Ultrastaging of Negative Pelvic Lymph Nodes to Decrease the True Prevalence of Isolated Paraaortic Dissemination in Endometrial Cancer

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Abstract

Objective: This study aimed to determine the prevalence of occult pelvic lymph node metastasis in patients with endometrial cancer (EC) with isolated paraaortic dissemination who underwent pelvic and paraaortic lymphadenectomy.

Methods: From 2004 to 2008, patients undergoing surgery for EC at our institution were prospectively treated according to a validated surgical algorithm relying on intraoperative frozen section. For the current study, we re-reviewed pathologic slides obtained at the time of diagnosis and performed ultrastaging of all negative pelvic lymph nodes to assess the prevalence of occult pelvic lymph node metastasis.

Results: Of 466 patients at risk for lymphatic dissemination, 394 (84.5%) underwent both pelvic and paraaortic lymphadenectomy. Of them, 10 (2.5%) had isolated paraaortic metastasis. Pathologic review of hematoxylin-eosin-stained slides identified 1 patient with micrometastasis in 1 of 18 pelvic lymph nodes removed. Ultrastaging of 296 pelvic lymph nodes removed from the 9 other patients (median [range], 32 [20-50] nodes per patient) identified 2 additional cases (1 with micrometastasis and 1 with isolated tumor cells), for a total of 3/10 patients (30%) having occult pelvic dissemination.

Conclusions: Ultrastaging and pathologic review of negative pelvic lymph nodes of patients with presumed isolated paraaortic metastasis can identify occult pelvic dissemination and reduce the prevalence of true isolated paraaortic disease. In the era of the sentinel lymph node (SLN) algorithm for EC staging, which incorporates ultrastaging of the SLNs removed, these findings demonstrate that use of the SLN algorithm can further mitigate the concern of missing cases of isolated paraaortic dissemination.

Keywords

endometrial cancer; isolated paraaortic metastasis; lymph nodes; stage IIIC; ultrastaging

Introduction

Many patients with endometrial cancer (EC) presumed to be confined to the uterus actually have extrauterine disease [1]. Thus, in 1988 the International Federation of Gynecology and Obstetrics introduced the concept of surgical staging for EC, which replaced the clinical

staging adopted in 1971 [2, 3]. Comprehensive surgical staging includes hysterectomy, bilateral salpingo-oophorectomy, pelvic washing, and pelvic and paraaortic lymphadenectomy [4]. However, after more than 25 years the therapeutic role of lymphadenectomy is still under debate, and consensus is lacking among gynecologic oncologists on the extent of surgical staging [5-8]. This controversy is mainly due to the results of 2 large, prospective trials comparing the addition of pelvic lymphadenectomy versus hysterectomy and bilateral salpingo-oophorectomy alone which failed to demonstrate survival benefits [9, 10].

Therefore, the use of sentinel lymph node (SLN) mapping in EC has gained acceptance among gynecologists and is supported by numerous prospective and retrospective studies that observed low false-negative rates (<5%) and high negative predictive values (>95%) [11, 12]. SLN mapping has revolutionized the staging process in presumed early-stage disease, largely replacing systematic pelvic and paraaortic lymphadenectomy in some institutions. Among the different techniques proposed for SLN mapping in EC, the use of cervical injection with indocyanine green is preferred [8, 13] and has been recently recommended by a consensus of the Society of Gynecologic Oncology [14].

Despite the literature supporting the use of SLN, a main concern and criticism of SLN mapping using cervical dye injection is that it does not adequately map the paraaortic area and may potentially miss instances of isolated paraaortic disease [15]. The overall frequency of paraaortic lymph node dissemination has been described as between 0% and 17% [16]. Kumar at al [17] demonstrated that in the presence of pelvic metastasis, 51% of patients had paraaortic lymph node dissemination, whereas in the absence of pelvic metastasis, only 3% had isolated paraaortic lymph node dissemination [17]. Similarly, other studies and reviews have shown that the risk of isolated paraaortic node metastasis ranges from 1% to 5% [17, 18].

