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Review article

Sentinel lymph node in endometrial cancer: A systematic review on laparoscopic detection

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ABSTRACT

Endometrial cancer (EC) is the most frequent gynecological malignancy in developed countries, and accounts for 6–9% of female malignancies. The prevalence is growing in overweight individuals and those with medical comorbidities such as diabetes and hypertension. Nodal status is a key determinant of the outcome and there is a strong rationale incorporating sentinel lymph node (SLN) biopsy in the management of EC. We performed a systemic review concerning studies investigating the role of laparoscopic detection of SLN in early-stage EC. The detection rate and sensitivity of the laparoscopic approach in SLN ranged from 69.6% to 100% and 58.6% to 100%, respectively. The combination of dye and radiocolloid detection substances is the best method for SLN detection in EC. The use of pericervical injection and the laparoscopic approach increase the detection rate of SLNs, especially in the iliac lymph node groups. The hysteroscopy injection technique highlights the presence of isolated para-aortic lymph node metastasis. However, the precise method of SLN biopsy in EC needs to be determined further.

Introduction

Endometrial cancer (EC) is the most frequent gynecological malignancy in the developed world and its incidence is increasing. Histological grade, depth of myometrial invasion, and lymph node status are the main prognostic factors in EC. Despite the increasing frequency of this disease, the treatment of this cancer in its early stage remains controversial, especially the role of comprehensive surgical staging, which includes pelvic and para-aortic lymphadenectomy for all patients. The proportion of women who have pelvic or para-aortic lymph node involvement in Stage I disease ranges from 4.7% to 13% or 0% to 3%, respectively, whereas in Stage II disease, the proportion of women with pelvic lymph node involvement ranges from 18.8% to 44.8%.[1–5]

In the recent revised 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system, the major changes involved systemic pelvic and/or para-aortic lymphadenectomy, for example, Stage IIIC1 indicating positive pelvic nodes and Stage IIIC2 indicating positive para-aortic nodes.[6] However, complete systemic pelvic and para-aortic lymphadenectomy may produce additional morbidity that may not result in additional survival outcome benefit, and the possibility of overtreatment in clinically early stage EC. The challenge is to identify a surgical technique that provides accurate staging information about nodal status while avoiding the potential of overtreatment in low-risk groups and undertreatment in patients with metastatic disease. This can avoid the potential unnecessary morbidity associated with systemic lymphadenectomy, such as lymphedema, lymphocyst formation, and prolonged operative time.

The well-established concept of sentinel lymph node (SLN) sampling for malignancies is accepted for melanoma and breast and vulva cancer.[7–10] Based on the orderly, sequential flow of lymphatic fluid from the site of primary tumor to the lymphatic vessels, SLNs or lymphatic mapping is increasing in popularity among gynecological oncologists. In the era of minimally invasive surgery, a combination of laparoscopic hysterectomy and SLN biopsy provides an appealing alternative apart from traditional

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laparotomy staging. It produces better visualization or magnification and detection rate in early stage EC without compromising the diagnostic accuracy, as well as several other advantages of laparoscopic surgery.

Based on these considerations, we conducted a systematic review of the evidence regarding the efficacy of the laparoscopic approach for SLN biopsy in EC.

Methodology

Data sources and study selection

A comprehensive, systematic computer literature search for published English-language studies in humans was conducted using PubMed up to February 2012. The following keywords were used: "laparoscopic", "sentinel node" and "endometrial or endometrium or uterine cancer/carcinoma". The list of articles was supplemented by extensive crosschecking of reference lists of the identified articles. Review articles, letters, comments, meeting abstracts, unpublished data, and case reports were excluded. Inclusion criteria were: (1) laparoscopic approach in detecting sentinel nodes with a minimal sample size of >10 participants, and publications that provided identification of effectiveness and diagnostic performance of SLN detection techniques; (2) studies that used radiolabeled tracers and/or blue dye in the sentinel node procedure; and (3) studies that involved only early stage EC.

Data extraction

We recorded data from each of the selected studies. The following data were extracted: (1) authors and year of publication; (2) sample size; (3) tracers and methods used for SLN procedures; (4) number of SLNs resected per study; (5) detection rate and sensitivity of SLNs for each study; and (6) exact location of SLNs detected in each study. A positive SLN is a positive node that is identified with or without ultrastaging (serial sections or immunohistochemistry).

