evidence for applying the SN concept in

pelvic gynaecological cancers and the SN technology. We discuss recent reports on the application of the SN method in vulval, cervical and endometrial cancer.

Historical background

In 1960, Gould et al. established the term 'sentinel node' (SN) when they published their report on parotid gland cancer[1]. In 1977, Cabanas proposed the SN concept in the management of patients with penile cancer, and he reported that the lymphatic drainage of the penis merges into a group of lymph nodes called 'sentinel lymph nodes' (SLNs)[2]. He used lymphography to visualise the dorsal lymphatics of the penis draining to the lymph nodes close to the superficial epigastric vein. In 1992, Morton et al. introduced the SN method in the management of cutaneous malignant melanoma. Blue dye was injected around the lesion just before the operation and the nodes staining blue were removed via a small incision[7]. In 82% of cases, the SN was successfully identified; the false negative rate was less than 1%. The application of technetium-99m-labelled nannocolloid as a more sophisticated detection method for SN(s) was introduced into the management of malignant melanoma in 1993 by Alex and Kraig. They used both preoperative lymphoscintigraphy as well as an intraoperative handheld gamma probe, which increased the detection rate[8]. In 1993, Krag et al. reported a pilot study on the use of SN identification, using technetium-99m-labelled colloid, in the management of breast cancer; they achieved a detection rate of 81%[9]. In 1994, Giuliano et al. reported in a large series of 174 consecutive breast cancer patients the use of blue dye as a method for SN detection; the detection rate was 65.5% and accurately predicted the axillary nodal status in 95.6% of cases[10]. In the same year, Levenback et al. published the first feasibility study on SND in vulval cancer. They administered intracutaneous isosulfan blue and identified SN(s) in 77% of cases, with no false negatives[11]. At present, ongoing multicentre prospective observational studies (GOG173 and the European trial led by A. Van der Zee) are addressing the clinical implementation of SN detection in vulval cancer management. Since 1999, several series have been reported on the feasibility of SN detection in cervical and endometrial cancer as well as its validity[12–17]. The modality of injecting the dye or radioactive tracer for SN detection has still to be established in endometrial cancer. In cervical cancer, there is some concern whether the SN accurately predicts the pelvic lymph node status, however, most series demonstrate a low false negative rate[14,18] (see Table 2). For early-stage breast cancer and malignant melanoma, the SN concept has become the standard care without altering the survival rate but with a significant decrease in the morbidity of lymph node dissection[19–21].

Anatomical background: the lymphatic drainage of the female genital tract

The lymphatic vessels from the vulval region terminate primarily in the inguinal nodes. The fine lymphatic vessels from the labium minora, the fourchette, and the vaginal mucosa up to the level of the hymenal ring extend towards the anterior aspect of the labium minora where they emerge into few major collecting vessels[22]. The lymphatic vessels from the prepucium and the labium majora also join these main vessels, which terminate in the primary inguinofemoral lymph nodes. These first-line nodes are located medial to the saphenus vein and above the cribriform fascia and are called superficial nodes (about 8–10 in number); the deep nodes are situated in the openings in the cribriform fascia[23–25]. The uppermost deep lymph node located under the inguinal (Poupart) ligament is called the Cloquet or Rosenmüller node and leads to the lymphatics around the external iliac vessels. The lymphatic vessels from the vulva do not cross the midline except those coming from the median structures, i.e. the clitoris and perineum. Although lymphatics from the clitoris can lead directly to the pelvic nodes, practically there is no sole pelvic lymph node involvement without inguinal node metastasis[26]. In the case of positive inguinal nodes, however, pelvic node metastasis is present in 25% of cases.