A key component of the SLN algorithm proposed in the National Comprehensive Cancer Network guidelines for EC [19] is enhanced pathologic examination, also known as *ultrastaging*. This technique consists of evaluation for the presence of micrometastasis (tumor clusters >0.2-2.0 mm) and isolated tumor cells (single tumor cells or tumor clusters 0.2 mm) by immunohistochemistry (IHC) in lymph nodes that are negative at initial examination performed using hematoxylin-eosin (H&E) staining [20, 21]. Ultrastaging was found to identify occult paraaortic metastasis in 73% of patients identified as being positive for pelvic node metastasis and negative for paraaortic node metastasis [22]. However, the prevalence of occult pelvic lymph node metastasis in patients with isolated paraaortic disease remains unexplored.

In the current study, we aimed to investigate whether pathologic review followed by ultrastaging of negative pelvic lymph nodes of patients with presumed isolated paraaortic disease could identify occult pelvic metastasis and decrease the prevalence of true isolated paraaortic disease.

Methods

This study was approved by the Mayo Clinic Institutional Review Board. The study cohort was identified by retrospectively searching our patient database for the records of consecutive patients who underwent surgical staging of EC at Mayo Clinic, Rochester, Minnesota, from January 2004 through December 2008 and who had not denied research authorization. Patients who received neoadjuvant therapy, had invasive synchronous cancer, or had stage IV disease were subsequently excluded. During this time period, our prospective surgical algorithm recommended not performing lymphadenectomy in patients deemed to be at low risk for lymphatic dissemination according to intraoperative pathologic examination. These low-risk patients—historically approximately 30% of the total EC population—are those with either 1) endometrioid histologic type, myometrial invasion of 50% or less, grade 1 or 2 disease according to the histologic classification of the World Health Organization [23], and tumor diameter of 2 cm or smaller [24, 25] or 2) endometrioid histologic classification and no myometrial invasion regardless of grade. In contrast, patients considered at risk for lymphatic dissemination were candidates for systematic pelvic and paraaortic lymphadenectomy up to the renal vessels. Systematic pelvic and paraaortic lymphadenectomies were performed predominantly by laparotomy. Further details on the surgical strategy implemented at our institution during the study period have been previously reported [17, 26].

For this study, we included at-risk patients with stage IIIC EC who underwent both pelvic and paraaortic lymphadenectomy and further identified those with isolated paraaortic metastasis. Among these patients, the prevalence of occult pelvic lymph node metastasis was assessed by re-review of pathologic slides and ultrastaging. Briefly, we retrieved formalin-fixed, paraffin-embedded blocks of lymph nodes and H&E-stained slides obtained at the time of the surgery for diagnostic purposes, which were stored by the Tissue Registry at Mayo Clinic. First, all the H&E-stained slides were reviewed by an expert pathologist (G.L.K.) to confirm the presence of enough lymph nodal tissue and to confirm the diagnosis made at the time of surgery. Subsequently, we performed ultrastaging of the pelvic lymph nodes of the patients with confirmed negative pelvic lymph nodes and isolated paraaortic metastasis by following the protocol used at Mayo Clinic.

According to this protocol, ultrastaging was performed by cutting 2 adjacent 4-μm sections at the first level, and 1 4-μm sections at the second and third levels, 40 μm apart, from each formalin-fixed, paraffin-embedded block. At each level, 1 slide was stained with H&E, and the remaining slide at the first level was stained with IHC using anti-cytokeratin AE1/AE3 antibody (Ventana Medical Systems, Inc), for a total of 3 H&E sections and 1 IHC section per block. Lymph node metastases were classified as macrometastasis (tumor clusters >2 mm), micrometastasis (tumor clusters >0.2-2.0 mm), or isolated tumor cells (single tumor cells or tumor clusters 0.2 mm)[27]. As per an ongoing collaboration between Mayo Clinic and the University of Cagliari, Italy, part of the IHC sections were stained in the Department of Surgical Sciences at University of Cagliari, Italy, following the same protocol.

