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Prospective assessment of the prevalence of pelvic, paraaortic and high paraaortic lymph node metastasis in endometrial cancer

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Abstract

Objective—To prospectively define the prevalence of lymph node metastasis (LNM) in at risk endometrial cancer (EC).

Methods—From 2004–2008, frozen section based Mayo Criteria prospectively identified patients “not at-risk” of LNM (30% EC population; grade I/II, <50% myometrial invasion and tumor diameter ≤ 2cm) where lymphadenectomy was not recommended. The remaining 70% EC cohort was considered “at-risk” of LNM; where a systematic pelvic and infrarenal paraaortic lymphadenectomy was recommended. Patients were prospectively followed. The area between renal vein and inferior mesenteric artery (IMA) was labeled as high paraaortic area. For calculating the prevalence of LNM in high paraaortic area, the denominator was the population with known anatomic location of nodal tissue in relation to the IMA.

Results—Of the 742 patients, 514 were at risk; of which 89% underwent recommended lymphadenectomy. A mean ($\pm$ standard deviation) of 36 ($\pm$ 14) pelvic and 18 ($\pm$ 9) paraaortic nodes were harvested. The prevalence of pelvic and paraaortic LNM was 17% and 12%, respectively. In presence of pelvic LNM, 51% had paraaortic LNM. In absence of pelvic LNM, 3% had paraaortic

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LNM; of which 67% were located exclusively in high paraaortic area. Among patients with paraaortic LNM, 88% had high paraaortic LNM; and 35% had only high paraaortic LNM. The cases of paraaortic LNM with negative pelvic nodes seemed to cluster in moderate to high grade endometrioid EC with 50% myometrial invasion.

Conclusion—We present reference data for the prevalence of LNM in at-risk EC patients to guide lymphadenectomy decisions for clinical and research purposes.

Keywords

Lymph node metastasis; endometrial cancer; risk factors; lymphadenectomy

Introduction

Although the therapeutic benefits of lymphadenectomy in the treatment of endometrial cancer (EC) continues to be debated, regional lymph node metastasis (LNM) is well recognized as a dominant prognostic risk factor [1]. Knowledge of the status of lymphatic spread was deemed sufficiently meritorious to encourage a transition from clinical to surgical staging in 1988 [2]. For more than two decades, the presence or absence of lymphatic dissemination has been an essential element in determining adjuvant therapy and in allowing global comparative evaluations. With the recognition that paraaortic lymph nodes are frequently directly or secondarily involved and connote an even less favorable prognosis, the 2009 revised surgical staging system has further stratified regional nodal metastasis accordingly [3]. Subsequently, reports have emerged suggesting that consistent with the origin of secondary uterine vasculature, namely, the gonadal vessels, the paraaortic area between the inferior mesenteric artery (IMA) and renal arteries (high paraaortic area) is the primary site of aortic LNM [4] [5] [6] [7] [8] [9].

Within the gynecologic oncologic community there is a lack of consensus regarding the indications (when to do) and the extent (how much to do) of lymphadenectomy in managing EC. Examining the practice patterns among gynecologic oncologists, Soliman et al. reported that half of the respondents performed below IMA (low paraaortic) lymphadenectomy and only one in ten incorporated a dissection of the high paraaortic area [10]. Furthermore, the apparent absence of therapeutic benefit in two randomized studies assessing the value of lymphadenectomy in low stage patients has frequently been extrapolated to a broader spectrum of EC [11] [12]. At least in part, the low prevalence of regional LNM presents a challenge in appropriately balancing the potential benefits, risks and costs of performing a lymphadenectomy. [13]

With confirmation that approximately 30% of EC patients, readily identified via frozen section [4], can safely forego lymphadenectomy without compromising longevity [14], the merits of removing regional nodes in the remaining 70% requires readdressing. The literature is relatively sparse with regard to the prevalence of lymphatic dissemination and more importantly the prevalence of specific sites of LNM in these “at-risk” patients. Hence, the objective of this report is to provide knowledge of the prevalence of pelvic, paraaortic and high paraaortic LNM as a function of uterine histology, grade, myometrial invasion

(MI) and macroscopic extrauterine disease (MED) in the “at-risk” EC cohort which in turn will facilitate decisions regarding management.

