Full length article

Incidence of isolated para-aortic lymph node metastasis in early stage endometrial cancer

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ABSTRACT

Objective: To investigate the incidence of isolated para-aortic lymph node (PaLN) metastasis among patients with stage I endometrial cancer and negative pelvic lymph nodes.
Methods: The National Cancer Database was accessed and patients diagnosed between 2004 and 2015 with an endometrial carcinoma limited to the uterus who underwent extensive pelvic lymphadenectomy (defined as at least 10 lymph nodes removed), had negative pelvic lymph nodes, and underwent PaLN sampling/dissection (with at least 5 lymph nodes removed) were selected for further analysis. Comparisons were made with the chi-square test while a binary logistic regression was performed to identify independent predictors of isolated PaLN metastasis.
Results: A total of 14398 patients who met the inclusion criteria were identified. Median patient age was 63 years (IQR: 13). Most patients had endometrioid histology (79.8%) and stage IA disease (68.8%). The median number of pelvic LNs removed and examined was 18 (IQR: 10). The median number of PaLN removed and examined was 8 (IQR:5). The overall rate of isolated PaLN metastasis was 1.6%. By binary logistic regression presence of lymphovascular space invasion (OR: 5.38 95% CI: 3.99, 7.24) and substage IB (OR: 2.05, 95% CI: 1.54, 2.73) were associated with the presence of isolated PaLN metastasis.
Conclusions: Isolated PaLN in the absence of pelvic lymph node metastasis is extremely rare among patients with stage I endometrial cancer even in the presence of high risk characteristics.

Introduction

Endometrial cancer is the most prevalent malignancy of the female genital tract in the Unites States with a rising incidence [1]. Staging of early stage endometrial cancer includes simple hysterectomy with or without lymph node dissection/sampling (LND) [2]. The performance of LND aims in identifying patients with occult lymph node metastasis and guides adjuvant treatment recommendations [3]. On the other hand, performance of routine LND is associated with increased operative time, higher rate of intraoperative complications and significant morbidity. Recently the technique of sentinel lymph node mapping has gained popularity as an non-inferior alternative to systematic LND [4]. However, adoption of sentinel lymph node sampling can be associated with a failure to identify isolated metastasis to para-aortic lymph nodes (PaLNs) since mapping of the para-aortic area is not always feasible [5]. Based on prior studies, the reported incidence of isolated PaLN metastasis is approximately 1–3% [6–8]. The aim of the present study was to investigate the incidence of isolated para-aortic lymph node (PaLN) metastasis among patients with negative pelvic lymph nodes using a large hospital-based database and identify clinico-pathological characteristics that can aid clinical decisioning.

Materials and methods

Patients diagnosed between 2010 and 2015 with a microscopically confirmed invasive tumor of the uterus (ICD-O-3 site codes C54.0-C54.9, C55.9) were selected from the National Cancer Data Base (NCDB). The NCDB, established jointly by the American Cancer Society and Commission on Cancer of the American College of Surgeons, is a hospital-based database capturing approximately 70% of all malignancies diagnosed in the United States. Patient data are prospectively collected from participating commission-accredited cancer programs and are frequently audited to ensure

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their high-quality. All data are de-identified and available for research purposes. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytical or statistical methodology employed, or the conclusions drawn from these data.The present study was deemed exempt from the Penn Medicine Institutional Board Review.

Based on ICD-O-3 histology codes patients diagnosed with endometrioid (8380-8383) and non-endometrioid carcinoma (serous: 8441, 8460, 8461, clear cell: 8310, carcinosarcoma: 8950,8951, 8980, 8981) were identified. The collaborative staging variables were used to identify patients with disease confined to the uterus and absent distant metastasis (T1/Nx/M0). Those who had an extensive pelvic LND (defined as at least 10 pelvic lymph nodes removed and examined), with negative pelvic lymph nodes and undewent PaLN sampling/dissection (with at least 5 para-aortic lymph nodes removed), and known PaLN status, were selected for further analysis. Clinico-pathological variables extracted from the de-identified dataset were age (<65 or >=65 years), race (White, Black or Other/Unknown), substage (IA, IB or INOS, not otherwise specified), lymphovascular invasion status (LVSI) (present, absent or unknown) and tumor size (<2 cm, >=2 cm or unknown). Rate of isolated PaLN metastasis for endometrioid and non-endometrioid tumors was calculated stratified by substage and LVSI status. The chi-square test was used to compare the distribution of categorical variables while a binary logistic regression was performed to evaluate for pathological characteristics associated with isolated PaLN metastasis. All statistical analysis was performed with the SPSS v.24 statistical package (IBM Corp. Armonk, NY) and the alpha level of statistical significance was set at 0.05.