The uterine cervix has copious lymphatic drainage consisting of primary and secondary groups of lymph nodes[27]. The group of primary nodes consists of parametrial, paracervical, obturator, hypogastric, external iliac, and presacral lymph nodes. The common iliac, paraaortic and inguinal lymph nodes constitute the secondary group. Obturator nodes are the most likely to be involved by tumour metastasis followed by the external iliac, common iliac, and parametrial lymph nodes in locally advanced cervical cancer[28]. Skip metastasis, i.e. paraaortic lymph node involvement without pelvic lymph node metastasis, is rare, accounting for only 1% of cases[29,30]. The SN in cervical cancer is situated in the obturator region in 43% of cases and the external iliac region in 45%–84% of cases[13,18,29,30].

The lymphatic drainage pattern of the uterine corpus is much more complex, having a bipartite and bilateral drainage system. The lower uterine segment drains to the pelvic lymph nodes via the broad ligaments, and the upper segment of the corpus drains into the paraaortic lymph nodes via the ovarian lymphatics. In a feasibility study by Burke et al., injection of vital blue dye into the corpus revealed a wide variation in the location of pelvic lymph nodes taking up the blue dye[31].

Technique of sentinel node detection

There are two methods described for SN identification: vital dyes and radioactive tracers. The three dyes most

Table 1 **Sentinel node in vulval cancer**

Author [reference]	Year	Detection method	No. of cases	Groins dissected (*n*)	Detection rate (%)	Positive SN (*n*)	False negative SN (N)	NPV (%)	Ultra-staging
Levenback [65]	1995	BD	21	29	66	5	0	100	N
Decesare [58]	1997	ILS	10	20	100	3	0	100	N
Echt [12]	1999	BD	12	23	75	2	0	ND	N
Rodier [66]a	1999	ILS + BD	8	ND	100	1	0	ND	N
Ansink [67]	1999	BD	51	93	56	9	2	95	N
Terada [38]a	2000	ILS + BD	9	2	100	3	0	100	Y
De Hullu [68]	2000	ILS BD	59	107	100	24	0	100	Y
Sideri [69]	2000	ILS	44	77	100	13	0	100	N
De Cicco [70]	2000	ILS	37	55	100	8	0	100	N
Levenback [71]	2001	BD	52	76	88	10	0	100	Y
Boran [53]	2003	ILS	10	17	100	4	2	83	Y
Molpus [72]	2001	ILS + BD	11	16	91	3	0	100	Y
Tavares [73]	2001	ILS + BD	15	ND	100	3	0	100	N
Sliutz [74]	2002	ILS ± BD	26	46	100	9	0	100	Y
Moore [75]	2003	ILS + BD	21	31	100	7	0	100	Y
Puig-Tintore [37]	2003	ILS + BD	26	37	96	8	0	100	Y
Merisio [76]	2005	ILS	20	30	100	2	1	95	Y
Louis-Sylvestre [77]	2005	ILS ± BD	17	34	100	0	5	100	Y

aTherapeutic, no complete LND after SND; BD, blue dye method; ILS, intraoperative lymphoscintigraphy; NPV, negative predictive value; SN, sentinel node; ND, no data.

commonly used are isosulfan blue, patent blue violet, and methylene blue. In most studies the dye has been injected peri-tumourly, where most lymphatic vessels are, up to 20 min before surgery. Blue-stained lymphatic vessels and nodes can already be visualised a few minutes after injection. Intratumoural and intravascular administration have to be avoided as it can produce high background signal intensity ('shine through') and can decrease the rate of identification. The blue dye method is an inexpensive, rapid and visible technique, easy to handle and represents no radiobiological hazards. Hypersensitive reaction to the blue dye is extremely uncommon. The significant drawbacks of the blue dye method are the need for a larger incision for better visualisation and a lower detection rate (60%–90%) (see Tables 1 and 2). Radioactive tracers contain technetium-99m radioisotope bound to nannoparticles like colloidal sulphur or human albumin. To detect the node(s) with the highest uptake of technetium-99m, preoperative scintigraphy and an intraoperative handheld gamma probe are used. The radioactive tracer has to be injected also peri-tumourly, 1 day prior to surgery and a locoregional scintigraphy is performed the same day in order to roughly localise the site of the SN(s). An intraoperative handheld gamma probe is used to accurately localise the SN(s), using a 10-fold increase in radiation compared to basal count as a limit. Compared to blue dye, lymphoscintigraphy is a quantitative and highly sensitive method, but is costly and needs nuclear medicine studies and more preparation.

