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Sentinel lymph-node biopsy in endometrial cancer with two different tracers – first results of the prospective observational SNB-CE study

Biopsija varovalne bezgavke pri raku endometrija z dvema označevalcema – rezultati prvega dela prospektivne observacijske raziskave SNB-CE

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Abstract

Background: Endometrial cancer is the most common gynaecologic malignancy in the developed countries. The removal of retroperitoneal lymph nodes is the standard procedure to determine the stage of the disease. Sentry node biopsy (SNB) has been established as a method of choice for surgical staging of preoperatively presumably initial endometrial cancer. In 2014 we started a prospective two-part observational study at the Department of Gynaecological Oncology and Breast Oncology of the University Medical Centre Maribor. Our primary goal was to analyze the rate of SNB detection, while the secondary one was to determine the sensitivity of the SNB method. Our aim was to perform a pilot comparison of the retroperitoneal lymph node evaluation.

Methods: The first part of the SNB-CE study included 45 patients with initial endometrial cancer between 2014 and 2016. In all the patients, preoperative imaging was used to determine the local status of the disease and to confirm the absence of metastases. Initially, radioactive technetium (Tc99) and by the end of 2016 indocyanine green (ICG) were used to label the lymph node. We determined the level of lymph node detection, bilateral lymph node detection, and the sensitivity of the SNB to assess lymph node coverage.

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Results: The rate of detection and removal of the sentinel lymph nodes using Tc99 was 63.6% (CI 95% 55.6 – 87.1%). The nodes were found bilaterally in 52.3%. ICG detection and removal rates were 68.8% (CI 95% 61.2 – 95.0%). Sentinel lymph nodes were found bilaterally in all patients with lymph nodes present in the removed tissue (100%). The detection rate of sentinel lymph nodes using both markers was 87.5% (CI 95% 40.0 – 97.2%), all of them bilateral. The sensitivity of the SNB method to assess the status of retroperitoneal lymph nodes was 66.7%, a false negative lymph node occurred in one patient (2.4%).

Conclusion: There has been great progress in the last decade regarding the use of SNB in endometrial cancer. SNB is already incorporated into protocols of international guidelines. It has been demonstrated that the method has appropriate sensitivity with the ability to appropriately evaluate the stage of disease without systematic lymphadenectomy. Further research will show the feasibility of better tracers, better sites of tracer application as well as the long-term impact on the overall survival rate of patients treated using this method alone.

Izvleček

Izhodišča: Rak endometrija je najpogostejša ginekološka maligna bolezen v razvitih državah. Standardni poseg za določitev stadija bolezni je odstranitev retroperitonealnih bezgavk. Biopsija varovalne bezgavke (SNB) se uveljavlja kot metoda izbire kirurške postavitve stadija pri na videz začetnem karcinomu endometrija po oceni pred operacijo. Na Oddelku za ginekološko onkologijo in onkologijo dojk UKC Maribor smo leta 2014 pričeli izvajati prospektivno observacijsko raziskavo v dveh delih z namenom najprej analizirati stopnjo zaznave SNB in nato določiti občutljivost metode SNB za oceno retroperitonealnih bezgavk, nato pa opraviti pilotno primerjavo teh dveh označevalcev.

Metode: V prvi del raziskave SNB-CE je bilo vključenih 45 bolnic z začetnim rakom endometrija v letih 2014–2016. Pri vseh bolnicah smo pred operacijo s slikovnimi preiskavami opredelili lokalni status bolezni in potrdili odsotnost oddaljenih metastaz. Za označevanje varovalne bezgavke smo uporabljali radioaktivni tehnecij (Tc99) in ob koncu raziskovalnega obdobja leta 2016 zeleni indocianin (ICG). Določili smo stopnjo zaznave varovalne bezgavke, obojestranske zaznave varovalne bezgavke in občutljivost biopsije varovalne bezgavke za oceno zajetosti bezgavk.

