



Audit on Adequacy and Appropriateness of Lymphadenectomy in Endometrial Carcinoma

KEYWORDS

Adequacy of lymphadenectomy, endometrial cancer

*** Anitha Thomas**

MD, DNB, Associate Professor,
Department of Gynecologic
Oncology, Christian Medical
College, Vellore, Tamil Nadu, India,
632004. * Corresponding author

Rachel Chandy

Professor, Department of
Gynecologic Oncology Christian
Medical College, Vellore, Tamil
Nadu, India, 632004.

Grace Rebekah

Msc, Department of Biostatistics
Christian Medical College, Vellore
Tamil Nadu, India, 632004.

Angeline Gnanamalar

Department of Obstetrics and
Gynecology Christian Medical
College, Vellore Tamil Nadu, 632004

Ajit Sebastian

MD, Assistant Professor,
Department of Gynecologic
Oncology, Christian Medical
College, Vellore, Tamil Nadu, India,
632004.

Vinotha Thomas

Assisociate Professor, Department
of Gynecologic Oncology, Christian
Medical College, Vellore, Tamil
Nadu, India, 632004.

Ramani Manoj Kumar

MD, Department of Pathology, Christian Medical
College, Vellore. Tamil Nadu, India, 632004.

Abraham Peedicayil

MD, FRCOG Professor and Head, Department of
Gynecologic Oncology, Christian Medical College,
Vellore, Tamil Nadu, India, 632004.

ABSTRACT Aim : To audit the adequacy and appropriateness of pelvic and para aortic lymphadenectomy in endometrial carcinoma .

Methodology : A retrospective audit on the operative and surgicopathological details of endometrial cancers operated in our institution from 2011-2013 was done to assess the adequacy and appropriateness of pelvic and para-aortic lymphadenectomy

Results : Most patients (123/141, 87.2%) underwent pelvic lymphadenectomy and of these, 89 (72.7%) had more than 10 nodes removed. Only 29 patients underwent para-aortic node dissection and of these, 12 (24.1%) had more than 12 nodes excised.. Pelvic lymphadenectomy was performed as indicated by our guidelines in 110/121 (90.9%) whereas para-aortic lymphadenectomy was performed as required by our protocol in only 23/67 (34.3%).

Conclusions : Pelvic lymph lymphadenectomy seems appropriate and adequate, whereas para aortic lymphadenectomy was inadequate as well as under done. Reasons for non-compliance need to be probed further. Frozen section or pre operative MRI could help in better decision making with regards to pelvic and para aortic lymphadenectomy.

Introduction

Endometrial cancer is the most common gynecological cancer in developing countries with 43470 new cases and 7950 deaths in 2012 in United States. Most patients are diagnosed at an early stage of the disease and have good prognosis. The 5-year survival for localized endometrial cancer is 95.4%.¹ However, those with advanced stage disease have a guarded prognosis.

The current FIGO 2009 staging is a surgico-pathological one and includes pelvic and para-aortic lymph node assessment. Universal and comprehensive lymphadenectomy of the pelvic and para aortic regions is required for complete surgical staging. However, there is still a debate on role of lymphadenectomy in low risk patients, the adequate number of lymph nodes to be removed, and the boundaries or anatomic landmarks of dissection.

Lymph node metastasis is an important prognostic factor. In apparent early stage endometrial cancer, lymph nodes

can be found in <5 %². Both disease free survival and overall survival are better in patients who have negative nodes. However, in patients who have small endometrioid, well differentiated tumors with less than 50% myometrial invasion, the risk of nodal involvement is less than 3 %³. Since a third of endometrial cancer patients fall in to this low risk category, universal lymphadenectomy would be increasing risk without much benefit in these patients.

We have been following a policy of selective lymphadenectomy since 2011. The decision making process takes in to account perception of risk of nodal involvement based on histology, grade, size of tumor and depth of invasion. Also considered is the risk of complications such as bleeding, paralytic ileus, deep vein thrombosis, lymphocyst and lymphedema. The threshold of action was set such that lymphadenectomy would be done only if the risk of nodal involvement was more than 5 %. Lymphadenectomy would be omitted if patient had significant medical comorbidities.

There is no perfect method to assess the risk factors for nodal disease, and even histology and grade are sometimes revised by the pathologist. With a policy of selective lymphadenectomy, patients are at times required to undergo restaging or treated with pelvic radiation therapy only because staging was incomplete

We wanted to evaluate the adequacy and extent of lymphadenectomy in our patients with endometrial carcinoma who underwent surgical staging. We also wanted to analyze whether or not our protocol for selective lymphadenectomy using tumor size and depth of invasion by inspection of cut open uterus in the operating room and, grade and histology in pre-operative biopsy was being followed,

Methodology

A retrospective analysis was done of all endometrial cancers operated at a tertiary teaching hospital in Southern India from January 2011 to December 2013. The operative notes and histopathology notes from electronic medical records were used to retrieve information on the adequacy and appropriateness of lymphadenectomy.