Results

From January 2004 to December 2008, 790 patients with EC were treated surgically at our institution and had research authorization; of these, 99 met the initial exclusion criteria and 225 were excluded because of low risk of lymphatic dissemination (Figure). Among the 466 patients who were at risk for lymphatic dissemination and were candidates for complete lymphadenectomy, 28 had pelvic lymphadenectomy, 1 had paraaortic lymphadenectomy, and 394 (84.5%) had both; the other 43 had neither pelvic nor paraaortic lymphadenectomy because of comorbid conditions (Figure).

Among the 394 patients who underwent both pelvic and paraaortic lymphadenectomy, 10 (2.5%) were identified as having isolated paraaortic metastasis. Patient and tumor characteristics for these 10 patients are shown in the Table. The location of the isolated paraaortic metastasis in relation to the inferior mesenteric artery was both above and below the artery in 1 patient, only above the artery in 5 patients, only below in 2 patients, and unknown for the other 2 patients.

For 1 of these 10 patients, a micrometastasis was identified in 1 of her 18 pelvic lymph nodes by pathologic review of the diagnostic H&E slides before ultrastaging. Subsequently, on ultrastaging of all 296 pelvic lymph nodes from the remaining 9 patients with isolated paraaortic dissemination (median [range], 32 [20-50] nodes per patient), we identified 2 additional patients with positive pelvic lymph nodes. Thus, 3 of 10 patients (30%) had occult pelvic lymph node metastasis. The largest size of metastasis identified by ultrastaging was micrometastasis in 1 patient and isolated tumor cells in the other patient. Therefore, the prevalence of true isolated paraaortic metastasis in our cohort is 1.8% (7/394; 95% CI, 0.7%-3.6%).

Discussion

To our knowledge, this is the first study demonstrating that pathologic review and ultrastaging of pelvic lymph nodes of patients with isolated paraaortic dissemination can identify low-volume metastases that were not detected by routine pathologic examination at the time of diagnosis. In particular, with pathologic review and ultrastaging we detected low-volume metastases in the pelvic lymph nodes of 30% of patients with presumed "negative" pelvic lymph nodes and isolated paraaortic dissemination.

Isolated paraaortic dissemination is present in 1% to 5% of patients undergoing pelvic and paraaortic lymphadenectomy [18], and the incidence could be as high as 16% in the small cohort (13%) of patients with grade 2-3 endometrioid EC and myometrial invasion of 50% or greater [17]. In the SLN mapping era, although the application of the SLN algorithm using cervical dye injection has demonstrated accuracy in identifying patients with lymph node metastasis, the potential risk of missing isolated paraaortic disease remains one of the main concerns and criticisms, because cervical injection may not adequately map the paraaortic area [28]. An important step in the application of the SLN algorithm is ultrastaging, which allows for identification of low-volume metastases that are not detected with routine pathologic examination with H&E. For example, in a large series from

Memorial Sloan Kettering Cancer Center including 12.6% of patients with positive lymph nodes, the positive nodes were detected by the initial pathologic examination in only 6.9%, whereas H&E and ultrastaging identified an additional 4.5% of patients with low-volume metastasis that would otherwise have been missed [20]. Although in the current study we performed ultrastaging of all pelvic lymph nodes (not just the SLNs), on the basis of our findings we speculate that pelvic SLN mapping with ultrastaging may decrease the prevalence of true isolated paraaortic dissemination by identifying occult low-volume metastasis.

Of note, although paraaortic lymphadenectomy was performed in only 58% of patients in the FIRES trial [11], isolated metastatic lymph nodes located in the paraaortic area were identified in 3 patients. However, 2 of the patients had isolated paraaortic dissemination in the paraaortic SLNs, and in the other patient it was found after routine paraaortic lymphadenectomy when no SLNs were identified (1 of 340 patients [<1%] in the overall trial). Similarly, in a prospective study of patients with high-risk EC undergoing SLN followed by pelvic and paraaortic lymphadenectomy at MD Anderson Cancer Center [29], 1 patient was determined to have isolated paraaortic disease after the SLNs were not detected (1 of 101 [1%] high-risk patients). Therefore, isolated paraaortic disease is rare but may occur, and high-risk patients with "unmapped" SLNs seem to be at risk for it.

