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ORIGINAL ARTICLE

The Futility of Systematic Lymphadenectomy in Early-Stage Low-grade Endometrial Cancer

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Abstract

Lymphadenectomy is considered an integral part of comprehensive surgical staging of endometrial cancer but debate on the value of lymphadenectomy continues in early-stage endometrial cancer. The aim of our study was to determine the number of node positive patients in clinically early-stage low-grade (G1–G2) endometrioid endometrial cancer. We retro-prospectively analyzed the medical records of 155 women with endometrial pathology coming to the BLK cancer center between January 2015 and December 2017 and studied 60 patients of FIGO grade 1–2 endometrioid endometrial cancer confined to the uterus to determine the nodal positivity. Out of total 60 cases, 2 (3.3%) patients had positive nodes indicating the very low incidence of nodal positivity in clinically uterus confined low-grade endometrioid tumors. Both pelvic and para-aortic lymph nodes were positive in 1 patient. Skip metastases with para-aortic nodal positivity only while pelvic lymph nodes being negative were found in 1 (1.6%) patient. The necessity of comprehensive lymphadenectomy in endometrial cancer remains controversial. Sentinel node mapping can be a reasonably good alternative to strike a balance between systematic lymphadenectomy and no dissection at all in low and intermediate risk endometrial cancer.

Keywords Systematic lymphadenectomy · Early stage endometrial cancer

Introduction

Endometrial cancer (EC) is the most common gynecologic malignancy in developed countries and the incidence continues to rise. However, in developing countries like India, EC falls second in the list next to cervical cancer. The most frequently occurring histologic subtype is endometrioid adenocarcinoma. Seventy five percent of EC patients are diagnosed in stage I as the disease is frequently symptomatic at an early stage. Survival rates exceed 80% following primary surgery [1].

Historically, primary surgical staging included extrafascial hysterectomy, bilateral salpingo-oophorectomy, and pelvic + para-aortic lymphadenectomy. The role of lymphadenectomy in the management of apparent early-stage endometrial cancer continues to be debatable due to a lack of therapeutic benefit and increased risk of postoperative sequelae [2, 3].

One of the biggest challenge in defining the optimum surgical treatment of EC arises from inconsistencies in staging, particularly in lymphadenectomy which ranges from lymph node sampling alone in patients who are at an increased risk of nodal metastases to complete systematic lymphadenectomy in all cases of EC irrespective of clinical stage, grade, and depth of myometrial invasion. Complete lymphadenectomy up to the renal vessels is acceptable in high-risk EC and has a survival benefit while the surgical morbidity of same gets compounded in early-stage low-grade tumors in elderly patients with associated co-morbidities of obesity, diabetes, hypertension, hypothyroidism etc.

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There is an increasing interest to adopt sentinel lymph node (SLN) strategy in apparent early-stage EC as an alternative approach to systematic lymphadenectomy in order to select patients for systematic pelvic and para-aortic lymph node dissection.

Methods

A total of 458 patients of gynecological cancers were admitted, treated, and followed up at the BLK cancer center from January 2015 to December 2017. Among these, 155 patients had presented with an endometrial pathology, out of which 45 patients had benign disease including complex (7) and simple (2) hyperplasia and 2 patients had uterine leiomyosarcoma. Seven patients had a diagnosis of recurrent EC, 1 patient had residual disease with multiple lung metastatic nodules post incomplete surgery at another center and 5 patients of EC were managed conservatively, leaving a number of 95 newly diagnosed cases of EC who underwent primary surgical staging. Out of these, 60 patients had clinically uterus-confined EC with a preoperative diagnosis of endometrioid EC with grade 1–2.

The medical records of these 60 patients were retro-prospectively analyzed and studied. Patient demographics included age, body mass index (BMI), parity, menopausal status, and presence of co-morbidities like diabetes or hypertension or hypothyroidism. Preoperative grade and histology were studied. All patients of EC with uterus confined disease clinically and on imaging and G1 or G2 were included in the analysis. Exclusion criteria were preoperative diagnosis of grade 3 endometrioid tumors, non-endometrioid histologies, carcinosarcomas, and evidence of extra-uterine disease on abdominal imaging. Thus, 35 patients were excluded.

