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ORIGINAL ARTICLE

Role of Pelvic Lymphadenectomy in Intermediate-Risk Endometrial Cancer and Predictors of Nodal Positivity in Indian Patients

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Abstract

One of the most intense controversies in endometrial cancer revolves around the need for lymphadenectomy at the time staging. The study carried out to analyze the role of staging with pelvic lymphadenectomy in intermediate-risk stage I endometrial cancer—stage IA grade III and stage IB grades I and II. Review analysis of all the patients with stage I carcinoma endometrium intermediate risk treated at our institution between January 2006 and December 2014. All demographic data, tumor factors, adjuvant treatment, follow-up, and recurrence were recorded. Sixty-five were in intermediate-risk group, of which 21 were in low intermediate- and 44 in high intermediate-risk group, with 4 patients with positive pelvic node in each group. In patients with low intermediate-risk stage IA, grade III tumors, the nodal involvement was substantial even when the myometrial invasion was less than 50%. All grade 1 tumors did not have pelvic nodal metastasis. Overall percentage of pelvic nodal metastasis in our review of intermediate-risk carcinoma endometrium was 12%, with 19% in stage IA, grade III tumors, and 9% with stage IB, grade I and II tumors. A systematic lymphadenectomy should be done in patients with endometrial cancer who are at intermediate to high risk of lymph node metastases. The grade III histology is more likely to predict for nodal metastasis more than depth of myometrial invasion. It is recommended to stratify patients into risk groups to formulate guidelines for therapeutic lymphadenectomy.

Keywords Intermediate risk · Carcinoma endometrium · Lymphadenectomy · Staging

Introduction

The management of endometrial cancer has always been heterogeneous varying across different institutions and countries, particularly the lymph nodal staging. Endometrial adenocarcinoma ranks third among gynecological malignancies in our part of country, after cervix and ovarian cancer based on the MMTR database [1].

Most patients are present with an early-stage disease, and the overall survival for stage I is around 85–91% [2]. The significant prognostic factors are histological type and grade of the tumor, depth of myometrial invasion, lymphovascular invasion, and lymph node status [3]. Twenty percent of the patients with endometrial carcinoma extending outside of the corpus uterus (stages II and IIIA–B) and 10% of the patients with clinical stage I disease have nodal metastases. Therefore, lymph node dissection has been recommended as part of a comprehensive surgical staging [2].

The publication of 2 randomized trials and 1 meta-analysis [4–6] further increased the controversy on staging lymphadenectomy in early-stage endometrial cancer. Indeed, both the trials showed that pelvic node dissection did not improve disease-free and overall survival rates and concluded that it should not be recommended as therapeutic procedure, although it improved surgical staging.

Despite that the therapeutic value is being only supported by retrospective studies, lymph node dissection is the only way to fully stage the disease and to identify patients who are likely to benefit from adjuvant therapy. Finally, there is still a lack of accurate imaging procedures predicting the extent of extrauterine disease.

One of the major concerns of routine node dissection in endometrial cancer includes the fact that the vast number of women with clinically early-stage carcinoma endometrium does not have nodal involvement, and their survival rates are excellent without node dissection. Node dissection in these

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patients is overtreatment and has no benefit with the risk of surgical complications. Currently, the indication for node dissection in seemingly uterine-confined disease has been based on the depth of myometrial invasion and the grade of the tumor.

Despite the plethora of literature addressing the issue of lymphadenectomy in endometrial carcinoma, the place of lymph node dissection in managing presumed stage I endometrial cancer is still controversial.

Materials and Methods

Methodology

The study design is a retrospective analysis of all the patients with clinically stage I carcinoma endometrium treated at Cancer Institute between January 2006 and December 2014.

Method

All patients had a biopsy done by pipelle biopsy or dilatation and curettage to establish a histological diagnosis. In patients in whom preop diagnosis was not confirmed, the diagnosis was established intraoperatively by frozen section and then surgical staging was done.

