Sentinel lymph node detection with the use of SPECT-CT in endometrial cancer – analysis of two cases

Identyfikacja węzła wartowniczego z wykorzystaniem SPECT-TK w raku trzonu macicy – analiza dwóch przypadków

Sawicki Sambor[1], Kobierski Juliusz[1], Cytawa Wojciech[2], Wydra Dariusz[1]

[1] Department of Gynecology, Oncologic Gynecology and Gynecologic Endocrinology, Medical University of Gdańsk, Poland

[2] Department of Nuclear Medicine, Medical University of Gdańsk, Poland

Abstract

On the basis of two cases we discuss the important issues regarding the sentinel lymph node detection biopsy (SLNB) in endometrial cancer with combined cervical administration of the radiocolloid and the subserosal blue dye injection.

The first patient (endometrioid adenocarcinoma G2, invasion >50% myometrium) had 4 SLNs detected. Three were both hot and blue (detected on SPECT-CT). The fourth, paraaortic SLN was blue only. None of the lymph nodes contained metatstases.

The second patient (endometrioid adenocarcinoma G1, invasion >50% myometrium) had 4 SLNs detected. Three were blue (but two of them had also very low radioactivity). The fourth SLN was hot only. Blue only node contained macrometastasis. In the past patients underwent cervical amputation.

Diverse distribution of each tracer confirms the advantages of the combined tracers administration in SLNB. The radiotracer is the crucial component - uptake was present in 6 of 8 SLNs. Although the blue dye is more a complimentary method, its suberosal injection significantly increases the safety of the SLNB procedure. In the first case we have detected blue only SLN in paraaortic region which otherwise would be missed using the cervical approach only. More importantly, in the second case the tracer uptake was very limited due to the previous surgery and the blue dye administration allowed correct SLNs detection (including the metastatic node).

Presented clinical cases confirms that the combined cervical and subserosal tracers administration together with preoperative SPECT-CT constitute an optimal SLN detection method and correctly provides information about the regional lymph node status.

Keywords: **sentinel lymph node** / **endometrial cancer** / **lymphoscintigraphy** / / **SPECT-CTs** /

Corresponding authors:
Sambor Sawicki
Department of Gynecology, Oncologic Gynecology and Gynecologic Endocrinology
Medical University of Gdańsk, ul. Kliniczna 1 A
80-402 Gdańsk, Poland
fax: 058 341 80 03
e-mail: sambor@gumed.edu.pl

Otrzymano: **05.12.2011**
Zaakceptowano do druku: **10.08.2012**

Streszczenie

Na podstawie dwóch przypadków przedstawiono najważniejsze kwestie dotyczące techniki detekcji węzła wartowniczego (SLNB) w raku trzonu macicy przy zastosowaniu doszyjkowego podania radiokoloidu oraz podsurowicówkowego podania błękitu metylenowego.

U pierwszej pacjentki (gruczolakorak endometrialny G2, inwazja >50% mięśniówki) wykryto 4 SLN. Trzy były aktywne i niebieskie (potwierdzone w SPECT-TK), czwarty (przyaortalny) były tylko niebieski. W węzłach chłonnych nie stwierdzono przerzutów.

U drugiej pacjentki (gruczolakorak endometria lny G2, inwazja >50% mięśniówki) wykryto 4 SLN. Trzy były tylko niebieskie (ale dwa posiadały również bardzo niską aktywność), czwarty był tylko aktywny. Jeden tylko niebieski SLN zawierał przerzuty. Pacjentka w przeszłości przeszła amputację szyjki macicy.

Zróżnicowana dystrybucja znaczników potwierdza przydatność podania skojarzonego w detekcji SLN. Radiokoloid jest podstawową składową SLNB – aktywność wykryto w 6 z 8 wartowników. Mimo, że zastosowanie błękitu metylenowego stanowi metodę dodatkową, jego podanie podsurowicówkowe istotnie zwiększa bezpieczeństwo techniki.