Methods

This study was approved by the Institutional Review Board (IRB) of the Mayo Clinic, Rochester, Minnesota, USA. Based on rigorous prior analysis of the management of EC at our institution, a comprehensive prospective strategy for surgical staging was implemented in 2004 [4]. According to this strategy (supplemental Table), a subset (30%) of EC cases have minimal risk of LNM (“not at-risk” subgroup), in whom lymphadenectomy was not recommended [15] [14]. Foregoing lymphadenectomy in these “not at-risk” patients does not compromise survival and decreases the cost of EC management [14]. The remainder of cases were considered “at-risk”, where the probability of LNM appeared to favor definitive surgical staging. Surgical staging included lymphadenectomy and a thorough examination of the abdominal cavity to determine evidence of MED.

The anatomical landmarks for lymphadenectomy in at-risk patients have been described in detail elsewhere [4]. Briefly, lymph nodes from the eight lymphatic basins in the pelvis (bilateral common iliac, external iliac, internal iliac, and the obturator) and the four basins in the paraaortic region (bilateral infra- and supra-IMA regions; the latter up to the renal vessels) were collected separately. To assure standardization of lymphadenectomy, the number of pelvic and paraaortic nodes harvested were utilized as a surrogate for quality; lymph node counts were assessed on a periodic basis during the study period [16]. The degree of glandular differentiation and cytologic atypia were used to determine architectural grading according to the International Federation for Gynecology and Obstetrics [17]. Pathological review was performed by a single gynecologic pathologist (GLK). In accordance with the Minnesota Statute for Use of Medical Information in Research, women who did not consent to the use of their medical records for research purposes were also excluded.

The following definitions were utilized in this report: 1) “High paraaortic area” refers to the area between the renal veins and IMA. 2) “Low paraaortic area” refers to the area between the IMA and aortic bifurcation. 3) The denominator for measuring the prevalence of pelvic and paraaortic LNM was all at-risk patients who underwent a pelvic and paraaortic lymphadenectomy, respectively. 4) To assess the prevalence of paraaortic LNM in pelvic node negative patients, the denominator was the cohort declared pelvic node negative after pelvic and paraaortic lymphadenectomy. 5) For calculating the prevalence of LNM in high or low paraaortic area, the denominator was the population with known anatomic location of nodal tissue in relation to the IMA. Patients where the location of the paraaortic nodal tissue in relation to IMA was not recorded; were excluded from the specific calculations pertaining to the prevalence of high or low paraaortic LNM. MED implies presence of macroscopic extrauterine intraperitoneal disease, but does not include “palpable” retroperitoneal lymph nodes. Recognizing the potential for preoperative chemotherapy, radiotherapy or presence of other synchronous cancers to modify the calculated prevalence of nodal spread, patients (N=48) with these characteristics were excluded. Comparisons were evaluated using two-

sided chi-square tests. Statistical analyses were performed using the SAS version 9.2 software package (SAS Institute, Inc.; Cary, NC).

Results

Overall study population

During the time interval from January 2004 through December 2008, 790 EC patients presented for primary surgical management at our institution of which 48 were excluded due to the above-mentioned reasons.

Among the 742 patients, 228 were considered “not at-risk” and have been excluded from the present study. Of the 514 meeting the at-risk criteria, 89% (457/514) had lymphadenectomy. The reasons for foregoing lymphadenectomy have been described previously [16]. Pelvic and paraaortic lymphadenectomy was performed in 93% (424/457), pelvic only in 7% (32/457), and paraaortic only in 0.2% (1/457) (Figure). The specific site of the harvested paraaortic nodes in reference to the IMA (e.g., above versus below) was specifically designated in 76% (325/425). Mean ($\pm$ standard deviation) number of pelvic and paraaortic lymph nodes harvested were 36 ($\pm$ 14) and 18 ($\pm$ 9), respectively.