It should be noted that the surgical algorithm described here is historical and that the staging approach at Mayo Clinic has evolved. In fact, starting in 2013, surgical treatment of EC has incorporated the use of SLN mapping [30], with the majority of current patients being treated according to the SLN algorithm developed at Memorial Sloan Kettering Cancer Center [31], which is included in the National Comprehensive Cancer Network guidelines [19]. Moreover, the minimally invasive approach has replaced laparotomy, with 90% of patients undergoing minimally invasive surgery in 2013-2014 [32].

The strengths of our study include the large cohort of consecutive patients treated by following a prospective and validated surgical algorithm, including systematic pelvic and paraaortic lymphadenectomy up to the renal vessels, and stringent quality controls [33]. Another strength is the use of a standardized method of pathologic ultrastaging with specialized pathologic review. Despite the large cohort, our study is limited by the small number of patients with isolated paraaortic metastasis, which makes it difficult to draw conclusions on the exact prevalence of low-volume metastasis in the pelvic lymph nodes of these patients.

In conclusion, our study showed that pathologic review and ultrastaging of negative pelvic lymph nodes can decrease the prevalence of true isolated paraaortic dissemination by identifying occult low-volume pelvic metastasis. Although the risk of isolated paraaortic disease still exists and should be considered during the shared decision-making process between physician and patient, our study indirectly further supports the use of SLN mapping with cervical dye injection. In fact, it demonstrates that the SLN algorithm with pathologic ultrastaging may be more sensitive than pelvic lymphadenectomy because it can detect additional microscopic pelvic metastases that would otherwise be missed by routine evaluations.

Acknowledgments

Abbreviations

EC	endometrial cancer
H&E	hematoxylin-eosin
IHC	immunohistochemistry
SLN	sentinel lymph node

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Research Highlights

- Ultrastaging pelvic lymph nodes in isolated paraaortic disease can identify occult metastasis.

- Ultrastaging identified pelvic disease in 30% of patients with "isolated" paraaortic metastasis.

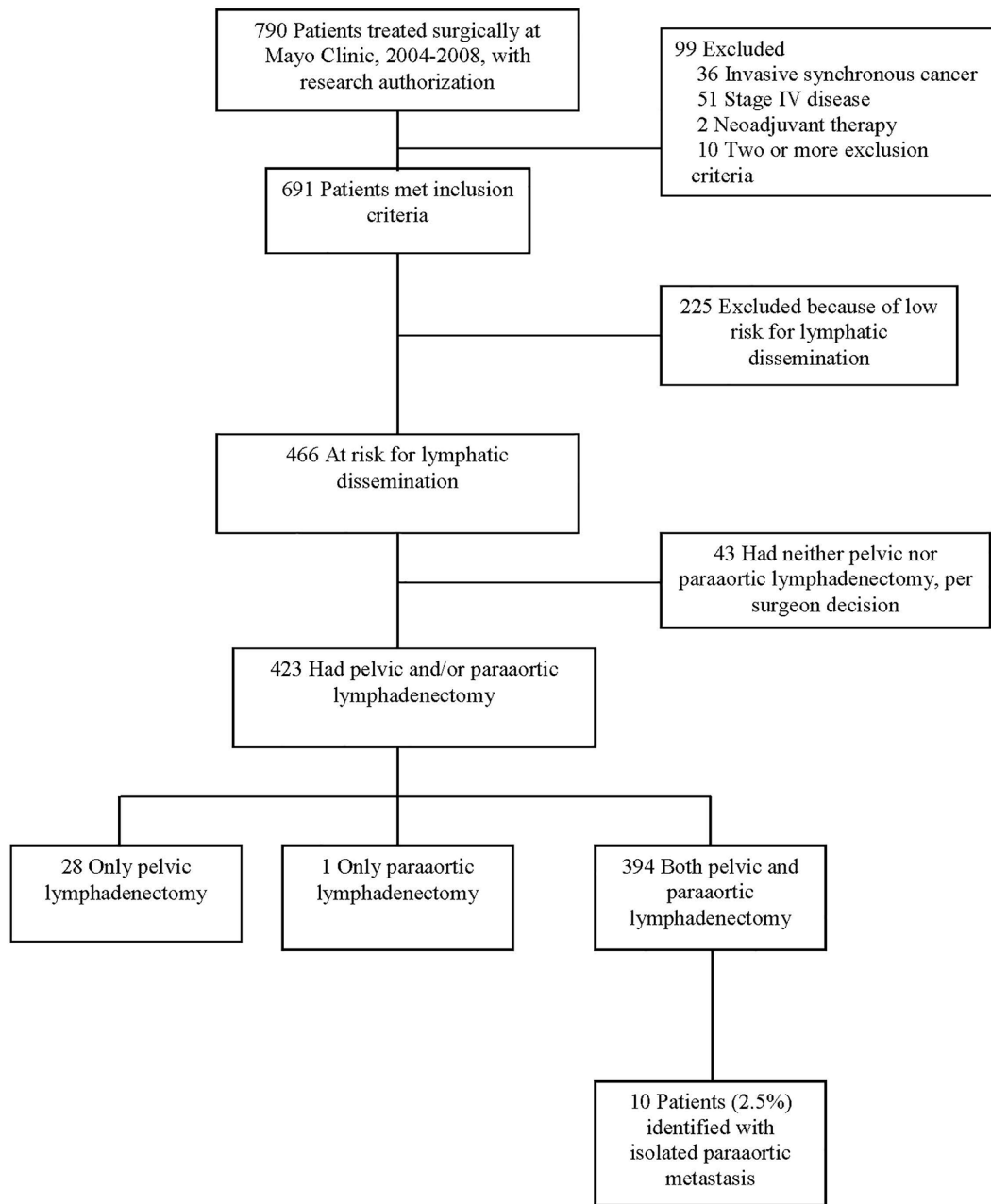- The prevalence of true isolated paraaortic metastasis is 1.8%.