W pierwszym przypadku wykryto niebieski przyaortalny SLN, który nie został by wykryty przy podaniu doszyjkowym. Co więcej, w drugim przypadku, wychwyt radiololoidu był znacznie ograniczony z powodu amputacji szyjki macicy – podanie błękitu metylenowego umożliwiło wykrycie SLN (w tym jednego z przerzutami). Przedstawione przypadki potwierdzają, że skojarzona technika wykrywania SLN z podaniem doszyjkowym radiokoloidu oraz podsurowicówkowym błękitu i zastosowaniem SPECT-TK stanowi optymalna metodę detekcji i właściwie ocenia status regionalnych węzłów chłonnych.

Słowa kluczowe: **węzeł wartowniczy** / **rak trzonu macicy** / **limfoscyntygrafia** / / **SPECT-TK** /

Introducion

The endometrial cancer is the fourth most frequent cancer in women in Poland with 4820 new cases in 2008 (1). Moreover the incidence of the endometrial cancer is still increasing – the burden of treatment will be even more important in future [1].

The sentinel lymph node biopsy (SLNB) has become a standard technique in malignant melanoma and breast cancer (2,3), in gynecologic oncology feasibility and safety of SLNB was confirmed in vulvar cancer [4] and cervical cancer [5, 6]. The first report on SLNB in endometrial cancer was published in 1996 by Burke et al [7]. In a recent meta-analysis of 26 studies on SLNB in endometrial cancer in 1101 procedures the detection rate and the sensivity was 78% and 93% [8]

There are two theoretical indications for SLNB in endometrial cancer. First one regards the patients with high risk of the nodal metastases (serous or clear-cell type, grade 3, more than 50% of myometrial invasion). In this group radical pelvic and paraaortic lymphadenectomy is indicated but in cases where no metastases are found this procedure provides no benefits for the patient and only increases the risk of the perioperative morbidity. Thus in this group the identification of negative SLNs could effect in abandoning the unnecessary lymphadenectomy. Also in patients with significant contraindications for surgery (e.g. morbid obesity), when the lymphadenectomy will not be performed, the SLNB might be the alternative for lymph node status evaluation. This can lead to better postoperative analysis of indications for the adjuvant treatment.

The second application of the SLNB regards the patients with low risk of the nodal metastases. There is a significant discrepancy between the preoperative/intraoperative and the final pathologic diagnosis. In two studies analyzing the concordance of the preoperative and postoperative pathological diagnosis, the tumor grade changed from the grade 1 to grade 2 or 3 in 23-29% of cases [9, 10].

Case et al. compared the intraoperative frozen section to the final results and found that depth of invasion and the tumor grade was upstaged in 28% and 38% respectively [11]. These data show that in some cases the adequate surgical staging is not done although indicated. In such cases the SLNB would provide information about the nodal status and help to determine adequate further treatment.

Single-photon emission computed tomography fused with computed tomography (SPECT-CT) is a nuclear medicine imaging technique providing three-dimensional image of the radioactive agent (nanocolloid-Tc99m) distribution imposed on a tomographic scan. This method allows precise preoperative localization of the sentinel lymph nodes. The SPECT-CT have been recently incorporated in the sentinel lymph node detection procedure in endometrial cancer [12].

In this paper we would like to present two interesting, representative cases in which we have performed the sentinel lymph node detection technique – on this basis the most important issues regarding this method will be discussed.

Material and methods

From February to November 2011, 44 patients with biopsy proven endometrial cancer were included in a prospective, non-randomized study analyzing the feasibility of SLNB. From this group two cases has been described. Inclusion criteria were: endometrial cancer (endometrioid, clear cell, serous), grade 1-3, no evidence of disease outside the corpus, no contraindications for the abdominal surgery. Patients with prior radiotherapy of the pelvis or pelvic lymphadenectomy were excluded.

Preoperative evaluation was based on physical and gynecological examination, chest x-ray, MRI, transvaginal ultrasound and routine laboratory tests. Therapeutic strategy was based on the presence of the nodal metastases risk factors. The pelvic and paraaortic lymphadenectomy was performed in

case of: serous or clear-cell type, grade 3, more than 50% of myometrial invasion and cervical involvement. In remaining patients ("low-risk" group) only the sentinel lymph node biopsy was performed. The SLN were submitted for the ultrastaging (200µm, H&E, AE1/3), all remaining lymph nodes have been submitted for the routine pathological examination (H&E).