Within the lymphadenectomy cohort (N=457), the prevalence of pelvic and paraaortic LNM was 17% and 12%, respectively. Simultaneous LNM in both the pelvic and paraaortic regions were detected in 9%, while LNM restricted to the paraaortic area only were observed in 3%. The detailed prevalence stratified by histology subgroups and nodal regions is provided in Table 1. Noteworthy, LNM was detected in 72% (31/43) of patients with MED compared to only 14% (57/414) in the absence of MED ($p<0.001$).

Table 2 (endometrioid EC) and 3 (non-endometrioid EC) provide detailed and “clinician friendly” data for the risk of LNM stratified by MED, MI and grade. None of the patients with endometrioid histology and no MI were considered part of the “at-risk” group (Table 2). Hence, nodal involvement in the face of no MI was limited to non-endometrioid cancers only (7/29=24%). The overall risk of pelvic and/or paraaortic nodal involvement in the “at-risk” EC group with 50% MI was 39% (55/140).

Paraaortic LNM and their location

Considering all patients with negative pelvic lymph nodes (and available information of the paraaortic area)—Overall, 11 of 351 (3%) patients with negative pelvic nodes had paraaortic LNM. Of these 11, location relative to the IMA was available in 9; 6 (67%) had only high LNM whereas 2 had LNM in only the low paraaortic area. The remaining patient had LNM in both high and low paraaortic areas. Therefore, 7 of the 9 (78%) patients with paraaortic LNM and negative pelvic nodes had disease in the high paraaortic area.

The patients with paraaortic LNM with negative pelvic nodes seemed to cluster in the subgroup with endometrioid histology and 50% MI. In endometrioid tumors with 50% MI and no MED, the risk of paraaortic LNM with negative pelvic nodes increased with grade (0% vs. 13% vs. 27% for grade 1, 2, and 3 respectively; $p=0.03$). When considering the

patients with negative pelvic with positive paraaortic lymphnodes; in endometrioid histology, none of 5 patients with MED had paraaortic lymphnode metastasis (table 2, bottom section). The corresponding number for the non-endometrioid histology was 1 out of 6 (table 3, bottom section).

Considering all patients with positive pelvic lymph nodes—Overall, 12% (42/349, table 1) patients with endometrioid histology had pelvic LNM; 9% (31/332) in absence of MED whereas 65% (11/17) in presence of MED (table 2). Overall, 32% (34/107, table 1) patients with non endometrioid histology had pelvic LNM; 20% (16/82) in absence of MED whereas 72% (18/25), in presence of MED (table 3). When we restricted the analysis to patients with positive pelvic nodes and available information of the paraaortic area; of the 73 with pelvic LNM, 37 (51%) had paraaortic LNM (45% endometrioid; 58% non-endometrioid). Of these 37, 25 had a documented relation to IMA; 92% (23/25) had high paraaortic LNM and 24% (6/25) had only high paraaortic LNM with negative nodes in the low paraaortic area.

Considering only patients with positive paraaortic lymph nodes—In endometrioid histology, a total of 8% (26/325) had paraaortic LNM; (20/310=7%) in absence of MED whereas (6/15=40%) in presence of MED. In non endometrioid histology, a total of 23% (23/100) had paraaortic LNM; (10/76=13%) in absence of MED whereas (13/24=54%) in presence of MED. Among the 49 patients with paraaortic LNM, the location relative to the IMA was recorded in 34. Of these 34, 12 (35%) had LNM only in high paraaortic area, 4(12%) had LNM only in the low paraaortic area and 18 (53%) had LNM in low as well as high paraaortic area. Therefore, among patients with paraaortic LNM, high paraaortic LNM was detected in 88% (30/34) with no discernible difference between endometrioid (89%) and non-endometrioid (88%) histology subtypes. Alternatively, 82% of the patients with low paraaortic LNM had high paraaortic LNM. Table 4 provides a detailed summary of the data on LNM on the above three subgroups whereas Table 5 represents a literature review.