A combination of both techniques achieves a higher detection rate when compared to blue dye alone[32].

Histopathological evaluation

One of the key issues of the SN concept is the histological assessment of the lymph node specimen(s). The first step is intraoperative frozen section analysis, however, this has a low sensitivity for detecting metastases; the false negative rate of identifying micrometastases can be as high as 70%[33–36]. Standard sectioning with haematoxylin and eosin staining is not as sensitive as serial sectioning combined with immunohistochemistry (IHC) to detect micrometastases[6]. In vulval cancer, approximately 40% of SN (micro)metastases are only detected when using serial sectioning[37–39]. Serial sectioning, with reported variable intervals between 50 and 400 μm, and the use of a pancytokeratin antibody (AE1/AE3) enhances the detection rate of nodal micrometastases[14]. In contrast, Hakam *et al.* found no additional benefit of serial sectioning[40]. Lymph node micrometastasis in breast cancer has now been included in the TNM classification, with micrometastases defined as clusters between 200 μm and 2 mm[41]. In endometrial cancer, detection of cytokeratin-positive micrometastases in presumed histologically node-negative patients may predict recurrent disease[42]. Molecular techniques such as real time polymerase chain reaction (RT-PCR) targeting detection of mutations or

Table 2   Sentinel node in cervical cancer

Author [reference]	Year	Detection method	Surgery	No. of cases	Detection rate (%)	Positive SN	False negative SN	NPV (%)	Ultra-staging
Echt [12]	1999	BD	LAP	13	23	2	1	ND	N
Dargent [13]	2000	BD	LSC	35	86	8	0	100	N
Verheijen [78]	2000	ILS + BD	LAP	10	80	1	0	100	Y
O'Boyle [79]	2000	BD	LAP	20	60	3	1	89	N
Kamprath [80]	2000	ILS	LSC	18	89	1	0	100	ND
Malur [81]	2001	ILS or BD	LAP/LSC	50	80	6	01	97	N
Lantzsch [82]	2001	ILS	LAP	14	93	1	0	100	Y
Levenback [30]	2002	ILS + BD	LAP	39	100	8	1	97	Y
Rhim [83]	2002	ILS + BD	LAP	26	100	5	1	95	N
Plante [32]	2003	BD	LSC	41	79	12	0	100	Y
		BD + ILS		29	93				
Dargent [14]	2003	BD	LSC	70	90	19	0	100	Y/N
Lambaudie [84]	2003	ILS + BD	LSC	12	92	2	1	89	Y
Barranger [16]	2003	ILS + BD	LSC	13	92	2	0	100	Y
Chung [85]	2003	ILS + BD	LAP	26	100	1	0	100	ND
Buist [86]	2003	ILS + BD	LSC	25	100	9	1	94	Y
Hubalewska [87]	2003	ILS + BD	LAP	37	100	5	ND	ND	ND
Van Dam [88]	2003	ILS	LSC	25	84	5	0	100	ND
Martinez-Palones [89]	2004	ILS + BD	LSCLAP	25	92	4	0	100	Y
Li [90]	2004	ILS	LAP	28	96	6	0	100	ND
Marchiole [91]	2004	BD	LSC	29	100	2	3	87.5	Y
Lelievre [17]	2004	ILS + BD	LSC	8	71	0	0	100	Y
Barranger [92]	2004	ILS + BD	LSC	18	100	5	0	100	Y
Niikura [93]	2004	ILS + BD	LAP	20	90	2	0	100	Y
Pijpers [94]	2004	ILS + BD	LSC	34	97	17	1	92	ND
Holub [64]	2004	BD	LSC	7	100	1	0	100	ND
Di Stefano [95]	2005	BD	LAP	50	90	9	1	97	Y
Silva [96]	2005	ILS	LAP	56	93	10	3	92	Y
Angioli [97]	2005	ILS	LSC	37	70	9	0	100	Y
Gil-Moreno [98]	2005	ILS + BD	LSC	12	100	0	0	100	Y
Rob [18]	2005	BD	LSC/LAP	100	80	20	1	99	Y
		ILS + BD		83	96.4	15	0	100	
Lin [99]	2005	ILS	LAP	30	100	7	0	100	Y