The study was approved by the Medical University of Gdańsk Ethics Committee, all the patients signed informed consent before study procedures.

SLN detection technique

On the day of surgery in the Department of Nuclear Medicine two superficial cervical injections of the Tc^{99m} labelled nanocolloid were administrated (1ml, 0,5mCi, Nano-Albumon, Medi-Radiopharma). After 60 minutes the SPECT-CT was performed. Any focal activity in the pelvis or abdomen was identified as a potential SLN. During surgery, four subserosal injections to the uterine fundus were done with the blue dye (Oterop Methylenblau, Sterop Pharmacobel). After opening the retroperitoneal space the SLNs were detected using the hand-held gamma probe (Neoprobe 2000, Neoprobe Corporation) and direct visualization of the blue nodes. According to the intraoperative findings the SLNs were labeled as "hot" and/or "blue". The definition for the detection of the SLNs was: the activity of at least 10-times above background and/or presence of the blue stained capsule or visible blue lymphatic vessels leading directly to the node.

Case reports

Case no 1.

Women 62 years old, with diagnosis of endometrioid adenocarcinoma G2. Patient had no comorbidities nor previous operations. Patient's weight was 68cm, height 164cm and BMI 25.3. Preoperative evaluation revealed tumor invading more than 50% of the myometrium. On SPECT-CT there were three active sites: right external iliac, right common iliac and left obturator (Figure 1).

Patient underwent total abdominal hysterectomy, bilateral salpingoophorectomy and pelvic/paraaortic lymphadenectomy. During the surgery 4 SLNs were detected. Three of them were both hot and blue, their localization corresponded with the preoperative SPECT-CT: right external iliac, right common iliac and left obturator. All 3 SLNs were highly active (app. 3000-11000 cps), the background activity was 40-60 cps. The fourth SLN was only blue and was located in left paraaortic region.

Pathological examination confirmed the preoperative diagnosis (endometrioid adenocarcinoma G2), the tumor infiltrates more than 50% of the myometrium and extends to the cervical canal, there were no nodal metastases (FIGO II). The total number of resected lymph nodes was 39 (19 pelvic and 20 paraaortic). Peritoneal cytology was negative.

Case no 2.

Women 62 years old, with diagnosis of endometrioid adenocarcinoma G1. Patient had arterial hypertension and underwent cervical amputation due to pelvic organ prolapse in the past. Patient's weight was 78cm, height 159cm and BMI 30.9. Preoperative evaluation revealed tumor invading less than 50% of the myometrium. SPECT-CT detected no active sites.