Our institutional policy of lymphadenectomy was to perform pelvic lymphadenectomy in endometrial cancer based on tumor histology, grade, size and depth of invasion into the myometrium. In early stage endometrioid, grade 1 adenocarcinoma, less than 2cm size and involving only the superficial myometrium (low risk for nodal involvement), lymphadenectomy was to be omitted. Endometrioid, grade 2 and grade 1 tumor > 2cm would warrant pelvic lymph node dissection (Intermediate risk). Para-aortic lymphadenectomy was to be done in grade 3 endometrioid, carcinosarcoma, clear cell or papillary serous carcinomas, myometrial invasion more than 50% and if there was extrauterine disease (High risk).

The lymphadenectomy was considered adequate when mean number of resected lymph nodes were at least 10 both for the pelvis and para-aortic area. This audit was done to evaluate whether adequate number of pelvic lymph nodes was removed and whether the indication for lymphadenectomy was appropriate based on our institutional guidelines.

Results

A total of 141 patients were included in this audit. During the study period all the staging and lymphadenectomies were done by laparotomy. Mean age of the patients who underwent surgical staging was 57 (30-79) years and mean BMI was 27.7(19-47). Of them 70 had stage IA (9.6%), 31 had stage IB (29%) and 9 of them stage II (8%) as given in Table 1. The most common histology was endometrioid adenocarcinoma which comprised 88.7% and 11.3% was non endometrioid carcinoma. High grade disease was seen in 18 patients (12.8%).

Pelvic lymphadenectomy was done in 123 patients of whom 13 were in low risk and not indicated by our guideline. Para-aortic lymphadenectomy was done in 29 patients of whom 6 were in the intermediate risk group (Tables 2 & 4). Lymph node positive disease was found in about 6 (10.6%) patients all of whom had pelvic node metastasis as well. There were no isolated paraaortic node metastasis. All of these patients underwent indicated para aortic node lymphadenectomy

Pelvic lymph nodes were tumour positive in 16/123 (13.1%)

and para-aortic nodes were positive in 6/29 (20.7%)

Table 1: Patient and tumour characteristics

Parameters	No of patients(n=141)	Percent (%)
Age	Mean 57 (30-79)	
BMI	Mean 27.7 (19-47)	
Stage of the disease		
IA	70	49.6%
IB	31	22.0%
II	9	6.4%
IIIA	5	3.5%
IIIB	3	2.1%
IIIC1	11	7.8%
IIIC2	4	2.8%
IVA	5	3.5%
IVB	3	2.1%
Histology – Endometrioid	125	
Non endometrioid	16	88.7%
Carcinosarcoma	7	11.3%
Clear cell carcinoma	1	
Papillary serous carcinoma	5	
Grade - I	81	57.4%
II	42	29.8%
III	18	12.8%
Depth of invasion –		
< 50% Myometrium	84	59.6%
≥ 50% Myometrium	57	40.4%
Size of tumor - ≤ 2cm	45	31.9%
> 2cm	96	68.1%
LVSI - Present	38	26.9%
Absent	103	73.1%

Table 2: Pelvic and Para-aortic lymphadenectomy

Parameters	Patients (n=141)	Percent (%)
Pelvic lymph node resection	123	87.2%
Positive pelvic lymph nodes	16/123	13.08%
Para-aortic lymph node resection	29	20.5%
Positive Para-aortic nodes	6/29	20.7%

Table 3: Adequate lymphadenectomy

Resected lymph nodes	Pelvic N=123	percent-age	Paraortic N=29	percent-age
< 10	34	27.7%	17	58.6%
≥ 10	89	72.7%	12	41.4%

Among these patients, 89 patients (72.7%) had adequate lymphadenectomy (≥ 10 lymph nodes) and 34 patients (27.7%) had inadequate lymphadenectomy. The mean number of pelvic nodes removed was 12(SD-7.8). Para aortic nodes dissection along with pelvic nodes dissection was done in 29 patients. Of these, 6 patients had posi-

tive nodes. Among these patients, 12 patients (41.4%) had adequate lymphadenectomy and 17 patients (58.6%) had inadequate lymphadenectomy. The mean number of para aortic nodes removed were 8(SD-5.6). Putting both the groups together, about two thirds of these patients (66.5%) underwent adequate lymphadenectomy.