All patients underwent primary surgical staging including hysterectomy with bilateral salpingo-oophorectomy, bilateral pelvic +/− para-aortic lymphadenectomy, and peritoneal fluid cytology. FIGO 2009 staging was followed to stage the patients.

The extent of surgical staging, duration of surgery, blood loss, length of hospital stay, duration of postoperative pelvic drains, drain output, wound infection, lymph nodal harvest, surgico-pathological stage and grade, tumor size and location, myometrial and lymphovascular invasion, node positivity, adjuvant treatment, and follow-up were noted. The diagnosis of synchronous endometrial and ovarian cancer was based on criteria outlined by Scully et al. [4].

Results

Among 95 patients of newly diagnosed EC, 70 (73.6%) patients had stage I disease. The most common histology was endometrioid adenocarcinoma in 80% (76/95) patients, followed by uterine papillary serous carcinoma in 11.5% (11/95), and malignant mixed mullerian tumor in 8.4% (8/95). Three patients had synchronous malignancies with two patients having co-existing endometrial and ovarian cancers while one patient had high-grade serous adenocarcinoma co-existing with breast ductal carcinoma in situ. Two patients had EC with ovarian metastases.

A total of 60 patients were included in our study. The median and mean age of our patients were 60.5 and 60.2 years, respectively (range: 28–76 years). Only 1 (1.6%) patient was aged less than 40 years, while 4 (6.6%) patients had age less than 50 years. Median and mean BMI of our patient population were 31.9 and 31.65 kg/m^2, respectively (range: 21.6–45 kg/m^2) attributing obesity as a high-risk factor for EC. Baseline patient characteristics are presented in Table 1.

Fifty four patients (90%) were postmenopausal and 6(10%) patients were premenopausal. Nulliparity was found in 10% (6/60) women, while 81.6% (49/60) women had parity 2 or more (range: P0–P9). Co-morbidities included hypertension in 30 patients, while 22 were diabetic, 14 were hypothyroid, 2 were asthmatic, 2 had past history of taking anti-tubercular treatment for endometrial tuberculosis, and pulmonary Koch's respectively. Endometrioid histology was reported in preoperative biopsy specimens of 49 patients, followed by complex atypical hyperplasia (possibility of well-differentiated adenocarcinoma could not be ruled out) in 9 patients. Two patients had dilatation and curettage reports of necrotic tissue and scanty tissue respectively, but since the hysteroscopic findings were highly suspicious for carcinoma, these 2 patients were taken up for an intra-operative frozen section analysis and proceeded to staging when frozen was reported as positive for malignancy.

Preoperative histological diagnosis of malignancy was present in 49 patients. Intra-operative frozen section for confirmation of malignancy was done in 11 patients due to preoperative complex atypical hyperplasia or inconclusive preoperative histopathology report but suspicious imaging findings. In addition, 2 cases who had suspicion of dual malignancy were subjected to frozen evaluation of ovarian mass which was reported as positive for malignancy. One patient had synchronous primary in the ovary and the other had ovarian deposits from EC. Forty-four (73.3%) patients had a primary tumor diameter of more than 2 cm, while only 16 (26.6%) patients had a tumor less than or equal to 2 cm. Thirty-seven patients had MI of less than 50%, 22 patients had more than 50% MI, and no MI was found in 1 patient. Peritoneal fluid cytology was positive in 2 patients with stage IAG2 tumor in one and metastatic deposit on right ovary upgrading the stage to IIIAG1 endometrioid EC in the other. The tumor was located in the endometrium in 53 patients, fundal region in 6 patients, lower uterine segment in 1, and synchronous and metastatic tumor respectively in the ovary in 2 patients.