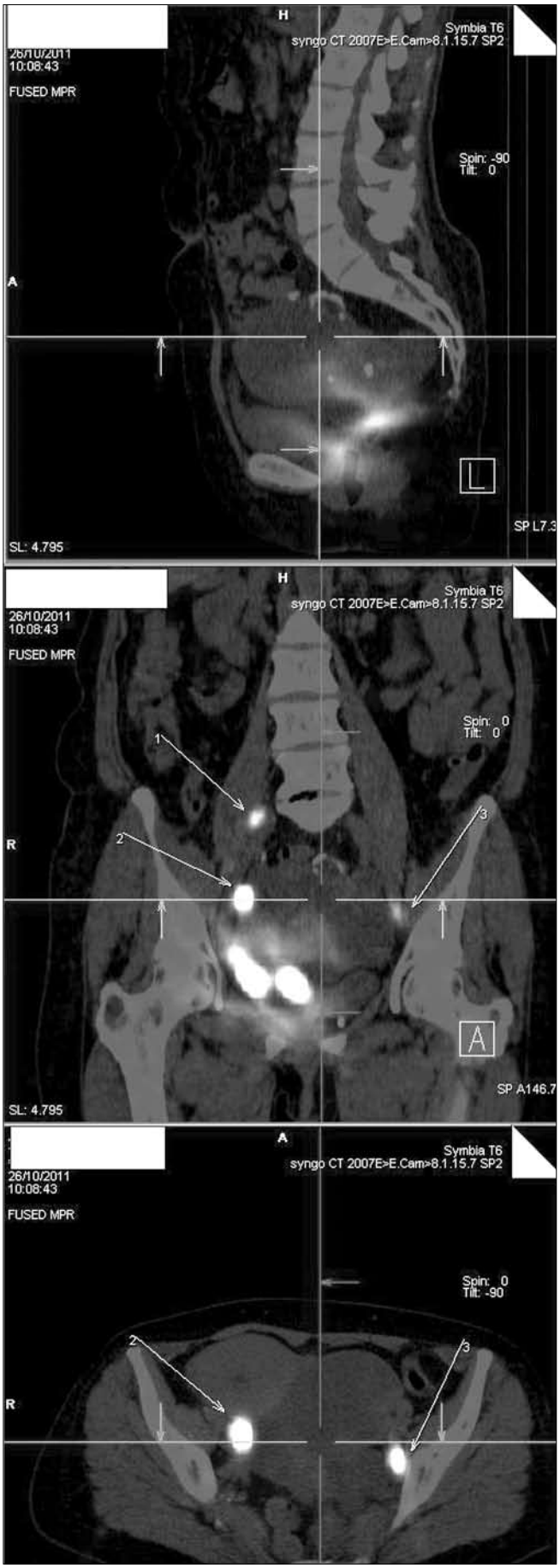

Figure 1. SPECT-CT scans of the detected sentinel lymph nodes in the first case.

Patient underwent total abdominal hysterectomy, bilateral salpingoophorectomy and pelvic lymphadenectomy. During the surgery 4 SLNs were detected. Three of them were blue: right external iliac, left external iliac and left obturator. The fourth SLN was hot only (app. 600 cps) and was located in left common iliac region. After removing the lymph nodes in two external iliac blue SLNs also a very low activity was detected (app. 200 cps). The background activity was 30-60 cps, there was also unusual, remarkably low parametrial activity.

Pathological examination diagnosed endometrioid adenocarcinoma G2 (upgraded in comparison to preoperative diagnosis), the tumor infiltrates more than 50% of the myometrium (the involvement of the outer half of myometrium was found only on microscopic evaluation). In one SLN (left obturator, blue only) the cancer macrometastasis was found, the remaining lymph nodes were negative (FIGO IIIC1). The total number of resected lymph nodes was 25. Peritoneal cytology was negative.

Discussion

Presented cases allow to extensively discuss the most important issues regarding the SLNB in endometrial cancer. In general, both cases confirm the feasibility of the method – SLNs were detected bilaterally, moreover in the second case the SLN was metastatic.

An important issue regarding the potential use of the SLNB in endometrial cancer regards the evaluation of the appropriate tracer injection site. It is not yet confirmed which technique (cervical, histeroscopic or submucosal injections) would precisely reflect the lymphatic drainage from the tumor site. We have decided to include the cervical and subserosal tracers administration due to higher detection rates reported in the literature [8-10, 13]. In a recent meta-analysis of 1101 SLNB procedures in endometrial cancer the superior detection rated was related with the cervical injection comparing to the hysteroscopic approach [8]. Robova et al. compared the hysteroscopic and subserosal tracers administration and obtained significantly lower detection rate with the hysteroscopic injection (50% vs. 73,1%) [13].

Diverse distribution of each tracer in our two cases confirms the advantages of the combined cervical administration of the radiocolloid and the subserosal blue dye injection. Most important component of the SLN detection is the administration of the radiocolloid. It allows preoperative detection of the potential SLNs, during surgery SLNs are precisely located with the handheld gamma-probe before tissue preparation. The cervical way of administration is very convenient and easy. Its accuracy has been already confirmed by the studies on SLNB in cervical cancer [5, 6]. In our two cases the radiotracer uptake was present in 6 of 8 SLNs (although in two SLNs with insufficient activity due to previous cervical surgery). The main issue regarding this approach is whether the cervical injection adequately corresponds with the lymphatic drainage from the uterine corpus. The data from studies analyzing the metastatic patterns in endometrial cancer suggest that in most of the cases metastases are found in pelvic region and isolated paraaortic metastases are rare. Abu-Rustum et al. described the incidence of isolated paraaortic nodal metastasis in patients with negative pelvic lymph nodes. In the group of 734 patients with negative pelvic nodes there were only 12 cases (1.6%) with positive paraaortic nodes [14]. In similar study Hirahatake et al. evaluated the incidence of lymph nodes metastases in a group of 200 patients with endometrial cancer. Pelvic lymph node metastases were observed in 20%, paraaortic lymph node metastasis were found in 9%. In analyzed group in 88,9% of the cases of positive paraaortic metastases the pelvic nodes were also involved. Only in two cases (2/200) there were isolated paraaortic metastases (1%) [15].