All patients who were eligible for the study had undergone total hysterectomy with bilateral salpingo-oophorectomy, peritoneal wash cytology, and complete pelvic lymph nodal dissection. Paraaortic sampling was done on the discretionary of the surgeon. Informed written consent was obtained from all patients. Procedures were conducted either by laparotomy or laparoscopy.

In the period up to 2009, patients with high-grade tumors were treated with one or two fractions of high dose rate (HDR) intracavitary application (ICA) brachytherapy prior to surgery as per the Institute protocol during the above period, and they were excluded from analysis.

We recorded parameters including age of patient, parity, BMI, mode of tissue diagnosis, imaging characteristics, intraoperative and postoperative complications, FIGO surgical stage, histologic type, grade of tumor, number of lymph nodes harvested, size of tumor, recurrence, and duration of follow-up.

We grouped our patients based on the 2009 FIGO surgical staging system and ESMO guidelines 2011 that were used for risk stratification of stage I carcinoma endometrium [7].

- *Low risk*: stage IA (G1 and G2) with endometrioid type
- *Intermediate risk*: stage IA G3 and stage IB (G1 and G2) with endometrioid type
- *High risk*: stage IB G3 with endometrioid type all stages with nonendometrioid type

Patients with intermediate-risk carcinoma endometrium operated at our institute were taken for this analysis. Low- and high-risk patients were excluded from the analysis. The patients were on regular follow-up.

Data Analysis

Univariate and multivariate analysis compared the role of pelvic lymphadenectomy in low intermediate- (stage IA Gr III) and high intermediate-risk (stage IB Gr I and II) carcinoma endometrium, in relation to demographic data, patient, and tumor characteristics.

Pearson's chi-square test by cross table and independent sample *T* test were used for analysis.

Results

We had around 221 patients with clinically presumed stage I carcinoma endometrium after excluding tumors with clear-cell and serous-papillary histology. We grouped our cases based on the FIGO 2009 system of staging and risk stratification based on ESMO 2011 guidelines. The 65 patients of intermediate risk were considered for analysis (Table 1). The mean age of the study population was 57.59 years and a mean BMI of 27.6 kg/m^2 (Table 2).

Size of Tumor

The median size of the tumor in our analysis was 4 cm with range of 0.5–8 cm. There was a trend towards significance when size of tumor was correlated with risk categorization ($p = 0.055$); however, the difference was not significant when correlated with pelvic node positivity ($p = 0.140$) [Table 3].

Nodal Yield

The median number of nodes dissected was 13, over a range of 5–25 nodes. The > 92% of patients had the required minimum of 6 nodes sampled. There was no significant difference between the total nodal yield and positive pelvic nodes and risk categorization ($p = 0.759$).

Table 1 Risk stratification of the sample

	No. of patients
Low risk (stage IA, Gr I, II)	136
Low intermediate (stage IA, Gr III)	21
High intermediate (stage IB, Gr I, II)	44
High risk	20

Table 2 Variables in relation to risk stratification

Patient factors	Low-intermediate risk	High-intermediate risk
No. of patients	21	44
Mean age in years	57.19	58
Mean BMI (kg/m^2)	26.93	28.27
Size of tumor in cm	3.44	4.12

In patients with low intermediate group, 4 had positive pelvic nodes, of which 3 patients had only one positive pelvic node, similarly in high intermediate-risk group, of the 4 patients with positive pelvic nodes, 2 were single node positive.

There was no difference between low and high intermediate-risk groups on correlating with positive pelvic nodes (p = 0.253) (Table 4).

Myometrial Invasion

Of the 65 patients with intermediate-risk carcinoma endometrium, there were 21 patients with grade III tumors with infiltration of < 1/2 of myometrium and 44 patients with > 1/2 myometrium invasion and considered for analysis of intermediate-risk endometrial cancer. Each had 4 cases of positive nodes. There was no significant difference between the two groups (p = 0.236) (Table 4).

Grade of Tumor

Preoperative grade of tumor determined from biopsy had showed grade II to be commonest in 38 patients, 58%. Five patients in our analysis did not have preoperative confirmatory biopsy and were identified on hysterectomy specimen.