Results

A total of 14398 patients who met the inclusion criteria were identified. Median patient age was 63 years (IQR: 13) while the majority were of White race (85.9%). Most patient had endometrioid tumors (79.8%) and stage IA disease (68.8%). Information on LVSI was available for 13170 patients and was present in 18.8% of cases. The median number of pelvic LNs removed and examined was 18 (IQR: 10). The median number of PaLN removed was 8 (IQR:5); 35.1% of patients had extensive PaLND (defined as at least 10 L Ns removed). The overall rate of isolated PaLN metastasis was 1.6% (234/14398) while the median number of positive PaLN was 1 (IQR: 1). More specifically the rate was 1.5% for patients who had 5–9 para-aortic LN removed and 1.8% for those who had at least 10 para-aortic LN removed, p = 0.13. Table 1 depicts the clinicopathological characteristics of patients with stage I uterine carcinoma and negative pelvic LNs stratified by the presence of isolated PaLN metastasis. Table 2 presents the rate of isolated PaLN metastasis stratified by histology, substage, and LVSI status for patients with complete data for all variables. The lowest rate (0.5%) was noted among patients with endometrioid tumors, stage IA disease in the absence of LVSI, while the highest rate (7.4%) was observed among patients with non-endometrioid tumors stage IB disease in the presence of LVSI. Table 3 summarizes the clinico-pathological factors associated with isolated PaLN metastasis by binary logistic regression.

Discussion

In the largest dataset to date, we confirm a very low incidence of isolated PaLN metastasis for patients with early stage endometrial cancer and negative pelvic LNs even among patients with high-risk characteristics such as non-endometrioid histology, LVSI and stage IB. By binary logistic regression the presence of LVSI and substage IB were associated with isolated PaLN metastasis.

Table 1
Clinicopathological characteristics of patients with stage I endometrial carcinoma and negative pelvic lymph nodes who had at least 5 para-aortic lymph nodes removed stratified by the presence of isolated para-aortic lymph node (PaLN) metastasis.

	PaLN negative	PaLN positive	p-value
Age			0.14
<65 yrs	8132 (57.4%)	123 (52.6%)	
>=65 yrs	6032 (42.6%)	111 (47.4%)	0.48
Race			
White	12159 (85.8%)	202 (86.3%)	
Black	1154 (8.1%)	15 (6.4%)	
Other/Unknown	851 (6%)	17 (7.3%)	
Stage			<0.001
IA	9812 (69.3%)	93 (39.7%)	
IB	4002 (28.3%)	131 (56%)	
INOS	350 (2.5%)	10 (4.3%)	
Histology			0.08
Endometrioid	11310 (79.9%)	176 (75.2%)	
Non endometrioid	2854 (20.1%)	58 (24.8%)	
LVSI			<0.001
Absent	10617 (75%)	81 (34.6%)	
Present	2344 (16.5%)	128 (54.7%)	
Unknown	1205 (8.5%)	25 (10.7%)	
Tumor size			<0.001
<2 cm	2164 (15.3%)	16 (6.8%)	
>=2 cm	9648 (68.1%)	192 (82.1%)	
Unknown	2352 (16.6%)	26 (11.1%)	
Number of PaLN removed			0.13
5–9	9210 (65%)	141 (60.3%)	
>=10	4954 (35%)	93 (39.7%)	

Table 2
Rate of isolated para-aortic lymph node metastasis among patients with stage I uterine carcinoma and negative pelvic lymph nodes who had at least 5 para-aortic lymph nodes removed stratified by histology, substage and presence of lymphovascular invasion (n = 13170).

	Endometrioid	Non-endometrioid
Stage IA, LVSI negative	0.5 % (31/6415)	0.7% (11/1618)
Stage IB, LVSI negative	1.5% (32/2098)	1.3% (4/313)
Stage IA, LVSI positive	3.9% (30/775)	3.6% (11/303)
Stage IB, LVSI positive	5.5% (59/1078)	7.4% (21/282)

Table 3
Clinico-pathological predictors of isolated para-aortic lymph nodes metastasis among patients with stage I uterine carcinoma and negative pelvic lymph nodes who had at least 5 para-aortic lymph nodes removed.

	OR (95% CI)
Histology	
Endometrioid	Ref
Non-endometrioid	1.24 (0.91, 1.68)
LVSI	
Absent	Ref
Present	5.38 (3.99, 7.24)
Unknown	2.49 (1.58, 3.94)
Stage	
IA	Ref
IB	2.05 (1.53, 2.73)
INOS	3.02 (1.54, 5.93)
Size	
<2 cm	Ref
>=2 cm	1.62 (0.96, 2.73)
Unknown	1.10 (0.58, 2.07)