Rezultati: Stopnja zaznave in odstranitve bezgavke ob uporabi radioaktivnega označevalca je bila 63,6 % (CI 95% 55,6–87,1 %). Varovalno bezgavko smo našli obojestransko v 52,3 %. Stopnja zaznave in odstranitve bezgavke z ICG je bila 68,8 % (CI 95% 61,2–95,0 %). Varovalno bezgavko smo našli obojestransko pri vseh bolnicah, pri katerih je bila v odstranjenem tkivu varovalna bezgavka (100 %). Stopnja zaznave varovalne bezgavke ob uporabi obeh označevalcev je bila 87,5 % (CI 95% 40,0–97,2 %), pri vseh obojestransko. Občutljivost metode varovalne bezgavke za oceno statusa retroperitonealnih bezgavk je bila 66,7 %, le pri eni bolnici je bila varovalna bezgavka lažno negativna (2,4 %).

Zaključek: Področje uporabe SNB pri raku endometrija je v zadnjem desetletju odločilno napredovalo. Uporabljena metoda je postala že del protokolov mednarodnih priporočil. Metoda ima dobro občutljivost in zmožnost ocene stadija bolezni brez potrebe po sistematični limfadenektomiji. Nadaljnje raziskave bodo pokazale, ali obstajajo boljši označevalci in boljša mesta apliciranja označevalca ter dolgoročni vpliv na celokupno preživetje bolnic, pri katerih se uporablja zgolj ta metoda.

1 Introduction

Endometrial cancer is the most common gynaecological cancer in the developed world with an incidence rate of 13.6 per 100,000 women. 80% of patients are diagnosed early. The five-year survival rate in early, regional and metastatic disease is 95%, 68% and 17%, respectively (1). When imaging methods fail to show evidence of disease outside the uterus, surgical treatment of the presumed early-stage endometrial cancer follows with hysterectomy and adnexectomy (2). Due to the possibility of regional lymph node metastases, even in the early stage of endometrial cancer, surgical staging, classically performed with lymphadenectomy, is also recommended.

Sentinel lymph node biopsy (SNB) has established itself as a surgical staging method of choice in presumed early-stage endometrial cancer. It is minimally invasive compared to pelvic and paraaortic lymphadenectomy and also enables sentinel lymph node ultrastaging, leading to better identification of micrometastases or isolated tumour cells. SNB is an acceptable compromise between the more extensive lymphadenectomy (LND), which leads to increased morbidity without improving survival rates, and surgery without surgical staging. Different sites have been investigated in the past for the detection of sentinel lymph nodes using ultrastaging with contrast agent applications. The cervix has proven to be

the most accessible site with a high sentinel lymph node detection rate. Contrast agents researched and used to identify sentinel lymph nodes in endometrial cancer are radioactive technetium-99 (Tc-99), blue dye (methylene and isosulfan), and indocyanine green (ICG).

In 2014, the Department of Gynaecological Oncology and Breast Oncology at the University Medical Centre Maribor began conducting a prospective observational study in two parts. The first part, the primary purpose, was to determine the level of sentinel lymph node detection and the secondary was to determine the sensitivity of SNB for the assessment of retroperitoneal lymph nodes; the aim was to perform a pilot comparison of the two different retroperitoneal lymph node evaluation methods. In this article, we present the results of the first part of the study, which included patients up to the end of 2016.

2 Methods

The study, called SNB CE, was conducted between 2014 and 2016 and included all consecutive patients with early-stage endometrial cancer, all of whom agreed to participate in the study and signed an informed consent form. In all patients, we used preoperative imaging methods (gynaecological and abdominal ultrasound and chest radiography) for local staging and to confirm the absence of distal metastases. The radioactive isotope Tc99 was used to label the sentinel lymph node; at the end of the research period in late 2016, we obtained appropriate technical support for the introduction of another marker, namely indocyanine green (ICG). We have used both markers since.

We injected the Tc99 radioactive isotope into the cervix at least two hours before surgery, but no more than 16 hours beforehand. Four syringes containing 1 mCi (40 MBq) each were used for the submucosal injections of the isotope in four quadrants of the cervix at the 3, 6, 9 and 12 o'clock positions. Therefore, the cumulative dose of the radioactive marker was 4 mCi (150 MBq). We used the NANOCOLL 500 mcg kit (GE Healthcare, Chicago, Illinois, ZDA).

