Application of sentinel nodes in gynaecological cancer therapy

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The sentinel-node procedure was introduced in cancer therapy in order to reduce the morbidity that is associated with full lymphadenectomy without compromising survival rates. In gynaecological cancer the application of the sentinel-node procedure has been investigated in vulvar, cervical, and endometrial cancer.

In vulvar cancer, the Groningen International Study on Sentinel nodes in Vulvar cancer (GROINSS-V) showed that it was safe to omit inguinofemoral lymphadenectomy in patients with a negative sentinel node. Eligible patients who underwent the procedure had unifocal squamous-cell cancer of the vulva, with a maximum diameter of 4 cm and no suspicious groin nodes at palpation. In the case of a negative sentinel node, no inguinofemoral lymphadenectomy was performed, and patients were followed up regularly. Both short-term and long-term treatment-related morbidities were significantly lower when only the sentinel node was removed. Groin recurrences were observed in 2.3% of the patients with a negative sentinel node [1]. An analysis of the patients with a positive sentinel node showed an increasing risk for involvement of non-sentinel nodes with increasing size of the metastasis in the sentinel node. Furthermore, the prognosis was significantly worse for patients with sentinel-node metastases >2 mm [2]. More recently Levenback and colleagues published the results of the Gynaecologic Oncology Group study on the sentinel node procedure in vulvar cancer (GOG-173). They included 452 patients; all patients underwent inguinofemoral lymphadenectomy after sentinel-node detection. They found a false-negative predictive value of 3.7%. In women with a tumour <4 cm, the false-negative predictive value was 2.0%, a result resembling that of GROINSS-V [3]. Pitfalls of the sentinel-node procedure are gross nodal involvement that may obstruct lymph flow and thereby cause bypassing of the sentinel node and confusion about the number of sentinel nodes [4]. Preoperative groin imaging with computed tomography (CT), magnetic resonance imaging (MRI) or ultrasound (US) is mandatory to exclude gross nodal involvement, while preoperative lymphoscintigraphy gives adequate information on the number of sentinel nodes per groin and presence of unilateral or bilateral sentinel nodes. Controversies remain regarding the method of preoperative imaging, the therapeutic benefit of inguinofemoral lymphadenectomy in case of micrometastases in the sentinel node, and alternative treatment options in patients with a positive sentinel node. An ongoing second observational study, GROINSS-V-II, is investigating the safety of radiotherapy instead of inguinofemoral lymphadenectomy in patients with a positive sentinel node. Preoperative imaging is mandatory in this study to exclude gross nodal involvement. The GOG has joined GROINSS-V-II; this international collaboration will help shorten the duration of studies in rare malignancies like vulvar cancer.

In cervical cancer single-institution case series had already demonstrated the feasibility of the sentinel-node concept, when Altgassen and colleagues in 2008 published the results of their multicentre study on the detection rate and diagnostic accuracy. The detection rate of pelvic sentinel nodes was 88.6% in 590 patients. They also showed a significantly higher detection rate when blue dye and a radioactive tracer were combined. The sensitivity was 77.4% overall, but 90.9% in women with tumours $\leqslant$2 cm. They concluded that the sensitivity of the sentinel-node concept was low, but that patients with tumours $\leqslant$2 cm might profit from this concept [5]. The results of the SENTICOL study, by Lécuru and colleagues, showed that in 139 stage IA1 with LVSI-IB1 cervical cancer patients the sentinel-node procedure yielded a sensitivity of 92.0% and a negative predictive value (NPV) of 98.2% for detection of nodal metastasis. No false-negative results were observed in those patients in whom the sentinel node was identified bilaterally. They concluded that the sentinel-node procedure has a high sensitivity and NPV, and is especially reliable in patients in whom the sentinel node is detected bilaterally [6]. These results were confirmed in a recent study by Cibula and colleagues in their study in 645 patients [7]. The same authors showed that the presence of micrometastases in

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the sentinel node was associated with a significant reduction in overall survival, which was equivalent to that in patients with macrometastasis. No prognostic significance was found for isolated tumour cells [8]. Recently a single-institution study showed that when comparing a prospectively collected patient cohort (in whom a pelvic lymphadenectomy was omitted in the case of a negative sentinel node) with historic controls in whom a full lymphadenectomy was performed, the sentinel-node technique yielded a higher proportion of patients with lymph-node metastases, indicating a higher sensitivity of the sentinel-node technique [9]. However, the clinical impact of sentinel-node biopsy in cervical cancer needs to be further evaluated in observational or preferably randomised studies comparing sentinel-node biopsy with sentinel-node biopsy plus lymphadenectomy (NCT01157962).