Those data suggest that in endometrial cancer the paraaortic metastases mostly derive from the pelvic metastases.

In order to detect potential SLNs in paraaortic region we decided to administrate the blue dye superficially to the uterine fundus. The cervical injection of the blue dye would double the radiocolloid nodal uptake, resulting only in better visualization of the SLNs.

Although the blue dye administration is rather a complimentary method in SLNB its suberosal injection significantly increases the safety of the procedure. In the first case we have detected blue only SLN in paraaortic region, which otherwise would be missed using the cervical approach only. More importantly, in the second case the tracer uptake was very limited due to the previous surgery and the blue dye administration allowed correct SLNs detection (including the metastatic node).

The intraoperative detection of the blue only SLN is difficult when the node is not located just under the peritoneum. From our experience, in most cases it is possible to find very fine, intensively blue, lymphatic vessels leading directly to the SLN – this allows SLN detection even in obturator fossa or high in paraaortic region.

The detection of the metastatic SLN in the second case is an extremely important finding and is a crucial argument confirming the potential application of the SLNB into the treatment protocol. In this patient the initial diagnosis was the endometroid adenocarcinoma G1, during preoperative evaluation the deepness of tumor invasion was less that 50% of the myometrium so there were no indications for the lymphadenectomy. Even on macroscopic pathological examination the tumor invasion seemed confined to the internal half and the largest diameter of the tumor was 15mm. Finally, only the microscopic evaluation revealed tumor invasion of more than 50% and detected grade 2. In such patient the nodal status after initial surgery remains uncertain. Direct adjuvant radiotherapy without confirmation of the nodal involvement would be unreasonable due to general low incidence of nodal metastases – this would probably lead to overtreatment. For the same reason additional surgery in most cases would not provide any benefit and could only lead to higher morbidity due to high incidence of significant co-morbidites, advanced age and obesity. Thus this case clearly shows that the SLNB may improve the surgical staging in presumably "low risk" patients and decrease the unnecessary surgery or adjuvant radiotherapy. Moreover the SLN might be send for the intraoperative frozen section and in case of metastases radical lymphadenectomy could be performed. On the margin, the randomized studies have not confirmed therapeutic impact of the pelvic and paraaortic lymphadenectomy thus the positive SLN might be sufficient reason for adjuvant radiotherapy [16, 17]. Of course, this is only a hypothesis which needs to be confirmed in prospective studies.

The first case shows also potential limitation of the cervical administration. Previous cervical amputation caused almost complete blocking of the tracer flow. Although such cases are rare, this type of the surgery should be regarded as contraindication for the cervical approach in SLNB.

Another interesting aspect of the combined tracers administration used in our study is the presence of the SLNs that are both hot and blue. Despite different sites of the tracers injection such SLNs were found in both cases (although in case no 2 with limited activity). This suggests that frequently the lymphatic drainage from the corpus and the cervix has uniform route. This observation is concordant with studies analyzing the localization of the nodal metastases in endometrial cancer mentioned above [14, 15].

The SPECT-CT incorporated to the SLNB in our study is an useful method which enables precise localization of the potential SLN. In general, most of the necessary data regarding the SLNs location are provided with the planar lymphscintigraphy or the SPECT alone but the addition of the tomographic imaging enables the anatomical localization of the SLNs. This constitutes the most important advantage of this technique which prevents overlooking the SLNs and allows less extensive tissue preparation during the SLNB. In the second case SPECT-CT did not show any active spots although during the surgery we have found one SLN with sufficient activity (app. 600 cps). The potential explanation is that the tracer uptake was significantly delayed due to impaired lymphatic drainage (cervical amputation), and was not present in the SLN at the time of SPECT-CT.