BD, blue dye method; ILS, intraoperative lymphoscintigraphy; LSC, laparoscopy; LAP, laparotomy; NPV, negative predictive value; SN, sentinel node; ND, no data.

specific gene expressions can even further increase the detection rate of micrometastases. However, the clinical significance of PCR-detected micrometastases remains controversial and requires further prospective validation in a large series [43,44].

Sentinel node in gynaecological cancers

Vulval cancer

Vulval cancer accounts for only 4% of all gynaecological cancers; the mean age of patients is approximately 75 years. In the UK nearly 1000 new patients are diagnosed and more than 350 die every year (Cancer Research UK). Vulval cancer patients represent a special group in gynaecological oncology; impaired tissue healing capacity due to age and common medical problems (e.g. diabetes, hypoproteinaemia, chronic hypertension, obesity) results in a significant postoperative complication rate. Although, the 85% rate of wound breakdown and the 30%–70% rate of chronic leg oedema following en block radical vulvectomy and bilateral groin node dissection have dropped significantly with the introduction of less extensive surgical techniques, e.g. triple incision technique, radical or wide local excision, the early and late postoperative complication rate following complete groin node dissections are still rankling [45].

As the most significant independent risk factor indicating poor survival is the presence of multiple lymph node metastases, knowledge of the lymph node status is crucial in the selection of a high risk group requiring adjuvant treatment, i.e. radiation or chemoradiation. Inguinal lymph node metastasis in patients with presumed early-stage vulval cancer can be up to 27%, suggesting that the majority of patients undergo a potentially morbid procedure without any benefit [46]. Although some encouraging early reports on ultrasound guided fine needle aspiration of lymph nodes and on a special MRI technique using ultra-small-iron-particle

(Sinerem, Comibdex) have been published, to date there is no reliable method to identify microscopic tumour involvement of the regional lymph nodes[47,48].

In 1979, DiSaia considered the superficial inguinal lymph nodes as the first draining sites in the lymphatic chain of the vulva[49]. He proposed limited inguinal node dissection in the case of negative superficial nodes. However, in a Gynecologic Oncology Group (GOG) study published by Stehman *et al.*, an unexpectedly high incidence of groin node recurrence following superficial groin node dissection was found[50,51]. Recurrence in the groin is known to be most likely fatal in outcome, which emphasises that any attempt to adopt a more conservative approach to groin node dissection must be carefully and critically evaluated.

In 1994, Levenback reported the use of blue dye in the detection of SN(s) in vulval squamous cell carcinoma and found that the presence of metastasis in the SN was representative of the whole inguinal region[11] (see Table 1). In 1997, Decesare *et al.* published the first series on SN detection in vulval cancer using Tc-99m and further studies proved the SN concept to be a feasible and reliable method (Table 1). The negative predictive value of the SN method in vulval cancer appeared to be 100% in most studies, with the identification rate nearly 100% in those studies using the combined method. Skip metastases, i.e. true negative SN (using serial sectioning + IHC) with positive nodes at a higher level in the lymphatic chain, are found rarely; only a few case reports have been published on false negative SNs[40,52,53].

Indication for SND in vulval cancer

The aim of SN detection is purely diagnostic; only patients with clinically negative groin nodes can be considered for SND. Apparently enlarged/metastatic lymph nodes should be completely debulked in a therapeutic manner. The primary tumour should not invade the anus, urethra or vagina and peritumoural injection of dye/tracer should be feasible. Some authors defined a tumour diameter of equal to or less than 4 cm as a critical limit for SND[54].