Table 4: Lymphadenectomy as per protocol

Risk Group (need for lymphadenectomy)	PLND*-Indicated n-121	PLND not indicated but done	PLND indicated & not done	PAND** indicated n-67	PAND-not indicated but done	PAND-indicated & not done
LOW(no nodes) n=20		13				
INTER-MEDIATE (pelvic only) n=54	51		3		2	
HIGH (pelvic and para aortic) n=67	59		8	27		44

*PLND-pelvic lymphadenectomy done in total of 123 patients

**PAND- Para aortic lymphadenectomy done in total of 29 patients

Among the 141 patients, pelvic lymphadenectomy was done as indicated in 110 (89.4%) , overdone in 13patients(10.5%) , and missed in about 11(9.1%) where indicated. Para-aortic lymphadenectomy was done as indicated in 27(93.1%), overdone in 2 of the 29 patients and missed in 44(65.7%) patients where it was indicated .

Discussion

There are various risk factors that determine lymph node metastasis. Grade of the tumor and myometrial invasion are the most common risk factors that determine the probability of lymph node metastasis. Creasman et al² reported the incidence of lymph node metastasis in early stage endometrial cancer was 3% in grade 1, 9% in grade 2 and 18% in grade 3 tumors. Lymph node metastasis in those who had less than 50% myometrial invasion was 5% and it increased to 20% if the myometrial invasion was more than 50%. According to this study there was no evidence of lymph node involvement in low risk patients and they concluded that surgical staging was not necessary in low risk patients. Lymph node metastasis correlates with size of the tumor. In a patient with lesion size less than 2cm, the risk of nodal involvement was as low as 4%⁴, whereas when the growth was more than 2cm, the risk was about 15% and up to 35% in cases where the entire cavity was involved. Cervical involvement was associated with 15% risk of lymph node metastasis.⁵ Extrauterine spread of the disease and positive peritoneal cytology increase the chances of pelvic and para aortic lymph node metastasis.

Several retrospective studies showed a better outcome in patients who had lymph node dissection suggesting a therapeutic role of lymphadenectomy in endometrial cancer. Kilgore et al reported that there was a significant difference in 5 year survival rate in patients who had pelvic

lymphadenectomy (90% vs 70%).⁶ Todo et al reported a combination of pelvic and para-aortic lymphadenectomy increased survival compared with pelvic lymphadenectomy alone.⁷ However from large prospective randomized controlled studies like the ASTEC trial, the investigators concluded that lymphadenectomy does not improve the overall survival in early endometrial cancer.⁸

Till now there is no defined number of lymph nodes to be removed to ensure an adequate lymphadenectomy. Lutman et al suggested that there was an improved survival with high risk histology when 12 or more nodes are removed.⁹ In ASTEC trial , the mean number of lymph nodes removed was 12 pelvic lymph nodes. The reason being is that removal of larger number of lymph nodes may remove occult metastasis. The extent of nodal dissection to include the para-aortic nodes is important in endometrial cancer. The lymph nodes along external iliac, internal iliac vessels, obturator fossa and common iliac vessels are removed in pelvic lymphadenectomy. Para-aortic nodes dissection is usually performed up to the level of the inferior mesenteric artery with some surgeons recommending dissection up to the level of renal vessels. The Inferior mesenteric artery is only a landmark of convenience and has no significance with regard to lymphatic drainage or the pelvis. Some studies have suggested that the significant lymph node metastasis occurs even above the inferior mesenteric artery.¹⁰ In our institution, we chose to keep the cut off as at least 10 nodes per group to call it adequate lymph node dissection. The nodal yield usually improves with specialized surgical oncology training. In the absence of adequate training there would be hesitancy in performing adequate dissection especially behind the great vessels. In some cases only lymph node sampling would be opted for. Training in gynaecologic pathology would also lead to differences in nodal counts.

This audit on the indication for lymphadenectomy revealed that, in the low risk group pelvic lymphadenectomy was overdone in 13 patients . This probably was due to the preoperative overestimation of the tumor size. In the Intermediate group(>2cm , grade 1,2 tumors), there were 3 patients who did not undergo pelvic lymphadenectomy due to underestimation of the tumor size or due to patient factors such as obesity or co-morbidities. On the other hand, 6 patients had unindicated para aortic nodes dissection probably due to overestimation of myometrial invasion. In the high risk group (Non endometrioid, grade 3, deep myometrial invasion), 8 out of 121patients who were indicated to have pelvic lymphadenectomy did not have this done . Majority of these patients were missed due to underestimation of deep myometrial invasion. 44(65.7%) patients who were indicated to have para aortic nodes were missed mainly due to underestimation of myometrial invasion and a few due to upgrading of the post operative histology to grade 3(in 3 patients) and non endometrioid tumors(in 5patients).Both these problems could probably be overcome by performing on table frozen section to determine the most accurate estimation of myometrial invasion and histopathology. Intraoperative gross examination has been reported to have lesser sensitivity and specificity than intraoperative frozen section.¹¹ The other option for myometrial invasion is a pre op MRI examination which could give us appropriate information on myometrial invasion. Studies have proven that contrast enhanced MRI and diffusion weighted image sequencing could be very accurate in detecting deep myometrial invasion.¹² In 2 patients where we performed limited surgery due to medical comorbidities , indicated lymphadenectomies were omitted.