Table 1 Baseline patient characteristics

Characteristics	Number (*n*)	Percentage (%)
Age (years)		
Median	60.5	
Range	28–76	
>/= 60	31	51.6
< 60	29	48.3
BMI (kg/m^2)		
Median	31.9	
Range	21.6–45	
Menopausal status		
Premenopausal	6	10
Postmenopausal	54	90
Parity		
Nulliparous	6	10
Primiparous	5	8.3
Multiparous	49	81.6
Range	0–9	
Co-morbidities		
Hypertensive	30	50
Diabetic	22	36.6
Hypothyroid	14	23.3

BMI body mass index

Systematic pelvic and para-aortic lymphadenectomy was done in 44 patients, while pelvic lymphadenectomy alone was done in 16 patients. Six out of the 16 patients who had only pelvic lymphadenectomy done had preoperative biopsy report of complex endometrial hyperplasia and the intra-operative frozen section reported as— "complex atypical hyperplasia, possibility of well differentiated carcinoma would be ruled out on a permanent section only." The advanced age and co-morbidities of remaining ten patients did not allow longer operative time exposing them to the adverse affects of prolonged anesthesia. The para-aortic nodal dissection was done below the inferior mesenteric artery (IMA) in 33 cases while up to the renal vein in 11 patients. The median number of pelvic and para-aortic lymph nodes removed were 25.5 (range: 9–48) and 8 (range: 0–25). Both pelvic and para-aortic lymph nodes were positive in one patient. Skip metastases with para-aortic nodal positivity only while pelvic lymph nodes being negative were found only in one (1.6%) patient. In both the patients with para-aortic nodal positivity, the surgery included nodal retrieval below IMA. Pelvic node positivity was thus observed in 1.6% (1/60) patients and para-aortic nodal positivity in 3.3% (2/60) patients. Lymphovascular space invasion (LVSI) was positive in seven patients while indeterminate in one patient. Out of these, only two patients with LVSI positivity had lymph nodal metastases on final histopathology report. Three patients were upstaged to stage 3 with para-aortic node positivity in two and ovarian metastases in one. Pathologic variables have been given in Table 2.

Table 2 Pathologic variables

Variables	Number (n)	Percentage (%)
Preoperative histology		
Endometrioid	49	81.6
CAH	9	15
Scanty tissue	1	1.6
Necrotic tissue	1	1.6
Preoperative grade (G)		
G1	27	45
G2	16	26.6
CAH	9	15
Unknown	8	13.3
Myometrial invasion		
Less than 50%	36	60
More than 50%	22	36.6
No myometrial invasion	1	1.6
Complex hyperplasia	1	1.6
Tumor diameter		
</= 2 cm	16	26.6
> 2 cm	44	73.3
LVSI		
Positive	7	11.6
Indeterminate	1	1.6
Negative	52	86.6
Pelvic lymph node dissection		
Done in (total number of pts)	60	100
Negative	59	98.3
Positive	1	1.6
Para-aortic lymph node dissection		
Done in (total number of pts)	44	73.3
Negative	42	70
Positive	2	3.3

CAH complex atypical hyperplasia, *LVSI* lymphovascular space invasion

Adventitial injury to right ureter occurred in one patient and required ureteric stenting for 6 weeks. Inadvertent injury to inferior venacava (IVC) occurred during para-aortic nodal dissection in one patient and was successfully repaired. IVC was interestingly found on the left side of aorta in one case. Major postoperative complications were excessive drain output and paralytic ileus in 17 and 8 patients respectively. The most common complication observed in the follow-up period was incisional hernia in 25 (41.6%) patients (Table 3).