Conclusions

Presented clinical cases confirms that SLNB in endometrial cancer is feasible and correctly provides information about the nodal status. The combined cervical and subserosal tracers administration together with preoperative SPECT-CT constitute an optimal detection method.

References

1. Wojciechowska U, Didkowska J, Zatoński W. Nowotwory złośliwe w Polsce w 2008 roku. Warszawa: *Centrum Onkologii Instytut.* 2010.
2. Garbe C, Eigentler T. Diagnosis and treatment of cutaneous melanoma: state of the art 2006. *Melanoma Res.* 2007,17, 117–127.
3. Sato K, Shigenaga R, Ueda S, [et al.]. Sentinel lymph node biopsy for breast cancer. *J Surg Oncol.* 2007, 96, 322–329.
4. Van der Zee A, Oonk M, De Hullu J, [et al.]. Sentinel node dissection is safe in the treatment of early-stage vulvar cancer. *J Clin Oncol.* 2008, 26, 884-889.
5. Wydra D, Sawicki S, Wojtylak S, [et al.]. Sentinel node identification in cervical cancer patients undergoing transperitoneal radical hysterectomy: a study of 100 cases. *Int J Gynecol Cancer*. 2006, 16, 649-654.
6. Diaz J, Gemignani M, Pandit-Taskar N, [et al.]. Sentinel lymph node biopsy in the management of early-stage cervical carcinoma. *Gynecol Oncol.* 2011, 120, 347-352.
7. Burke T, Levenback C, Tornos C, [et al.]. Intraabdominal lymphatic mapping to direct selective pelvic and paraaortic lymphadenectomy in women with high-risk endometrial cancer: results of a pilot study. *Gynecol Oncol.* 1996, 62, 169-173.
8. Kang S, Yoo H, Hwang J, [et al.]. Sentinel lymph node biopsy in endometrial cancer: meta-analysis of 26 studies. *Gynecol Oncol.* 2011, 123, 522-527.
9. Abu-Rustum N, Khoury-Collado F, Pandit-Taskar N, [et al.]. Sentinel lymph node mapping for grade 1 endometrial cancer: is it the answer to the surgical staging dilemma? *Gynecol Oncol*. 2009, 113, 163-169.
10. Ballester M, Dubernard G, Lécuru F, [et al.]. Detection rate and diagnostic accuracy of sentinel-node biopsy in early stage endometrial cancer: a prospective multicentre study (SENTI-ENDO) *Lancet Oncol.* 2011, 12, 469-476.
11. Case A, Rocconi R, Straughn J Jr, [et al.]. A prospective blinded evaluation of the accuracy of frozen section for the surgical management of endometrial cancer. *Obstet Gynecol.* 2006, 108, 1375-1379.
12. Pandit-Taskar N, Gemignani M, Lyall A, [et al.]. Single photon emission computed tomography SPECT-CT improves sentinel node detection and localization in cervical and uterine malignancy. *Gynecol Oncol.* 2010, 117, 59-64.
13. Robova H, Charvat M, Strnad P, [et al.]. Lymphatic mapping in endometrial cancer: comparison of hysteroscopic and subserosal injection and the distribution of sentinel lymph nodes. *Int J Gynecol Cancer.* 2009, 19, 391-394.
14. Abu-Rustum N, Gomez J, Alektiar K, [et al.]. The incidence of isolated paraaortic nodal metastasis in surgically staged endometrial cancer patients with negative pelvic lymph nodes. *Gynecol Oncol.* 2009, 115, 236-238.
15. Hirahatake K, Hareyama H, Sakuragi N, [et al.]. A clinical and pathologic study on para-aortic lymph node metastasis in endometrial carcinoma. *J Surg Oncol.* 1997, 65, 82-87.
16. Kitchener H, Swart A, Qian Q, [et al.]. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. *Lancet.* 2009, 373, 125-136.
17. Panici P, Maggioni A, Hacker N, [et al.]. Systematic aortic and pelvic lymphadenectomy versus resection of bulky nodes only in optimally debulked advanced ovarian cancer: a randomized clinical trial. *J Natl Cancer Inst.* 2005, 97, 560-566.