Technique

The combined use of radiolabelled tracer and blue dye seems to be the most efficient method in the identification of SN in vulval cancer. Lymphoscintigraphy and handheld gamma probe have a high detection rate, which is augmented by the dye; the blue dye in turn can eliminate the 'shine through' effect of the primary lesion and can visualise SNs close to the primary tumour. Tc-99m-labelled colloid (15 mBq) and 2 ml blue dye should be injected subcutaneously into the junction of the tumour and the normal skin, at four sites around the lesion. A total of 60 mBq Tc-99m-labelled colloid and 8 ml blue dye is injected around the tumour. Preoperative administration of Tc-99m 2 h before the operation is feasible for vulval cancer, however, early administration (1 day prior to surgery) and lymphoscintintigraphy can help to roughly localise the SNs. With a handheld gamma probe the SN(s) can be localised, then a minor incision is sufficient to remove the SN(s). The SN must be sent for frozen section analysis; if the frozen section proves positive for metastatic involvement a complete inguinofemoral lymph node dissection (LND) has to be performed. Theoretically, SNs found negative by frozen section have to undergo serial sectioning and IHC, and in the case of a positive result, a second step LND must be carried out. However, until the results of prospective multicentre studies such as the GOG173 and the European trial on the clinical implementation of SN, a complete inguinofemoral LND must be carried out after SND. If there is no SN detected by the combined method, complete inguinofemoral LND must be performed.

Cervical cancer

Cervical cancer is a leading cause of cancer death worldwide; however, the introduction of a well-organised screening program based on cervical exfoliative cytology has diminished its incidence in industrialised countries. According to Cancer Research UK, 3000 patients are still diagnosed with cervical cancer each year, and 1100 patients die of it every year in the United Kingdom. Although surgical treatment has become less radical during the past decades, the current gold standard for the management of patients with stage IA2–IB1 cervical cancer (tumours with a maximum diameter of 4 cm) is still radical hysterectomy with full diagnostic pelvic LND. Knowledge of the pelvic lymph node status is crucial in decision-making about the treatment, as radical hysterectomy has to be abandoned if metastasis is found in the pelvic nodes. The rate of pelvic lymph node metastasis (LNM) for FIGO stage IA2 cancer is 7%, and for IB1 cancer it does not exceed 20%, implying that the vast majority of patients will not benefit from pelvic LND[22]. However, LND is associated with significant complications, e.g. lymphocyst formation, leg oedema, nerve damage, neurogen bladder, which develop more frequently if postoperative radiotherapy is administered[55–57]. Cervical cancer patients with negative pelvic nodes benefit from radical hysterectomy, while those with histologically proven LNM require primary chemoradiation.

In view of the morbidity of pelvic LND, attempts have been made to establish the SN concept in cervical cancer. Since the first study published by Echt *et al.* in 1999, the SN technique has been improved significantly and high detection rates as well as low false negative SN rates have been achieved proving the feasibility of the SN concept in cervical cancer (see Table 2).

Indication and technique

Only patients with clinical stage IA2 and IB1 are candidates for SND. The principles of the method are similar to that of SND in vulval cancer, i.e. the combined detection technique with serial sectioning and IHC can provide the highest identification rate and negative predictive value.

Injection of radioactive tracer subepithelially around the tumour must be performed on the day prior to surgery. Pelvic and abdominal scintigraphy to roughly localise the site(s) of SN(s) has to be done on the same day. The blue dye must be injected into the same sites of the cervix during anaesthetic induction just prior to the operation; a lower amount of blue dye (<4 ml) has been proved to be inferior[13,16,30]. Laparoscopic removal of the SNs guarantees the lowest morbidity[13]. Until results from prospective randomised trials are available, complete pelvic LND in addition to a radical hysterectomy must be performed in the case of negative SN(s).