The time taken for the surgical staging was on an average 3.5 h (range: 2–6 h). Average blood loss was 332.5 ml (range: 150–600 ml). All patients were managed in surgical ICU postoperatively for 2 days on an average. The average length of hospital stay was 7.2 days (range: 5–16 days). Pelvic drains were removed on an average of 5 days once the drain output reached below 50 ml. Excessive drain output of more than 500 ml per day occurred in 17 (28.3%) patients of our study requiring prolonged placement of intra-abdominal drains (range 4–28 days). Excessive drain output in one of our patients continued for about 4 weeks requiring the drain to be

Table 3 Postoperative complications

Complication	Number of patients (percentage)
Excessive drain output	17 (28.3)
Paralytic ileus	8 (13.3)
Wound Infection	7 (11.6)
Wound dehiscence	1 (1.6)
Atrial fibrillation	1 (1.6)
Hypoxia and tachycardia	1 (1.6)
B/L pleural effusion requiring BIPAP	1 (1.6)
Pseudo-thrombocytopenia	1 (1.6)
Deep vein thrombosis	1 (1.6)
Urinary incontinence	1 (1.6)
Incisional hernia	25 (41.6)

kept for 28 days postoperatively. Postoperatively, nine patients developed minor abdominal wound sepsis, which responded well to antibiotics as per the culture sensitivity report and wound management. One patient had burst abdomen which required re-suturing under general anesthesia.

Both the node positive patients in our study had G2 tumors with tumor size of more than 2 cm, myometrial invasion of more than 50% and positive LVSI. The final results in node positive and node negative patients have been tabulated in Tables 4 and 5. These patients were treated with adjuvant chemotherapy, external beam radiation, and vaginal brachytherapy. Adjuvant treatment in the remaining patients consisted of brachytherapy in 22 patients: external beam pelvic radiation therapy and vaginal brachytherapy in 3 patients, while chemotherapy in 3 patients. The node positive patients are being followed up at 6 and 13 months respectively, while the rest of our patients have a range of 1–35 months of follow-up.

Discussion

Although EC is conventionally thought to be a cancer of the postmenopausal women, only 15% are diagnosed before age 50 years and only 5% before age 40 years [5]. In our study, only 1 (1.5%) patient was less than 40 years of age while 4 (6.25%) patients had age less than 50 years. Ninety percent of our study population was postmenopausal. Eighty percent of patients of EC are diagnosed at stage I. Our center had an incidence of stage I EC as 73.6%. Majority of these have low-risk EC (FIGO grade 1 and 2 endometrioid EC with less than 50% myometrial invasion) [6].

The significance of lymph node dissection in early-stage low-grade endometrioid cancer of uterus is uncertain due to the overall favorable prognosis. Various studies have been published with regard to the node positivity in low-grade early EC. Abu Rustum and colleagues documented that in-patients with endometrioid EC stage IAG1–2 and tumor diameter less than 2 cm, the probability of positive lymph nodes or lymph node recurrence is less than 1%. In the remaining patients of endometrioid EC, the risk of positive nodes (pelvic/para-aortic) is more than 4% in stage IA tumors and more than 10% in stage IB tumors [7]. Creasman et al. stated that within stage I disease, 3–5% of women with grade I tumors and superficial myometrial invasion will have lymph node involvement. This percentage rises to around 20% in women with stage IB grade 3 tumors. Pelvic lymph node metastases occurs in about 10% of women with clinical stage I EC [8]. Mariani and colleagues at the Mayo clinic had published data on surgical triage of early EC patients and found a lymph node involvement in only 5% patients of early EC [6]. A review of 1109 patients with clinical stage I–II EC showed lymph nodal involvement in only 11% of patients by Benedetti-Panici et al. [9].

Our study showed a nodal positivity of 3.3% (2/60) in early-stage low-grade EC. Both the patients of our study had uterus confined disease to begin with having grades 1 and 2 respectively. On final histopathology report, both patients had G2 tumors of size more than 2 cm with more than 50% myometrial invasion and positive lymphovascular invasion.

In the Mayo Clinic experience, Bakkum-Gamez et al. considered a systematic lymphadenectomy as adequate if at least 22 pelvic and 10 para-aortic lymph nodes had been resected [10]. Chan et al. demonstrated that removal of 21 to 25 nodes provided an 80% probability of detecting at least one positive lymph node [11]. The median number of pelvic and para-aortic lymph nodes removed in our study were 25.5 (range: 9–48) and 8 (range: 0–25) respectively. No national or international accepted guidelines exist for what is regarded as an adequate systematic lymphadenectomy in terms of nodal harvest, and therefore the oncosurgeon performing the surgery herself is the only one to decide whether the lymphadenectomy she performed was complete or not. Two retrospective reviews have shown that patients had an improved survival when at least 10–12 nodes were removed during lymphadenectomy in EC [12, 13].