Discussion

We have thoroughly analyzed patterns of LNM in a uniformly staged large cohort of “at risk” EC patients. Focusing on the “at risk” cohort (excluding the roughly 30% of all cases of EC with almost zero chance of nodal disease) is important for two reasons. First, increasingly these ultra-low risk patients will not be staged and applying statistics to predict risk of nodal disease which was based on such cases will become less relevant. And second, it is this “at-risk” cohort where accurate patterns of spread data are necessary to inform decision making that can impact survival. In the present study we report that: a) prevalence of pelvic/paraaortic LNM is strongly associated with high grade, deep MI and MED; b) when paraaortic LNM is present, in the vast majority of cases (88%) dissemination includes nodes located in the high paraaortic area – frequently nodes in the high paraaortic area are the only paraaortic nodes involved (35%); c) roughly half of cases with pelvic LNM will have spread to paraaortic nodes; d) in EC without MED, paraaortic LNM with negative pelvic nodes are generally rare except for moderate to high grade lesions with deep MI

(13-27%, Table 2); e) when paraaortic LNM with negative pelvic nodes are present they are most commonly found only in the high paraaortic area (67%).

Having likelihood models derived from a comprehensive, methodical, prospective staging protocol will serve practitioners well in both surgical (e.g. need for staging) and therapeutic (e.g. individualized adjuvant therapy) planning. This information will also facilitate the identification of women most appropriate for clinical trials evaluating the potential benefits of lymphadenectomy. How can these data guide lymphadenectomy and postoperative treatment decisions in EC patients? We have developed several common scenarios to illustrate the value of this data.

Scenario 1: Newly diagnosed EC patient undergoing primary surgery with available intraoperative frozen section to determine grade and depth of MI

It is not the purpose of this paper to define the accuracy of frozen section in EC, which varies in the different institutions [18]; suffice it to say that in many institutions it is used for surgical decision-making. When frozen section can be reliably used to assess grade and MI; the data in Tables 2 and 3 can guide the need and delineate the extent of optimal surgical staging necessary. In our study, the overall prevalence of LNM (any nodal group, table 1) was 19% (total cohort), 14% (endometrioid histology) and 35% (non-endometrioid histology). Also, LNM was detected in 72% (31/43) with MED compared to only 14% (57/414) without MED ($p<0.001$).

Scenario 2: Treatment planning after hysterectomy when no lymphadenectomy has been performed

Table 2 and 3 provide prevalence of nodal metastasis based on final pathologic evaluation for histology, MI, and grade. In this scenario, these data can guide the clinician and the patient to make an informed decision for a reoperation for definitive staging, adjuvant therapy, or neither based upon sound data. In this situation, the clinician may have the advantage of final pathology being available on the uterine and adnexal specimen and knowing the prevalence especially of pelvic LNM will be paramount. In our study, the prevalence of pelvic LNM (table 1) was 17% (overall), 12% (endometrioid histology) and 32% (non-endometrioid histology). The prevalence of pelvic LNM was 11% (47/414) in absence of MED and 69% (29/42) in presence of MED.