The SN is located in the obturator region in 43% of cases and in the external iliac region in 45%–84% of cases[13,18,30]. Skip metastasis, i.e. paraaortic lymph node involvement without pelvic SN metastasis is rare and accounts for only 1% of cases[28,30,59]. Parametrial lymph nodes are often involved by tumour cells and represent a difficulty in detection by a handheld gamma probe due to the 'shine through' effect of the primary tumour. However, these nodes are removed if a radical hysterectomy is performed or irradiated in the case of primary chemoradiation.

The data published during the past 6 years provide evidence that SND in cervical cancer is a feasible and highly accurate method to estimate nodal status. The detection rate with the combined method is 80%–100%, the false negative rate is as low as 3%–11% and the negative predictive value is 90%–100% (see Table 2). The application of SND is potentially a useful method to select a subgroup of high risk patients for primary chemoradiation (i.e. positive SNs), by avoiding the morbidity of both radical hysterectomy and complete pelvic LND.

Endometrial cancer

The incidence of endometrial cancer has shown an increasing trend in industrialised countries. In the UK, 6000 new patients with endometrial cancer are diagnosed every year, with a yearly mortality rate of 1500 (Cancer Research UK). Most of the patients (75%) present with early stage disease confined to the uterus. Among patients with LNM, 50% have pelvic LNM only, 30% have both pelvic and paraaortic LNM, and 20% have paraaortic LNM alone. The current standard of surgical treatment is total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH&BSO) with or without LND. The selection of patients who benefit from LND and the extent

of LND, however, still remain controversial. Complete pelvic and paraaortic LND is associated with significant morbidity, e.g. lymphocyst, lymphoedema, ileus, vascular and urologic injuries; however, less than half of the high risk patients will not have any LNM found by conventional histopathology.

There is little evidence on the feasibility of SND in endometrial cancer. The complex lymphatic drainage as well as the difficulty in injecting radioactive tracer preoperatively questions the feasibility and validity of the SN method in endometrial cancer. In the few publications available, the method of delivery of the tracer was either injection into the cervix, subserosally into the corpus, or into the endometrium during preoperative hysteroscopy. Blue dye methods has proved to be highly unreliable with variable detection rates between 0% and 100%[15,17,60–64]. Conclusions are difficult to draw as there was only one study where all patients underwent both pelvic and paraaortic LND. There was no consensus on the detection method for SN(s) as well as on the histopathological method to identify micrometastases. In a series of 28 endometrial cancer patients who underwent office hysteroscopy, subendometrial injection of Tc-99m was performed followed by dynamic scintigraphy. TAH&BSO with pelvic and paraaortic SND + LND using a handheld gamma probe were performed on each patient[62]. A detection rate of 82% and sensitivity of 100% was achieved. Interestingly, SNs were identified by scintigraphy within 10 min after the injection indicating that the injection of the tracer can be performed on the same day as the operation[62].

The high incidence of endometrial cancer, the difficulty of identifying a high risk group preoperatively, and the significant morbidity of pelvic and paraaortic LND indicate that further studies must be conducted on the feasibility and clinical value of the SN concept in endometrial cancer.

Conclusion

With the widespread use of less radical oncosurgical practice, SND has found its clinical role in the management of breast cancer and malignant cutaneous melanoma providing reliable information on the lymph node status with significantly decreased morbidity. Similar trends in gynaecological oncology have been observed in the past decade; according to several small series, the combined use of blue dye and lymphoscintigraphy for SND seems to be a reliable technique for vulval cancer. The role of the SN method for cervical cancer is being delineated but is still equivocal for endometrial cancer. Before the standard application of the SN technique as a diagnostic tool, the results of large multicentre trials must be critically evaluated; it must be proved that SND has no negative impact on survival but reduces morbidity. The SN technique must be standardised, as well as the histopathological evaluation of the SN(s).

The clinical significance of micrometastases detected by highly sensitive techniques, i.e. IHC or PCR, must also be clarified in the future.

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