The average time taken in performing paraortic node dissection may be around 30-45 minutes in a patient with normal BMI. In an institution with high volume cases this could mean a rush to complete the cases. In such situations, there is a possibility of underestimating the myometrial invasion and hence not doing it in indicated cases.

After this audit all our patients have at least an ultrasound of the pelvis to estimate lesion size. We have also asked our pathologist to get familiar in doing frozen section to determine, histology, grade and depth of myometrial invasion. We have also started doing sentinel lymph node biopsy, a completely different approach to the nodes, along with the current policy of pelvic and para-aortic lymphadenectomy

In conclusion, 85.8% of our patients required either pelvic or para-aortic lymphadenectomy. Majority of patients had undergone pelvic lymphadenectomy as indicated whereas in the high risk group where para-aortic lymphadenectomy was indicated a significant proportion of patients (65.7%) were missed. The main reason for this was the failure to diagnose deep myometrial invasion on naked eye examination.

In order to obtain high yield of lymph nodes, standard surgical and pathology techniques should be followed with adequate training of the surgeons to be competent enough to perform pelvic and para-aortic lymphadenectomy. Each centre should have a policy, based on evidence based guidelines, for addressing lymph nodes in patients with endometrial cancer and have periodic audits for course correction.

There are no conflicts of interest or financial disclosures.

References

- 1 Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2013
- 2 Creasman WT1, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. *Cancer*. 1987 Oct 15;60(8 Suppl):2035-41.
- 3 Neubauer NL, Lurain JR. The Role of Lymphadenectomy in Surgical Staging of Endometrial Cancer. *Int J Surg Oncol*. 2011;2011:814649. doi: 10.1155/2011/814649. Epub 2011 Jul 10
- 4 J. C. Schink, J. R. Lurain, C. B. Wallemark, and J. S. Chmiel, "Tumor size in endometrial cancer: a prognostic factor for lymph node metastasis," *Obstetrics and Gynecology*, vol. 70, no. 2, pp. 216-219, 1987
- 5 P. J. Disaia, W. T. Creasman, R. C. Boronow, and J. A. Blessing, "Risk factors and recurrent patterns in stage I endometrial cancer," *American Journal of Obstetrics and Gynecology*, vol. 151, no. 8, pp. 1009-1015, 1985
- 6 Kilgore LC, Partridge EE, Alvarez RD, Austin JM, Shingleton HM, Noojin F 3rd, et al. Adenocarcinoma of the endometrium: survival comparisons of patients with and without pelvic node sampling. *Gynecol Oncol*. 1995 Jan; 56(1):29-33.
- 7 Todo Y, Kato H, Kaneuchi M, Watari H, Takeda M, Sakuragi N. Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis. *Lancet*. 2010 Apr 3; 375(9721):1165-72.
- 8 Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. *The Lancet*. 10; 373(9658):125-36.
- 9 Lutman CV, Havrilesky LJ, Cragun JM, Secord AA, Calingaert B, Berchuck A, et al. Pelvic lymph node count is an important prognostic variable for FIGO stage I and II endometrial carcinoma with high-risk histology. *Gynecol Oncol*. 2006 Jul; 102(1):92-7.

- 10 AlHilli MM, Mariani A. The role of para-aortic lymphadenectomy in endometrial cancer. *Int J Clin Oncol*. 2013 Apr;18(2):193-9. doi: 10.1007/s10147-013-0528-7. Epub 2013 Feb 15.
- 11 Alcazar JL, Dominguez-Piriz J, Juez L, Caparros M, Jurado M. Intraoperative Gross Examination and Intraoperative Frozen Section in Patients With Endometrial Cancer for Detecting Deep Myometrial Invasion: A Systematic Review and Meta-analysis. *Int J Gynecology Cancer*. 2016 Feb;26(2):407-15
- 12 Das SK, Niu XK, Wang JL, Zeng LC, Wang WX, Bhetuwal A, Yang HF. Usefulness of DWI in preoperative assessment of deep myometrial invasion in patients with endometrial carcinoma: a systematic review and meta-analysis. *Cancer Imaging*. 2014 Nov 12;14:32