There was a change in postoperative grade in 17 patients, 26.1%. In preoperative grade I tumors, there was an escalation to higher grade in 60% patients. In grade II tumors, there was escalation to postoperative grade III in 15%. Preoperative grade III tumors were downgraded in 17% patients.

LVSI

Three patients in our review had lymphovascular space invasion. All three were stage IB disease. One patient had full-thickness myometrial invasion. There were no pelvic nodal metastases in this patient population. However, one patient had recurrence after disease-free survival of 1 year.

Postoperative Complication

Forty-eight patients had no postoperative complication; 9 had wound infection in immediate postoperative period. One patient developed lymph cyst managed with aspiration, and 1 developed lymphedema, both occurring with open staging. One patient had ureteric injury following laparoscopic staging and had postoperative uterovaginal fistula and required reexploration and ureteric reimplantation.

Adjuvant Treatment

Nine patients did not receive any adjuvant treatment, 2 patients defaulted adjuvant treatment, and 54 patients received adjuvant radiation. Adjuvant chemotherapy was received by 6 patients.

Overall Survival

The mean follow-up in the study population was 37 months with a range of 2–98 months. There were 2 deaths in the study population (n = 65); during the follow-up period, one was due to preexisting carcinoma breast and others due to recurrence of endometrial cancer. The median overall survival was 85.5 months in the study population. In patients without pelvic nodal metastasis, median overall survival was 88.6 months compared with 77.1 months in patients with positive pelvic nodal metastasis. However, the difference was not statistically significant (p = 0.188).

Similarly, there was no significant difference when overall survival was correlated with risk categorization. The median overall survival in low intermediate group was 83.52 months and 87.5 months in high intermediate-risk group (p = 0.757).

Disease-Free Survival

The DFS was calculated from the date of completion of treatment to the date of recurrence in patients with recurrences and from date of completion of treatment till the date of last follow-up in all other patients. The median DFS for the study population was 84.51 months. For patients with negative

Table 3 Tumor size on correlation with risk categorization and pelvic node positivity

Tumor size	Low intermediate	High intermediate	Total/%	Node −ve	Node +ve
< 2 cm	6	3	9/13.8	9	0
2–4 cm	9	23	32/49.2	26	6
> 4 cm	6	18	24/36.9	22	2
Total	21	44	65	57	8

Table 4 Nodal positivity on correlation with risk categorization and myometrial invasion

		Pelvic node metastasis		Total	*p* value
		Absent	Present		
Risk categorization	Low intermediate	17	4	21	
	High intermediate	40	4	44	0.253
Myometrial invasion	Absent	1	0	1	
	< 1/2	16	4	20	0.236
	> 1/2	40	4	44	
Total		57	8	65	

pelvic nodes, the median DFS was 85.19 months and 77.14 months in patients with positive pelvic nodes. There was no statistical significance between the two groups (p = 0.458).

Likewise, there was no significant difference between low intermediate- and high intermediate-risk groups with regard to DFS (p = 0.546).

Discussion

Endometrial cancer, with an increasing incidence, happens to be the most common cancer of genital tract in women in developed countries, with increasing incidence in our country. The controversy regarding lymphadenectomy in endometrial cancer has been mainly focused on the management of patients with clinical early disease and favorable histological characteristics, with systematic lymphadenectomy practiced in all high-risk patients.

Increasing body mass index has been strongly associated with increasing risk of endometrial cancer which was again evident in our study. The median BMI in our study was 27.70, and 69.2% of patients were in overweight/obese category. Sixty-six percent of our patients had comorbid illness with 50% of those having both diabetes and hypertension. This again correlated with common association of endometrial cancer, obesity, and metabolic diseases.

Due to the limitations of clinical assessment of carcinoma endometrium, FIGO switched from clinical staging published in 1977 to surgical staging back in 1988, following results of GOG 33 study [8]. However, guidelines for assessing lymph node status were not formulated; hence, controversy still exists between various treatment groups in terms of indication and extent of lymphadenectomy, particularly in women with early-stage I endometrial cancer.