Our results are in accordance with prior smaller studies. In a large single-institution retrospective study that included 847 patients who underwent both pelvic and para-aortic lymphadenectomy only 12 (1.6%) had isolated PaLN metastasis [8]. In another series of 161 patients who had at least 8 negative pelvic LNs, the rate of isolated PaLN metastasis was 1.2%. Authors performed a review of literature and concluded that the

cummulative incidence of isolated PaLN metastasis is 1.7% (103/6024) [7]. A higher incidence (3%) was reported in a prospective study of 351 patients by Kumar et al (2014) [6]. In that study, the highest rate was noted in patients with high grade lesions with deep myometrial invasion. The location of the positive PaLNs relative to the inferior mesenteric artery was available in 9 patients. Interestingly, 7 of the 9 (78%) had disease in the high paraaortic area while only 3 patients had disease in the low para-aortic LNs [8]. In a recent systematic review of literature, Todo et al pooled data from 25 studies, and noted an overall 2.7% rate of isolated para-aortic LN metastasis; 1.6% (29/1781) among studies that included patients who had less than 10 L N removed and 3.5% (64/1819) among patients who had at least 10 L N removed [9]. Similar to our results, in a study that included 641 patients, LVSI (OR: 4.8) was identified as an important risk factor for the presence of PaLN metastasis along with the presence of positive pelvic lymph nodes (OR 18.8). In that study rate of isolated PaLN among patients with negative pelvic LN was 13.3% (14/105) and 0.2% (1/458) in the presence and absence of LVSI respectively. However, possibly due to a much larger sample size, in our study the rate of isolated PaLN metastasis among patients with LVSI was much lower and ranged from 3.6% to 7.4% based on the presence of other features such as substage and histology [10].

Estimation of the prevalence of isolated para-aortic lymph nodes is currently of great interest given the introduction of sentinel lymph node biopsy technique in the staging of endometrial cancer. Smith et al (2017) presented a pooled analysis of data from 55 studies; the overall detection rate of sentinel lymph node mapping was 81% with a sensitivity to detect metastases of 96% confirming its non-inferiority to standard LND [11]. In that study, the paraaortic detection rate ranged from 0% to 84%, with a pooled average of 17% (95% CI, 11–23, 41 studies) [11]. A recent meta-analysis also compared the sentinel lymph node technique to standard lymphadenectomy [12]. Authors pooled data from 6 studies that included 1249 patients in the sentinel lymph node and 2287 patients in the LND groups respectively. Detection rate of positive pelvic LN was higher in the sentinel lymph node group (OR: 2.03, 95% CI: 1.3, 3.18), while rates of positive para-aortic LN detected were comparable (OR: 0.93, 95% CI: 0.39, 2.18). Moreover, recurrence-free and lymph node recurrence rates were similar between the two groups [12]. However, with the most commonly used technique of cervical dye injection the para-aortic lymph node basins fails to map in the majority of cases. Higher rates have been reported with uterine corpus injections (subserosal, deep myometrial or peritumoral with hysteroscopic guidance) [13]. More specifically the rate of para-aortic mapping following uterine corpus injections is as high as 39% compared to 2% for the standard cervical injection [13]. Combination of cervical and corpus injections may aid in identifying sentinel lymph nodes in both pelvic and para-aortic basins. Recently, Eoh et al (2018) described a two-step sentinel lymph node mapping technique that included bilateral uterine cornual dye injections under laparoscopic visualization followed by uterine cervix injections with a sentinel lymph node detection rate of 86% (43/50) for the para-aortic area [14].

It should be noted that modern ultrastaging techniques employed in the algorithm of SLN detect the presence of isolated tumor cells (ITCs) and micrometastasis. A recent study that analyzed 414 patients who underwent sentinel lymph node biopsy revealed that ITCs are associated with a higher risk of para-aortic metastasis, while none of the patients with negative pelvic lymph nodes had isolated para-aortic metastasis [15]. Based on these results, we can speculate that a large number of patients with isolated para-aortic LN metastasis may in fact harbor ITCs or micrometastasis at the pelvic LNs that were not identified by regular histopathologic techniques. As such the actual rate of isolated para-aortic LN metastasis may be even lower than 1.6% observed in our cohort. This theory is further supported by a recent prospective study investigating the application of sentinel lymph node technique in patients with high risk endometrial cancer; micrometastasis and ITCs were present in the sentinel lymph nodes of 13% of patients with para-aortic LN metastasis, decreasing the incidence of isolated para-aortic LN metastasis from 2.4% to 1% [16]. Similarly, in a retrospective study, that included 394 patients who underwent both pelvic and para-aortic lymphadenectomy, all pelvic lymph nodes of patients found to have isolated para-aortic LN metastasis (n = 10, 2.5%) underwent ultrastaging; 3 patients were found to have occult pelvic dissemination decreasing the true incidence of isolated para-aortic LN metastasis to 1.8% [17].

Several limitations of the present study should be noted. Firstly, given the absence of central pathology review possible histology misclassifications cannot be excluded. Moreover, the exact location of the PaLNs dissected was not available thus we cannot comment on the location of the positive PaLN (low or high para-aortic area). In conclusion, based on the largest cohort to date, isolated PaLN metastases in the absence of pelvic lymph node metastasis are extremely rare among patients with disease limited to the uterus even in the presence of high-risk features. Results of the present investigation suggest that in the absence of a positive pelvic lymph node, performance of para-aortic LND can be omitted given the very low incidence of isolated LN metastasis for patients with low risk characteristics such as absence of LVSI.

Declaration of Competing Interest

Nothing to report.

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