Because of the considerable increase in morbidity and possible lack of survival advantage after systematic pelvic and para-aortic lymphadenectomy in EC, the role of lymph node dissection is always on discussion, especially in low-grade early-stage disease with pure endometrioid histology. Chan JK et al. studied data from the US National Cancer Institute database on 39,396 women of EC and compared 12,333 women who underwent staging including lymph node dissection with 27,063 women who did not undergo lymphadenectomy, and found no benefit of lymph node dissection in patients with stage I, G1–2 [14].

There is wide variation in clinical practice regarding the indications and extent of lymphadenectomy among the gynae-oncosurgeons in managing EC patients particularly with respect to the early-stage low-grade EC with

Table 4 Results in node positive patients

Node positive patients ($n = 2$)

	Age (y)	Histology	G	Tumor Size (cm)	Tumor location	MI	LVSI	Stage	Cytology	Pelvic nodes	P/A nodes	F/U (mth)
Pt 1	53	Villoglandular	2	> 2	Endometrium	> 50%	+	IIIc2	neg	pos	pos	6
Pt 2	76	Endometrioid	2	> 2	Fundus + body	> 50%	+	IIIc2	neg	neg	pos	13

y years, *G* grade, *MI* myometrial invasion, *LVSI* lymphovascular space invasion, *P/A* para-aortic, *F/U* follow-up, *Pt* patient, + present, *neg* negative, *pos* positive

Table 5 Results in node negative patients

Node negative patients (n=58)

Age (years)	<40	40-60	>60	
	1	27	30	
Final histology	Endometrioid	54		
	Mucinous Endometrioid	1		
	MMMT	1		
	UPSC	1		
	Hyperplasia	1		
Grade (G)	G1	G2	G3	Hyperplasia
	29	25	3	1
Tumor size (cm)	</= 2	>2		
	16	42		
Tumor location	Endometrium	Fundus	LUS	Ovary (syn+mets)
	52	5	1	2
Myometrial invasion (MI)	No MI	<50%	>50%	Hyperplasia
	1	36	20	1
Lymphovascular space invasion	Absent	Present	Indeterminate	
	52	5	1	
Stage	IA	IB	III	Hyperplasia
	37	19	1	1
Cytology	Negative	Positive		
	56	2		
Pelvic nodes	Negative			
Para-aortic nodes	Negative			
Follow up (months)	Range : 1-35			

MMMT malignant mixed mullerian tumor, *UPSC* uterine papillary serous carcinoma, *syn* synchronous, *mets* metastases

endometrioid histology. Retrospective single institution studies advocate complete lymphadenectomy for all grades of tumor [15, 16]. In contrast, a series of US database supports complete lymphadenectomy for high-grade tumors only [17]. MRC ASTEC trial showed no benefit in terms of overall or recurrence-free survival for pelvic lymphadenectomy in women with early EC [3]. A systematic lymph node dissection at most centers in stage I G1–2 tumors is done merely to stage, prognosticate, and decide adjuvant treatment without any therapeutic benefit of preventing recurrence or for that matter increasing the overall or progression-free survival. Having said that, the authors of the present study advocate the adoption of utilizing the advantage of sentinel node mapping techniques as a trade-off between no nodal dissection and complete lymphadenectomy in low-grade endometrioid EC clinically confined to the uterus. Although lymphadenectomy helps to stage the disease which eventually guides the adjuvant treatment, lymphadenectomy per se does not seem to have a therapeutic value except prognosticating the disease.