The study GOG 33 also showed grade of tumor, depth of myometrial invasion, and lymphovascular space invasion as factors predicting increased risk of nodal metastasis [8]. After the publication of this study, three main strategies regarding lymph nodal dissection have been analyzed: (1) systematic dissection of pelvic and paraaortic nodes in all patients, with basing adjuvant therapy on the results of complete surgical staging; (2) estimating risk of nodal metastasis and recurrence chances based on tumor factors such as grade of tumor, invasion into myometrium, lymphovascular space invasion, and size of tumor; and (3) performing systematic lymph nodal dissection based on the intraoperative evaluation for risk factors including grade of tumor, invasion into myometrium, and tumor size. The subsequent studies on lymphadenectomy in early-stage carcinoma endometrium have been greatly influenced by these different strategies.

Supporters of the strategy of not performing nodal dissection argue that this will decrease risk associated with nodal dissection, but will allow for adjuvant treatment of patients based on the risk factors for nodal metastasis and increased risk of recurrence. Critics counter the argument that in the absence of histologic proof of positive nodes, more patients will be subjected to adjuvant therapy which may be unnecessary if nodes did not harbor tumor deposits and planned adjuvant therapy may be inadequate in patients who have nodal metastasis.

The changes that occurred with the staging system of endometrial cancer are crucial not only in aiding planning treatment strategies but also influence how we understand the published literature. Articles prior to 2009 include patients who were classified differently than the current practice. Acknowledging this, we need to be aware that patients in these studies may be at a significantly lower risk of recurrence, such as the “Stage IA” based on 1988 staging compared with “stage IA” according to 2009, patient that may have up to 50% myometrial invasion. In actuality, depth of invasion in myometrium is a continuous variable with risk increasing with every additional millimeter of invasion. One also have to understand that before 2009, proportionately lower risk cervical glandular involvements were grouped with stage II, who are now incorporated into stage I disease.

On the contrary, we found that in our patients with low intermediate-risk stage IA, grade III tumors, the nodal involvement is substantial even when the myometrial invasion is less than 50% (stage IA). One may conclude that there is a place for pelvic node dissection in grade 3 tumors in the presence of myometrial invasion, irrespective of the depth of

invasion. All patients with grade 1 tumors did not have pelvic nodal metastasis, even though the depth of myometrial invasion was > 1/2.

USG was the commonest imaging modality in our study as per institute protocol. Few patients had MRI scan in doubtful extension to the cervix. In all patients with positive pelvic nodes, they were not picked up in preop imaging/intraop nodal palpation. Two patients who were suspected to have pelvic nodal involvement on preop imaging did not have nodal metastasis. Three patients with suspicious nodes on intraop palpation also did not have metastasis, stating neither preop imaging with USG/intraop palpation helps to identify nodal metastasis.

In our study, there was no difference in nodal yield irrespective of modality of surgical staging, with both open and laparoscopic staging yielding around 13 nodes.

In our review, grade I tumors were upgraded in 60%; this finding could be due to considering only grade I tumors with > 1/2 myometrium invasion for analysis. In review analysis by Obermaier of well-differentiated endometrial adenocarcinoma, it was upgraded in 20.4% of cases. [9]

Frumovitz in his review of 153 patients with grade 1 or 2 carcinoma endometrium compares preoperative grade of tumor and final pathology [10]. There was 32% (49 patients) discrepancy amidst preoperative and final biopsy. Thirty-seven (27%) of the patients had their tumor upgraded or had high-risk histology other than endometrioid carcinoma.

On correlating risk of myometrial invasion with pelvic nodal metastasis, there was no difference between whether myometrium involvement was < 1/2 or > 1/2. This result of nil significance could be due to analyzing only grade III tumors when < 1/2 myometrium involvement.

Of all 8 patients with pelvic node-positive tumor in our study population, 7 had tumor size of at least 4 cm. One had tumor size of 2.5 cm. This again correlates with previous reviews by Mariani et al., Mayo Clinic risk stratification for avoiding staging lymphadenectomy [11]. He had stratified type I endometrioid tumors, grades 1 and 2, depth of invasion less than half, and size of tumor < 2 cm do not benefit from staging lymphadenectomy. In our review, even though the depth of infiltration was > 1/2 of myometrium, grade I and II tumors did not have pelvic nodal metastasis when tumor size was < 2 cm.