During surgery, the pelvis and lower paraaortic area (under the inferior hypogastric artery) were examined for the presence of the sentinel lymph nodes. The peritoneum was opened above the fluorescent or Tc99-labelled lymph ducts and/or lymph nodes. If no such sites were detected prior to peritoneal opening, the retroperitoneal space above the external and common iliac vessels was accessed, and the paravesical and lateral pararectal spaces were carefully dissected for a more detailed examination. Before dissecting individual sites, radioactive areas were first searched in stages during the procedure.

It was important that we first imaged and recorded radioactive areas before turning on the infrared light (in patients in whom ICG was also used). Afterwards, we then turned on the infrared light and looked for ICG positive areas. Only after locating all radioactive/fluorescent sentinel lymph nodes separately on each side of the pelvis were all lymph nodes removed separately in three groups: a) radioactive; b) fluorescent; c) radioactive and fluorescent. We then prepared these three groups of lymph nodes for pathological examination.

After removing the sentinel lymph nodes(s), a systematic pelvic LND was made, which included the external iliac, obturator and common iliac regions. Type I dissection was performed as suggested in the standardization of the procedure (3). Total hysterectomy with bilateral adnexectomy was performed in all patients.

Statistical data processing followed. We determined the level of sentinel lymph node detection, defined as the proportion of patients in whom the sentinel lymph node was found, and the level of bilateral sentinel lymph node detection, defined as the proportion of patients in whom the sentinel lymph node was found in both hemipelves. The SNB sensitivity was calculated to assess the status of the retroperitoneal lymph nodes and the percentage of false-negative sentinel lymph nodes. We used descriptive statistics in the SPSS program. The study was approved by the Republic of Slovenia National Medical Ethics Committee (19. 3. 2014; UKC-MB-KME-10/14).

3 Results

We included 45 women with endometrial cancer in the study. Their basic characteristics are presented in Table 1. Most patients had type I endometrial cancer (endometrioid cancer); others had type II.

Among the 45 patients who participated in the study, 29 (64.4%) patients received a radioactive marker (Tc99), eight (17.8%) ICG and eight (17.8%) both markers.

We included 37 patients in the Tc99-labelled group. During surgery, unplanned technical problems arose in four patients, which led us to withdraw from further attempts at SNB. In the group that had Tc99-labelled SNB (n = 33), we found the radiation site in 28 women (84.8%). In all patients in whom a radiation site was found, the removed tissue was then sent for histological examination. In 7 out of 28 cases, the pathohistological examination showed that only fat tissue was removed instead of a lymph node. Overall, the method allowed us to adequately detect lymph nodes on at least one side in

Table 1: Patient characteristics.

Mean age (n=45)		65.4 ± 10.7 years
Disease stage (FIGO)	I	35 patients (77.8%)
	II	3 patients (6.7%)
	III	6 patients (13.3%)
	IV	1 patients (2.2%)
Histological type of cancer	type I	40 patients (88.9%)
	type II	5 patients (11.1%)
LVSI presence		18 patients (40.0%)

Legend: FIGO – The International Federation of Gynecology and Obstetrics, LVSI – lymphovascular invasion.

21 out of 33 cases, i.e. 63.6% (CI 95% 55.6–87.1%). The sentinel lymph node was found bilaterally in 11 out of 21 patients in whom the true sentinel lymph node was removed, i.e. 52.3%.

In the ICG-labelled group (n = 16), the fluorescent region was identified in 15 out of 16 patients (93.75%). In four cases (25%), the pathohistological examination showed that only fat tissue was removed instead of a lymph node. With the use of ICG, the rate of lymph node detection and removal was 68.8% (CI 95% 61.2–95.0%). The sentinel lymph node was found bilaterally in all 11 patients in whom the sentinel lymph node was actually found in the removed tissue (100%).

In eight patients, both markers were injected and analyzed, and the sentinel lymph node was identified in 7 out of the 8 (87.5%) patients (CI 95% 40.0–97.2%). The sentinel lymph node was identified by both methods in five patients (62.5%). In one patient, the sentinel lymph node was identified with Tc99 only, and in one patient with ICG only. In one patient, no sentinel lymph nodes were found by any method. In cases where the sentinel lymph node was identified, using both markers was successful in bilateral identification of the sentinel lymph nodes. In 80% of patients in whom a sentinel lymph node was found with both markers, the sentinel lymph nodes differed with different markers, thus showing different lymph nodes. In one case, the lymph nodes also differed histologically (the radiolabelled lymph node was negative and the ICG-labelled lymph node was positive).