Scenario 3: Treatment planning after hysterectomy and pelvic-only lymphadenectomy

Overall when pelvic nodes are negative only 3% of cases will harbor paraaortic LNM. However a higher risk cohort exists based upon grade and MI where risk is as high as 27% (moderate to high grade endometrioid EC with 50% MI) in whom additional therapy should be planned. Conversely in the presence of pelvic nodal disease it is critical to understand that roughly half of women will harbor paraaortic LNM and subsequent planning should consider how to manage the paraaortic node basins. In this scenario, the availability of pathology report on the pelvic nodes will greatly facilitate further management. With positive pelvic nodes, the prevalence of paraaortic LNM was 51% (overall), 45% (endometrioid histology) and 55% (non-endometrioid histology). With negative pelvic

nodes, the prevalence of paraaortic LNM was 3% (overall), 3% (endometrioid histology) and 5% (non-endometrioid histology). The effect of MED is well illustrated in table 2 and 3.

Scenario 4: Pelvic and paraaortic lymphadenectomy have been performed but limited to the low paraaortic nodes

When both pelvic and low paraaortic nodes are negative, the probability of having LNM in the high paraaortic area is very small with the notable exceptions mentioned in scenario 3 (Table 2). However, if pelvic nodes are positive with negative lower paraaortic nodes, approximately 12% of these patients (Table 5) will still have occult high paraaortic LNM. Finally, when low paraaortic LNM is detected, and the status of high paraaortic nodes is unknown; its imperative to include the high paraaortic area in the radiation fields if radiation is being planned as the risk of LNM in the high paraaortic area exceeds 80%. In our study, 49 patients had paraaortic LNM, of which anatomic distinction in relation to IMA was available in 34. Of the 34, 30 (88%) had tumor dissemination above the IMA (89% endometrioid, 88% non-endometrioid), and 12 (35%) had paraaortic dissemination above (but not below) the IMA (37% endometrioid; 31% non-endometrioid). These prevalence data remained similar with or without MED.

This study has several strengths. It is a large cohort of consecutive patients, which minimizes selection bias. All patients underwent a uniform and predetermined surgical staging procedure which limits variation due to different practice patterns by different surgeons. We eliminated patients without risk of LNM to highlight patterns of metastatic disease in a uniform risk cohort and in those cases which require the most decision making in comprehensive treatment planning. The limitations of this study include its single institutional nature with inbuilt referral bias. Also despite a large study cohort (n=742) there were relatively small numbers in individual subgroup analyses for paraaortic LNM with negative pelvic nodes. To address the latter, we included available data from the literature on the topic of paraaortic LNM with negative pelvic nodes and the anatomic location of paraaortic LNM (Table 5). These data confirmed: a) the overall low probability of paraaortic LNM with negative pelvic nodes (3%); b) the observation that the vast majority of cases with paraaortic LNM include the high paraaortic area; c) in a subset of cases high paraaortic nodes are the only paraaortic nodes involved (Table 5) and d) the present study contributes nearly half of the patients reported in the literature for analysis of the location of paraaortic LNM. In the representative analysis on the surgical safety of the lymphadenectomy technique at our institution conducted during the first half of the present prospective study; we reported no mortality (n=0/281) and one obturator nerve injury repaired intraoperatively (n=1/281) with a median blood loss of 300 ml and a median hospital stay of 4 days [4]. Detailed reports of complications have been published by our group previously [13] [14].

It is important to note that we provide the prevalence of lymphnode metastasis stratified by histology, myometrial invasion, grade and presence or absence of macroscopic extrauterine disease. In the absence of randomized clinical trials, these prevalence data can guide the surgeon to carefully select patients for lymphadenectomy depending on the risk predictors of the given patient. Hence, the decision of lymphadenectomy and the level of dissection can be individualized as well. Any particular risk suggested by our data may justify

lymphadenectomy in one particular patient and may not in a different patient; depending on patient's wishes, co-morbidities and other characteristics of the tumor.