Yanazume et al., in their retrospective study involving 228 patients, evaluated the improvement in identifying low-risk patients on frozen section when tumor size was taken into consideration. They had used tumor size of ≤ 3 cm as the cutoff and found accurate prediction of absence of nodal metastasis in patients with tumor size of ≤ 3 cm and less than half invasion of myometrium in grade I and II carcinoma endometrium [12]. Also in our study, there was trend towards significance when tumor size was correlated with myometrial invasion ($p = 0.055$).

Lymphovascular space invasion was seen in 3 patients in our review, although there were no pelvic nodal metastases in that group. There was one recurrence with lung metastasis after DFS of 1 year, which again implies the increased risk of relapse in this patient subgroup. Breit et al., in their review of 239 patients with carcinoma endometrium who underwent surgical staging, found 2.6 times increased risk of relapse in presence of lymphovascular space invasion. They also reported increased pelvic nodal metastasis in tumors with lymphovascular space invasion (multivariate analysis, $p = 0.001$) [13].

Complications pertaining to pelvic nodal dissection occurred in 3 patients (4.6%). Lymphocyst occurred in 1 patient (1.5%) and lymphedema in 1 (1.5%). This correlated with review of Orr et al. who had reported 1.5% and 0.7% risk of lymph cyst and lymphedema following pelvic lymphadenectomy for carcinoma endometrium [14]. Lymphedema in our patient could also be accentuated by the postoperative radiation.

Overall percentage of pelvic nodal metastasis in our review of intermediate-risk carcinoma endometrium was 12%, with 19% in stage IA, grade III tumors, and 9% with stage IB, grade I and II tumors. This again explains the risk of increasing pelvic nodal metastasis with increasing grade than depth of myometrial invasion.

Our review correlated with incidence of pelvic nodal metastasis in previous published literature (Table 5). A significant number of patients are upstaged with routine pelvic nodal dissection in intermediate-risk endometrial cancer.

Many published literatures have reported that complete lymph nodal dissection may improve survival, but these evidence have been mainly retrospective and susceptible to selection bias. Nevertheless, two prospective randomized

Table 5 Comparison of nodal positivity with other studies

Study	Stratification	No. of patients	Positive pelvic nodes (%)
Creasman et al. [8]	IA Gr III and IB Gr I and II	164	14.6
Cragun et al. (retrospective) [15]	Apparent stage I	252	9.5
MRC ASTEC (randomized) [6]	Intermediate and high risk	264	12
Our review	IA Gr III and IB Gr I and II	65	12.3

Staging adjusted to FIGO 2009

studies MRC ASTEC trial and Italian trial by Panici et al. have shown that the pelvic lymph node dissection has no therapeutic significance and provides prognostic detail in apparent stage I carcinoma endometrium.

Sentinel lymph node mapping techniques have evolved in the treatment of endometrial cancer with increasing detection rates with laparoscopy and robotic surgeries. Cervical injection of blue dye or radiocolloid is being used. Randomized trials will further guide the usefulness in the staging and prognostication of endometrial.

Conclusion

The following restrictions with our study must be acknowledged. First, this was a retrospective study involving limited number of patients, and only restricted interpretation can be derived from our data regarding the prognostic impact of lymph node metastases.

The grade III histology is more likely to predict for nodal metastasis more than depth of myometrial invasion, although the grade and myometrial infiltration are independent risk factors affecting lymph node involvement. Stratification of patients can be considered in future studies to formulate guidelines. Sentinel node mapping trials could lend more clarity in the benefit of lymphadenectomy in intermediate-risk tumors.

Altogether, review of the literature provides solid ground for lymph node dissection in patients with intermediate-risk carcinoma endometrium. The less invasive modality should be preferred. Future studies might use molecular biology parameters that might define better risk categorization and optimization of adjuvant therapies.

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Compliance with Ethical Standards

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

Ethical Approval This study was approved by the Institutional Ethics Committee.

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