In systematic type I LND, which followed SNB, 23.1±11 (median 22.0) lymph nodes were removed on average. Overall, we examined the success of sentinel lymph node labelling in 41 patients, as four patients experienced technical problems that were unrelated to the sentinel lymph node marker. In 82.9% of patients (n = 34), the sentinel lymph node area was detected and removed. In 31 out of 41 patients, the sentinel lymph nodes found with Tc99 or ICG were negative. In 2 out of 41 patients, the sentinel lymph node was positive, and the other lymph nodes were negative, and in one patient, the sentinel lymph node was a false negative. In 11 out of 45 patients, however, we did not detect or search for sentinel lymph nodes.

The SNB sensitivity for correctly assessing the lymph node status was therefore 2/ (2 + 1), 66.7%. One out of 41 patients had a false negative sentinel lymph node (2.4%).

4 Discussion

Our results showed that the sentinel lymph node detection rate was above 80% and highest when both markers were used. The sentinel lymph node detection rate when using Tc99 alone was 63.6%, and when using ICG alone, 68.8%. The SNB sensitivity for correctly assessing the status of retroperitoneal lymph nodes was 66.7%, and in 2.4%, the protective lymph node was false negative.

The main goal of SNB is to find the first sentinel lymph node involved in the metastatic spread of cancer (2). Past studies and their meta-analysis showed a 70-100% detection rate of the sentinel lymph node, depending on the type of marker used and site of its application. The highest levels of sentinel lymph node detection were achieved with cervical marker application using ICG or a combination of a radiolabelled marker with blue dye (4-6). Our results are similar to the first published results in the literature, as is common when introducing a method into clinical practice, when lower levels of sentinel lymph node detection are expected due to the learning curve (5). This was also the reason we found the sentinel lymph node more frequently with a combination of two

markers. In the first patients, we had a relatively high proportion of patients in whom the radioactive parts (7 out of 33 patients) or fluorescent parts (4 out of 16 patients) were removed, but histological analysis showed only fat tissue without lymph nodes. This is also expected when introducing a new method into clinical practice. It should be noted that obesity is an important risk factor for the most common endometrioid carcinomas of the endometrium (7). Obesity and thus poorer visibility of the retroperitoneum during surgery can make it difficult to find a sentinel lymph node (8-10). Thus, the gamma camera can detect radioactivity hiding deeper under the fat. However, when using ICG, capillaries can become damaged despite exercising extreme caution, and small amounts of spilled blood can fluoresce, thus showing a false location of the sentinel lymph node. Therefore, after removal of the sentinel lymph nodes, type I LND was performed in the included patients in accordance with the recommendations (3), thus avoiding a potentially worse oncological treatment outcome.

We found the sentinel lymph nodes in both hemipelves in only 52.3% of patients with the Tc99 radioisotope, and in 100% of patients with ICG, in whom the true sentinel lymph node was removed. Results are consistent with those from the literature, where it was shown that the use of ICG or a combination of multiple markers is connected with the highest level of bilateral lymph node detection (8,11-17). The recently published report by Čas et al. (18), who reported on their experience using ICG for sentinel lymph node detection, is consistent with our results. In their analysis, the sentinel lymph node was recognized with ICG unilaterally in 85.7% of cases and bilaterally in 80% of patients (18).

In the literature, the importance of bilateral sentinel lymph node detection is emphasized, i.e. that the sentinel lymph node is found and removed in both hemipelves. Studies have shown a high proportion of false negative sentinel lymph nodes in cases of unilateral removal. Abu-Rustum et al. have shown that the proportion of false negative lymph nodes dropped from 15% to 2% when using a protocol in which lymphadenectomy was performed on the side where the sentinel lymph node was not found (4,19,20).