A large number of EC patients are obese and so lymph node dissection becomes technically challenging particularly in the para-aortic area. Para-aortic lymph node dissection is associated with more operating time, risk of vascular or nerve injury, increased rates of postoperative ileus, increased perioperative blood loss, and a significantly more lymphorrhoea. Excessive drain output in the present study was found in 28.3% patients. Eight patients (13.3%) in our study developed postoperative ileus. Our study showed that in order to detect 2 node positive patients in clinically early-stage low-grade EC, a total of 60 patients had been subjected to the morbidity of systematic lymphadenectomy with associated postoperative sequelae. Since sentinel lymph node mapping focuses on finding positive nodes, it can potentially identify majority of endometrial cancer patients with lymphatic dissemination, the exceptions being those who present with isolated para-aortic metastases. However, direct para-aortic drainage in early-stage EC is estimated to occur in only 1% of cases [18]. Also in our study, para-aortic metastases were seen in 1.6% of patients.

Sentinel lymph node mapping and selective lymphadenectomy during the early stage of EC comprised an effort to achieve a survival benefit and decrease adverse effects of lymphedema or delayed postoperative recovery. In gynecological cancers, the most frequent use of sentinel lymph node procedure is in vulvar cancer. Sentinel lymph node biopsy is underutilized in EC in Indian scenario due to lack of infrastructure, financial implications, knowledge, expertise, and practice variations among treating surgical teams, necessity of trained histopathologists for ultrastaging and the need to validate the results at a particular center as an initial step towards implementing SLN mapping as a routine practice. Now, there has been a growing interest of sentinel lymph node techniques in EC where lymph node mapping can be viewed solely as a staging procedure allowing appropriate triage of patients for adjuvant therapy. The rationale of sentinel lymph node mapping is to detect and selectively remove the first node(s) in a regional lymphatic basin that receives lymph flow from the primary tumor. Pathologic status of the removed sentinel node can accurately predict the node status of the patient. Therefore, if the sentinel node is negative, a systematic lymphadenectomy can be avoided resulting in reduced morbidity associated with this major surgical intervention.

Sentinel nodes can be identified by two methods either with the help of vital stains or radioactive isotopes. The three dyes used most commonly are isosulfan blue, patent blue violet, and methylene blue. The most common radioactive material used is the technetium 99 labeled sulfur colloid. Detection of radioactivity in nodal basin requires the use of gamma probe. Indo-cyanine green (ICG) is another agent that relies on the use of near infra-red imaging on a minimally invasive platform. So far, only a few retrospective series have studied SLNB, and these have had small sample sizes, used various injection sites, and reported detection rates of 45–94% and false negative rates of 0–33% justifying further prospective validation [19].

The NCCN guidelines have now incorporated the Memorial Sloan Kettering algorithm for SLN mapping in the management of EC. Sentinel node mapping is not routinely being done at our cancer center for EC, but since the results of SLN research in EC are promising, the authors would definitely incorporate the practice of same in near future. The main interest in the concept of sentinel node mapping in early-stage EC is to avoid the morbidity of complete lymphadenectomy without compromising the identification of patients who will benefit from adjuvant treatment.

The limitations of our study include single institution data and the retrospective nature. Retrospective studies are known to have an element of bias.

Conclusion

The role of lymphadenectomy in early-stage EC still remains controversial as far as its indications, anatomic extent and therapeutic value are concerned. EC patients with clinically stage I low-grade disease (G1–2) with less than 50% myometrial invasion seem to be at low risk of lymph node metastases and may go away without a systematic lymphadenectomy avoiding the associated surgical morbidity.

Although systematic pelvic and para-aortic lymphadenectomy is strongly recommended in patients with type 2 EC (clear cell, serous, carcinosarcomas), patients with endometrioid histology particularly the low-grade early-stage ones can effectively be managed with a sentinel node mapping instead of a complete lymphatic node dissection. SLN biopsy represents a compromise between no node dissection and full

nodal dissection. In addition, ultrastaging of the sentinel lymph nodes helps in detecting micrometastases otherwise undiagnosed by conventional histology, even in those patients who are at low risk, on the basis of grade and depth of myometrial invasion [20].

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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