In conclusion, our study excluded approximately all “not at-risk” EC patients who do not need lymphadenectomy (approximately one-third of the overall population) [14] [19] [20] and provided the information on the prevalence of LNM for the remainder “at-risk” EC patients. Our data provide contemporary risk-stratification in a clinically useful format. This information may help for selecting patients for surgical staging of EC, directing adjuvant treatment, as well as for identifying the patient subgroups who may be appropriate for inclusion in clinical trials evaluating the therapeutic role of lymphadenectomy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research Highlights

- Without compromising the oncologic outcomes, 30% endometrial cancer patients do not need lymphadenectomy (the “not at risk subgroup”).
- Our reference data inform lymphadenectomy and adjuvant therapy decisions in the “at risk subgroup” (remaining 70%) of endometrial cancer.
- Paraaortic lymphadenectomy, when undertaken, ought to include management of the high paraaortic area (between renal vein and inferior mesenteric artery).

Figure.

Overview of the population of endometrial cancer patients operated at Mayo Clinic during the time period 2004-2008. Note that the present study included the 457 patients considered "at risk" who had lymphadenectomy (LND) (areas with grey background).

Table 1

Prevalence of lymph node metastasis in the “at-risk” population of endometrial cancer stratified by histology and nodal regions; 2004-2008.

	Pelvic	Paraaortic	Pelvic and paraaortic	Paraaortic only[†]	Any nodal region
Endometrioid	12% (42/349)	8% (26/325)	6% (18/325)	3% (8/285)	14% (50/349)
Non-endometrioid	32% (34/107)	23% (23/100)	19% (19/99)	5% (3/66)	35% (38/108)
P-value*	<0.001	<0.001	<0.001	0.47	<0.001
Total	17% (76/456)	12% (49/425)	9% (37/424)	3% (11/351)	19% (88/457)

[†] Of the 424 patients who had both pelvic and paraaortic lymphadenectomy, 351 had negative pelvic nodes (denominator).

* P-value designates comparisons between histology categories

Table 2

Lymph node metastasis stratified by grade, myometrial invasion and presence of macroscopic extrauterine disease in endometrioid endometrial cancer; 2004-2008.

Endometrioid histology			
Site of LNM	Grade	Myometrial invasion	
		MI <50%	MI 50%
		% LNM	% LNM
No macroscopic extrauterine disease			
Pelvic	1	3.8 (5/130)	15.2 (5/33)
	2	7.3 (6/82)	17.1 (7/41)
	3	6.9 (2/29)	35.3 (6/17)
Paraaortic	1	0.8 (1/119)	9.4 (3/32)
	2	5.3 (4/76)	20.5 (8/39)
	3	0 (0/28)	25.0 (4/16)
Paraaortic with negative pelvic	1	0 (0/114)	0 (0/27)
	2	1.4 (1/70)	12.5 (4/32)
	3	0 (0/26)	27.3 (3/11)
Macroscopic extrauterine disease			
Pelvic	1	-	-
	2	0 (0/3)	80.0 (4/5)
	3	-	77.8 (7/9)
Paraaortic	1	-	-
	2	0 (0/3)	75.0 (3/4)
	3	-	37.5 (3/8)
Paraaortic with negative pelvic	1	-	-
	2	0 (0/3)	-
	3	-	0 (0/2)

Abbreviations: LNM, lymph node metastasis; MI, myometrial invasion

Table 3

Lymph node metastasis stratified by grade, myometrial invasion and presence of macroscopic extrauterine disease in non-endometrioid endometrial cancer; 2004-2008.

Non-endometrioid histology				
Site of LNM	Grade	Myometrial invasion		
		No MI	MI <50%	MI 50%
		% LNM	% LNM	% LNM
No macroscopic extrauterine disease				
Pelvic	2	0 (0/1)	0 (0/1)	-
	3	12.5 (3/24)	19.4 (7/36)	30.0 (6/20)
Para-aortic	2	0 (0/1)	0 (0/1)	-
	3	9.5 (2/21)	18.2 (6/33)	10.0 (2/20)
Para-aortic with negative pelvic	2	0 (0/1)	0 (0/1)	-
	3	5.6 (1/18)	3.8 (1/26)	0 (0/14)
Macroscopic extrauterine disease				
Pelvic	2	-	-	-
	3	75.0 (3/4)	57.1 (4/7)	78.6 (11/14)
Para-aortic	2	-	-	-
	3	25.0 (1/4)	28.6 (2/7)	76.9 (10/13)
Para-aortic with negative pelvic	2	-	-	-
	3	0 (0/1)	0 (0/3)	50.0 (1/2)