The detection rates were calculated as the number of patients with at least one detected pelvic or para-aortic SLN, divided by the total number of patients who underwent labeling and SLN mapping. Sensitivity was estimated as the proportion of true positives (patients with positive pelvic or para-aortic SLNs) among the patients with positive pelvic or para-aortic lymph nodes. Negative predictive value was found by dividing the number of true negatives (patients with negative pelvic SLNs) by the number of all patients without pelvic lymph nodes metastasis.

Results

Up to February 2012, the initial search retrieved nine out of 29 articles from Pubmed. After screening, only nine articles concerning laparoscopic detection of SLNs in EC fulfilled the inclusion criteria. An overview of the results from the studies included in the analysis is presented in Tables 1–3.

A total of 328 patients were included in the nine reviewed studies, with a mean number of 36.56 ± 11.56 patients per study (median: 25 patients, range: 11–125 patients). In 311 out of 328 patients, reagent tracers were injected into the pericervical region, whereas 17 patients received hysteroscopy-guided injection. Seven studies used dual labeling tracers (patent blue plus radiolabeled colloid) and two studies used a single reagent tracer. Those using radiolabeled colloid had preoperative lymphoscintigraphy performed 1 day prior to the operation and intraoperative endoscope gamma probing for SLN mapping (Table 1).

The SLN detection rates varied from 69.6% to 100% for pericervical injection (mean: 87.66 ± 3.05) and 64.7% for hysteroscopy-guided injection. The low SLN detection rate of 64.7% was observed in the study by Perrone et al; probably due to the large number of detection failures in early cases due to the learning curve. The use of pericervical injection, mostly at four different sites, correlated with the increasing detection rate.

The range of SLN sensitivity and NPV were 58.8–100% and 10.5–100%, respectively (Table 2). The mean number of SLNs removed was 47.89 ± 8.77. The mean pooled bilaterality of SLNs was 50.80 ± 5.29%.

The most common site of SLNs was the iliac region, with 50–100% of the total. SLNs were detected in the para-aortic region by Barranger et al (2.5%) and Perrone et al (18.2%). The superiority of hysteroscopy-guided injection over pericervical injection for detection of isolated para-aortic SLNs in patients with EC was demonstrated by Perrone et al (Table 3).

Discussion

The concept of SLNs was first described in 1960 by Gould et al.[11] The main goal of this procedure is to reduce the extent of surgical

Table 1
Characteristics of studies reviewed.

Authors	Year	*n*	FIGO stage	Tracer used	Injection site	Detection methods		Pathological assessment
						Preoperative	Intraoperative	
Pelosi et al[16]	2002	16	Ib	Tc99m + PB	Cervical	Lymphoscintigraphy	Endoscope gamma probe Direct visualization	H/E and IHC
Gargiulo et al[18]	2003	11	Ib–IIa	Tc99m + PB	Cervical	Lymphoscintigraphy	Endoscope gamma probe Direct visualization	H/E and IHC
Holub et al[17]	2004	25	I	PB	Cervical	—	Direct visualization	NA
Barranger et al[28]	2004	17	Ia–II	Tc99m + PB	Cervical	Lymphoscintigraphy	Endoscope gamma probe Direct visualization	H/E and IHC
Delpech et al[29]	2007	23	Ia–II	Tc99m + PB	Cervical	Lymphoscintigraphy	Endoscope gamma probe Direct visualization	H/E and IHC
Ballaster et al[20]	2008	38	Ia–II	Tc99m + PB	Cervical	Lymphoscintigraphy	Endoscope gamma probe Direct visualization	H/E and IHC
Perrone et al[22]	2008	40	–	Tc99m	Cervical (23) Hysteroscopy (17)	Lymphoscintigraphy	Endoscope gamma probe Direct visualization	H/E and IHC
Barranger et al[21]	2009	33	I–II	Tc99m + PB	Cervical	Lymphoscintigraphy	Endoscope gamma probe Direct visualization	H/E and IHC
Ballester et al[12]	2011	125	I–II	Tc99m + PB	Cervical	Lymphoscintigraphy	Endoscope gamma probe Direct visualization	H/E and IHC

FIGO = International Federation of Gynaecology and Obstetrics; H/E = hematoxylin and eosin, IHC = immunohistochemistry; NA = not available; PB = Patent blue dye; Tc99m = Technetium 99m.