Finally, in endometrial cancer the sentinel-node procedure is still in a preliminary stage of evaluation. Different techniques of tracer injection have been proposed; however, there is no consensus about the most accurate method for identifying the sentinel node. Cervical and intramyometrial subserosal injections are safe and simple, but probably do not reflect the expected endometrial cancer lymphatic drainage. Also the detection rate is low. Hysteroscopical injection might better reproduce the drainage of the tumour; however, this is complex, costly, and also shows a high variability in detection rate. Different studies showed identification rates varying from 45% to 100% [10]. Recently transvaginal ultrasound-guided myometrial injection of the radioactive tracer was suggested as a safe, feasible method for sentinel-node detection [11].

In conclusion, GROINSS-V and GOG173 have provided adequate evidence for the safety of sentinel-node detection in selected early-stage vulvar cancer patients. The sentinel-node procedure is now part of standard therapy in vulvar cancer patients with a unifocal tumour <4 cm with no palpable lymph nodes. Only in the hands of an experienced multidisciplinary team should the procedure be considered safe. In cervical cancer, the sentinel-node procedure seems a promising tool, especially in patients with tumours $\leqslant$2 cm and when bilateral drainage is found. The results of a large randomised trial comparing sentinel-node biopsy to sentinel-node biopsy plus lymphadenectomy are expected in a few years. In endometrial cancer, studies are still evaluating the best diagnostic method.

Conflict of interest statement

None declared.

REFERENCES

[1] Van der Zee AG, Oonk MH, De Hullu JA, et al. Sentinel node dissection is safe in the treatment of early-stage vulvar cancer. J Clin Oncol 2008;26:884–9.
[2] Oonk MH, Van Hemel BM, Hollema H, et al. Size of sentinel-node metastasis and chances of non-sentinel-node involvement and survival in early stage vulvar cancer: results from GROINSS-V, a multicentre observational study. Lancet Oncol 2010;11:646–52.
[3] Levenback CF, Ali S, Coleman RL, et al. Lymphatic mapping and sentinel lymph node biopsy in women with squamous cell carcinoma of the vulva: a gynecologic oncology group study. J Clin Oncol 2012;30:3786–91.
[4] De Hullu JA, Oonk MH, Ansink AC, et al. Pitfalls in the sentinel lymph node procedure in vulvar cancer. Gynecol Oncol 2004;94:10–5.
[5] Altgassen C, Hertel H, Brandstädt A, et al. Multicenter validations study of the sentinel lymph node concept in cervical: AGO study group. J Clin Oncol 2008;26:2943–51.
[6] Lécuru F, Mathevet P, Querleu D, et al. Bilateral negative sentinel nodes accurately predict absence of lymph node metastasis in early cervical cancer: results of the SENTICOL study. J Clin Oncol 2011;29:1686–91.
[7] Cibula D, Abu-Rustum NR, Dusek L, et al. Bilateral ultrastaging of sentinel lymph node in cervical cancer: lowering the false-negative rate and improving the detection of micrometastasis. Gynecol Oncol 2012;127:462–6.
[8] Cibula D, Abu-Rustum NR, Dusek L, et al. Prognostic significance of low volume sentinel lymph node disease in early-stage cervical cancer. Gynecol Oncol 2012;124:496–501.
[9] Gortzak-Uzan L, Jimenez W, Nofech-Mozes S, et al. Sentinel lymph node biopsy vs. pelvic lymphadenectomy in early stage cervical cancer: is it time to change the gold standard? Gynecol Oncol 2010;116:28–32.
[10] Robova H, Rob L, Halaska MJ, Pluta M, Skapa P. Current status of sentinel lymph node mapping in the management of endometrial cancer. Expert Rev Anticancer Ther 2013;13:55–61.
[11] Torné A, Pahisa J, Vidal-Sicart S, et al. Transvaginal ultrasound-guided myometrial injection of radiotracer (TUMIR): a new method for sentinel lymph node detection in endometrial cancer. Gynecol Oncol 2013;128:88–94.