Abbreviations: LNM, lymph node metastasis; MI, myometrial invasion

Table 4

Summary of the probability of lymph node metastasis in the paraaortic area and their location in different subgroups of patients.

Subgroup	n [*]	% with PA LNM	% with high PA LNM [†]	% with high PA LNM with negative low PA nodes
Total “at-risk” population	425 [‡]	12% (49/425)	9% (30/325)	4% (12/325)
Patients with negative pelvic nodes	351	3% (11/351)	3% (7/275)	2% (6/275)
Patients with positive pelvic nodes [*]	73	51% (37/73)	46% (23/50)	12% (6/50)
Patients with positive paraaortic nodes	49	100% (49/49)	88% (30/34)	35% (12/34)

Abbreviations: PA, paraaortic; LNM, lymph node metastasis; IMA, inferior mesenteric artery; high paraaortic area, between renal veins and IMA

* Patients with available information of paraaortic lymph node status.

[†] Denominators based on patients with available information on location relative to IMA.

[‡] 425 patients in the “at risk” population had paraaortic lymphadenectomy; however 1 of them did not have pelvic lymphadenectomy.

Table 5

A chronological review of the endometrial cancer literature documenting paraaortic lymph node metastasis and their location in various subgroups of patients.

Study		Overall “at risk” population		Limited to patients with PA LNM		Limited to patients with pelvic LNM		Limited to patients with PA LNM and negative pelvic nodes
Author year	n [*]	PA LNM	PA LNM ^{**} with negative pelvic nodes	High PA LNM	High PA LNM with negative low PA	PA LNM	High PA LNM with negative low PA	High PA LNM with negative low PA
Hiratake 1997 [5]	200	18/200 (9%)	2/160 (1%)	7/11 (64%)	2/11 (18%)	16/40 (40%)	n.a.	n.a.
Matsumoto 2002 [6]	106	20/106 (19%)	2/81 (2%)	16/20 (80%)	5/20 (25%)	18/25 (72%)	n.a.	n.a.
Fotopoulou 2010 [7]	62	10/62 (16%)	2/51 (4%)	7/10 (70%)	n.a.	11/18 (61%)	n.a.	n.a.
Turan 2011 [8]	78	12/78 (15%)	3/64 (5%)	11/12 (92%)	7/12 (58%)	9/17 (53%)	4/17 (24%)	3/3 (100%)
Dogan 2012 [9]	161	7/161 (4%)	2/144 (1%)	6/7 (86%)	4/7 (57%)	5/16 (31%)	2/16 (13%)	2/2 (100%)
Kumar 2013 ^{***}	425	49/425 (12%)	11/351 (3%)	30/34 (88%)	12/34 (35%)	37/73 (51%)	6/50 (12%)	6/9 (67%)
Total	1032	116/1032 (11%) [*]	22/851 (3%) [*]	77/94 (82%)	30/84 (36%)	96/189 (51%)	12/83 (14%)	11/14 (79%)

Abbreviations: PA, paraaortic; LNM, lymph node metastasis; n.a., not available; IMA, inferior mesenteric artery; high paraaortic area, between renal veins and IMA; low paraaortic area, between IMA and aortic bifurcation.

* Data only for patients considered “at risk” and is not representative of the overall population of endometrial cancer.

** Excluding patients with positive pelvic nodes.

*** Overall, 11 of 351 (3%) patients with negative pelvic nodes had paraaortic LNM. Of these 11, location relative to IMA was available in 9.