Table 2
Diagnostic performance included.

Authors	No. of patients with detected SLNs	No. of SLNs removed	Mean no. of SLNs removed	Detection rate (%)	Bilateral DR	Sensitivity	Negative predictive value
Pelosi et al[16]	15/16	24	1.6	94	56.5	100	0
Gargiulo et al[18]	11/11	60	NA	100	35.2	100	100
Holub et al[17]	21/25	53	2.1	84	81	100	100
Barranger et al[28]	16/17	42	2.6	94	58.8	100	0
Delpech et al[29]	19/23	47	2.5	82.6	47.8	NA	10.5
Ballaster et al[20]	33/38	93	2.5	94	39.4	84	97
Perrone et al[22]	20/23	27	2.6	Cervical (69.6)	37.5	87	0
	10/17	14		Hysteroscopy (64.7)	27.3	58.8	
		Mean: 20		Total: 67.5	Total: 33.3	Total: 75	
Barranger et al[21]	27/33	71	2.5	81.8	54.5	NA	0
Ballester et al[12]	111/125	NA	3.0	89	69	84	97

NA = not available; SLN = sentinel lymph node.

intervention in early stage cancer, which preserves organ function and improves quality of life. The technique is based upon the concept that tumor cells migrating from a primary tumor will metastasize to one or a few lymph nodes before affecting other lymph nodes. If the histology of SLNs is negative, there is no further metastasis, thus avoiding further surgical intervention. The use of tracers such as blue dye and radiolabeled colloid around the area of the tumor allows identification of an SLN in the majority of patients. The status of SLNs can then predict accurately the status of the other regional lymph nodes.

SLNs for EC are still under investigation. Several studies have addressed the issue and have provided new data that suggest that this will be a valid approach, and perhaps a trade-off between no lymphadenectomy versus systematic lymphadenectomy in patients with low- and intermediate-risk EC.[12,13] The other concept of SLNs in EC is to avoid complete systemic pelvic and para-aortic lymphadenectomy in early stage EC, because 80% of patients with Stage I disease were found to be negative for lymph node involvement. The revised 2009 FIGO staging system for EC advocates that gynecological oncologists should perform both pelvic and para-aortic lymphadenectomy for accurate staging.[6] These are important for the prognosis of disease and subsequent treatment of the patients. In addition, with the recent controversies in the a randomised trial of lymphadenectomy and of adjuvant external beam radiotherapy in the treatment of endometrial cancer (ASTEC) and survival effect of para-aortic lymphadenectomy (SEPAL) studies regarding the role of lymphadenectomy in early stage EC, the SLN concept is more pertinent than ever.[14,15] Reducing the unnecessary morbidity related to lymphadenectomy while detecting the cases in which complete surgical staging is required would be a major breakthrough.

The uterus is a complex structure in which the lymphatic drainage varies. The techniques and sites of tracer injection are the major concern for SLN mapping in EC. Pericervical injection is the most often implemented for identification of SLNs in EC. The advantages of pericervical injection for SLN mapping are its feasibility, reproducibility, and low degree of invasiveness compared to other methods. However, it does not reflect lymphatic drainage of Stage I disease and it has more potential in Stage II disease. Although cervical injection can overlook some direct lymphatic drainage to the para-aortic area, the analyzed studies found that cervical dual labeling is associated with the highest rate of perioperative SLN detection; ranging in the pooled data from 69% to 100%.[13,16–22] To avoid missing promontory or para-aortic SLNs, fundal myometrial injection and hysteroscopy-guided injection can be advocated. Perrone et al showed that the SLN detection rate with the hysteroscopy-guided injection technique was only 64.7%, but there was significant isolated para-aortic SLN detection compared with that with pericervical injection (18.2% vs. 0%, $p < 0.05$).[22] The issues of hysteroscopy-guided injection are: it is a more complicated technique than direct cervical or uterine corpus injection, and there is a risk of disseminating malignant cells through the tubes. Hysteroscopic visualization of the endometrial cavity can be achieved with a pressure of 40 mmHg, which is lower than the 70 mmHg pressure needed for tubal spillage to occur, thus reducing the risk of malignant cell dissemination into the peritoneal cavity.[23] A recent meta-analysis of 26 studies revealed that the detection rate decreased when pericervical injection was not used, and the authors suggested that the "subserosal injection only" technique should not be used because it may decrease the sensitivity of SLN biopsy.[13]

The uterus is located at middle of pelvis and should have bilateral lymphatic drainage, thus it is important to discuss the bilateral detection rate of SLNs. However, the studies so far have not confirmed this hypothesis and the percentage of bilateralism varied between 33.3% and 81% (Table 2). The reasons for which a median organ can in some cases only drain to one side still remain to be clarified.[22] The most frequent site of nodal metastasis detection in EC when cervical injections are used is the pelvic area, especially in

Table 3
Location of SLNs in endometrial cancer.