Figure.
Flow Chart of the Study Population.

Table 1.

Characteristics of 10 Patients With Isolated Paraaortic Metastasis

Pt	Age at Surgery, y	Histologic Type	FIGO Grade	MI, %	Tumor Diameter, mm	Cervical Invasion	LVSI	Peritoneal Washing	Paraaortic Lymph Nodes		No. of Total Nodes Positive		No. of Pelvic Nodes		Largest Metastasis
									No. Removed	No. Positive[a]	Above IMA	Below IMA	Removed (All Negative) and Ultrastaged	Positive After Ultrastaging	
1	66	Endo	2	90	50	No	Yes	Pos	11	1	0	1	32	4	MMt
2	79	Ser	3	0	40	No	No	Pos	25	1	1	0	21	0	…
3	50	Endo	2	75	30	No	Yes	Pos	33	2	1	1	18	1[b]	MMt
4	78	Endo	3	53	10	No	Yes	Neg	10	1	0	1	38	0	…
5	57	Endo	3	69	28	No	Yes	Pos	27	3	Unk	Unk	50	0	…
6	60	Endo	3	88	45	No	No	Neg	11	1	Unk	Unk	23	0	…
7	65	Endo	2	25	30	No	No	Neg	24	1	1	0	36	0	…
8	75	Endo	2	60	60	No	Yes	Neg	14	1	1	0	44	0	…
9	64	Ser	3	22	68	No	No	Pos	27	1	1	0	32	0	…
10	55	Endo	2	55	50	No	No	Neg	9	1	1	0	20	2	ITC

Abbreviations: Endo, endometrioid; FIGO, International Federation of Gynecology and Obstetrics; IMA, inferior mesenteric artery; ITC, isolated tumor cells; LVSI, lymphovascular space invasion; MI, myometrial invasion; MMt, micrometastasis; Neg, negative; Pos, positive; Pt, patient; Ser, serous; Unk, unknown.

[a] All positive paraaortic lymph nodes were macrometastasis.

[b] Ultrastaging was not performed because MMt was identified by reviewing the diagnostic hematoxylin-eosin-stained slides before ultrastaging.