According to our data, the SNB sensitivity is relatively low (66.5%), which we attribute to the learning curve and a small sample size. Therefore, the proportion or patients with positive lymph nodes was low (4%). In the literature, the method's sensitivity is reported to be 77–98% with 4.2–23% of false negative lymph nodes (18,20-24). In our study, the proportion of false negative lymph nodes was low (2.4%), which can be partially attributed to the small sample size and a low proportion of patients with positive lymph nodes.

The role of systematic lymphadenectomy in the surgical treatment of early-stage endometrial cancer is still unclear, as research has shown that it does not affect survival but affects staging and adjuvant therapy (radiotherapy, chemotherapy) (1,3,26). Indications, anatomical aspects and the extent of lymphadenectomy are still a matter of discussion and individual decision, although proposals are emerging to standardize surgery for individual cancers (1,3). Therefore, the main purpose of a lymphadenectomy is to determine the disease stage. In early-stage endometrial cancer, risk factors for positive lymph nodes include the myometrial invasion depth of more than 50%, positive peritoneal cytology, presence of disease in the cervix, adnexa or omentum, tumour size more than 3 cm and non-endometrioid histology (27,28).

One of the main additional advantages of detecting sentinel lymph nodes is detecting low-volume metastases with sentinel lymph node ultrastaging. Metastases with small numbers of cancer cells include isolated tumour cells and micrometastases (29). This method enables micrometastasis detection, thus increasing the disease stage in early-stage endometrial cancer where lymphadenectomy might have been omitted (2). In our study population, micrometastases were present in one patient.

According to European guidelines, SNB could be a compromise between systematic lymphadenectomy, which is associated with increased post-operative morbidity and does not lead to increased survival, and no lymphadenectomy (1). The recommendations also state that SNB increases the micrometastasis and individual tumour cells detection rate, although the significance of these findings remains unclear (1).

According to the consensus ESMO-ESTRO-ESGO guidelines for endometrial cancer, lymphadenectomy is not indicated in patients with low-risk endometrial cancer (grades 1 or 2 with <50% myometrial invasion depth), as the risk of nodal involvement is low in these patients (1). The metastatic risk increases with disease stage. Despite this, preoperative disease staging does not often correlate with final staging, which is higher at 15–27% (26). None of the methods used to evaluate preoperative myometrial invasion depth or retroperitoneal lymph nodes (ultrasound and MRI) can reliably replace surgical staging. Because lymphadenectomy is no longer recommended in low-risk patients, and because low-risk cancer may be assessed as low-risk or medium-risk after surgery, SNB may prevent the need for reoperation;

systematic lymphadenectomy with all its complications is also not required.

Based on the results of our research, we recommend lymphadenectomy in moderate- and high-risk patients with endometrial cancer when SNB is being introduced, during the learning curve period. Therefore, the method is safe and effective when the centre and surgeon perform a sufficient number of yearly procedures, which is why centralization of hospitals into larger centres is advised. SNB is also associated with additional technological requirements and thus higher costs, which again speaks in favour of centralization. In our research, we also showed that the sentinel lymph nodes may differ when labelled with different markers under different protocols, which will require further investigation and appropriate caution. If at all possible, for the moment we advise that at least two markers are used, as this increases the rate of sentinel lymph node detection. At our department, the SNB-CE 2 study is already underway. Its primary outcome measure is sentinel lymph node detection with two different markers, and the secondary outcome measures are finding whether the sentinel lymph nodes match when labelled with two different markers under different protocols, as well as the effect of the protocol on the short-term oncological outcome by sentinel lymph node detection and omission of systematic lymphadenectomy in the hemipelvis when no sentinel lymph node is found. The study is not yet finished. The possibility of staging without systematic lymphadenectomy is of particular importance, particularly in low- and medium-risk cases of endometrial cancer. Further research will also show whether there are better sites for contrast agent application.

5 Conclusion

Much has been achieved in the last decade in the area of SNB in endometrial cancer. In some centres, SNB is already being used in clinical practice and surgery as a standard staging technique for endometrial cancer, and the method is already included in the protocols of international recommendations. Labelling with the studied markers shows an appropriate level of sensitivity with a low value of false negative results. Further research will show whether there are better sites for the application of contrast agents, the need to use more markers, and the long-term impact on the overall survival of patients using only this method.

Conflict of interest

None declared.

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