Authors		Iliac groups (%)				Common iliac (%)	Bifurcation of aorta (%)	Para-aortic (%)
		External iliac	Internal iliac	Interiliac	Obturator			
Pelosi et al[16]		100 (all detected in iliac group)			–	0	0	0
Gargiulo et al[18]		100 (all detected in iliac group)			–	0	0	0
Holub et al[17]		34	13.2		52.8	13.2	0	0
Barranger et al[28]		50 (medial EI)	52.4	31	9	5	0	2.5
Delpech et al[29]		57.4 (medial EI)			–	–	1	0
Ballaster et al[20]		75 (lateral EI)		16.2	–	7.5	1	0
Perrone et al[22]	Cervical	93.8 (iliac group)			0.6	0	0	0
	Hysteroscopy	90.9 (iliac group)			0.6	0	0	18.2
Barranger et al[21]		66.7	2.8	19.7	5.6	2.8	1.4	0
Ballester et al[12]		NA						5

EI = external iliac; NA = not available.

the external iliac region. Nodal metastasis is less frequently located in the common iliac region and bifurcation of the aorta. When hysteroscopy-guided injection is advocated, there is an 18.3% detection rate of SLNs in the para-aortic area.

The other main goal of our review was to underline the advantages of laparoscopy surgery in EC staging. Use of a minimally invasive approach in the staging and treatment of EC decreases perioperative morbidity and appears to result in comparable treatment effectiveness when compared with laparotomy in early stage EC.[24] A meta-analysis of four randomized trials compared women with endometrial carcinoma who underwent complete surgical staging with a minimally invasive approach versus conventional laparotomy. The authors concluded that although the operative time was longer in the laparoscopy group, there were some advantages when compared with laparotomy. In patients treated with laparoscopy, there was a decreased incidence of perioperative complications, namely, decreased blood loss. The authors also reported that the group that underwent laparoscopic staging had shorter hospital stays and faster return to normal activity. Of paramount importance in this meta-analysis was the fact that there was no significant difference between the numbers of lymph nodes yielded in both groups. Regarding cancer survival, pooled data from this study were limited because only two trials reported long-term follow-up, at a median of 44 and 79 months. However there were no significant differences between surgical groups in overall disease-free or cancer-related survival.[25]

A subsequent randomized study, conducted by the Gynecologic Oncology Group, assigned >2600 patients with EC to laparoscopy or laparotomy. All patients underwent hysterectomy and surgical staging including pelvic and para-aortic node dissection. The results showed that the minimally invasive approach was feasible and safe and the complication rates were similar regardless of the surgical approach. Longer follow-up is ongoing to determine whether there are differences in recurrence and survival between the laparotomy and laparoscopy groups.[26]

A recent study by Mais et al compared the SLN detection rate obtained through the laparoscopic or laparotomic approach after pericervical injection of vital dye in patients with early stage EC. They found that a higher SLN detection rate was obtainable through laparoscopy as compared with laparotomy (82% vs. 41%, $p = 0.008$). The different detection rates observed between these routes might depend on the different time elapsing between injection of the blue dye into the cervix and the surgical SLN assessment in the pelvic basin where the time interval for laparoscopy is always shorter than for laparotomy.[27]

Several reviews have analyzed the feasibility and clinical accuracy of SLNs in relation to the use of single or dual tracers, methods of detection, and site of tracer injection, but none of the reviews investigated the laparoscopic approach to SLN detection in EC. The advantage of laparoscopic surgery combined with the concept of SLNs helps to reduce surgical morbidity, especially in women with EC, who often have comorbidity such as obesity, hypertension, or diabetes. SLN detection improves the diagnostic accuracy of disease, which consequently improves disease treatment and then prognosis. The future development of SLNs includes standardized methods of laparoscopic detection and pathological examination.

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