

Whether complete lymphadenectomy is justified in high grade carcinoma of endometrium

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ABSTRACT

Background: Lymph node metastases are one of the most important prognostic factors in endometrial cancers. The objective of the study was to estimate incidence of nodal positivity in patients with high grade carcinoma endometrium.

Methods: Retrospective study of high-grade endometrial cancer patients who underwent curative treatment over a 6-year period. The nodal positivity was identified by a histology report. The nodal yield was determined by the number of nodes retrieved at the time of surgery. Pelvic and paraaortic nodal positivity was determined in high grade ca endometrium negative and the difference in overall survival among the patients with and without nodal positivity was determined.

Results: About 56 patients were involved in this analysis. Mean pelvic lymph node yield was 16.92 ± 5.34 lymph nodes and mean paraaortic lymph node yield was 9.47 ± 3.78 . The overall incidence of lymph node metastasis was 27% (15/56) in our study. Fourteen patients had pelvic lymph node metastasis, 6 (11.6%) patients with para-aortic lymph node metastasis and 1 (1.8%) patient had isolated para-aortic node metastasis. The overall survival of the study group for one year 98% and fourth year was 98% and 82.7% respectively. There were no differences in survival with respect to node positivity status (69.6 vs. 74.9 months, $p=0.41$).

Conclusion: Node positivity in high grade endometrial carcinoma was 27% and there were no differences in overall survival among the patients with nodal positivity. Routine assessment of nodal status for all patients with endometrial cancer shall guide in optimal staging and management.

Keywords: endometrial carcinoma, nodal status, staging laparotomy, lymph node metastasis

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INTRODUCTION

Endometrial cancer is the second commonest gynaecological cancer in India, next to cervical cancer. High-grade EC comprises only about 25%-30% of all EC cases, but accounts for 70%-75% of EC-related mortality [1].

Lymphadenectomy is considered an integral part of comprehensive surgical staging of EC but its role in the management of apparent early-stage EC continues to be in the grey zone due to lack of therapeutic benefit and increased risk of postoperative morbidity [2, 3]. The difficulties 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 tumours in elderly patients with associated comorbidities of obesity, diabetes, hypertension, hypothyroidism etc. [2].

Lymph node metastases are the most important prognostic factor in early-stage endometrial cancers [4, 5]. The 5-year progression-free survival was 90% in a 1991 analysis of the Gynaecologic Oncology Group (GOG)-33 database in unselected early-stage endometrial cancer patients without any lymph node metastases, which dropped to 75% in patients with pelvic and to 38% in patients with para-aortic lymph node metastases, respectively [6].

The primary objective of the study was to estimate incidence of nodal positivity and overall survival in patients with high grade carcinoma endometrium who underwent curative intent treatment. The secondary objectives were to estimate nodal yield, and to estimate pathologically proven para-aortic node positivity in those with pathologically negative pelvic lymph node.

METHODOLOGY

This was a retrospective study of high-grade endometrial cancer patients who underwent surgery during the period January 2014 to December 2019 at a tertiary cancer centre from South India. The permission from the institutional review board/institutional scientific committee was obtained before the start of the study (IRB:1616/IRB-SRC/13/MCC/14-11-2020/3).

All patients with high grade carcinoma endometrium who

underwent staging laparotomy and completion surgery were included. Their demographic details, clinical findings, radiologic assessment and staging, details of primary modality of treatment, local and general complications of surgery, survival rate, residual and recurrent disease, lymph node metastasis were retrieved from the case files. The nodal positivity was identified by a histology report. The nodal yield was determined by the number of nodes retrieved at the time of surgery. In patients who are pathologically negative for pelvic lymph nodes, the para-aortic node positivity was estimated. The differences in overall survival among the patients with and without nodal positivity were determined.

Statistical analysis

The categorical variables were expressed in frequency and percentages. The variables for univariate analysis were selected based on their clinical relevance. Univariate analysis for categorical

variables were done using chi square test and for continuous variables using t test or Mann Whitney U-test. Log rank test and Kaplan Meier test were used for estimating overall survival. Statistical analysis will be done using SPSS software version 20.1.

RESULTS

A total of 56 patients were included in the study. Mean age of the study population was 57.7 years ± 9 years (36-78). Clinicopathological factors are given in table 1. Serous carcinoma grade 3 was the commonest histological type (32 patients, 57.6%). Other predominant histological cell types were endometrioid grade 3 (13 patients, 23.4%). In our study 22 (39.3%) patients had less than half of myometrial invasion and 34 (60.7%) patients had more than half myometrial invasion. Only one patient (1.8%) had omental disease and it was a case of serous carcinoma.

Tab. 1. Clinicopathological characteristics of patients with high grade endometrial carcinoma from tertiary care cancer centre from South India

Total Number of Patients (n)	56
Mean age (years)	57.7 ± 9.6 (36 years –78 years)
Menopausal Status	
Pre-menopausal	12 (21.4%)
Post-menopausal	44 (78.6%)
Parity	
Nulliparous	10 (17.6%)
Parous	46 (82.1%)
Comorbidities	
DM	4 (7.2%)
DM+HTN	3 (5.4%)
DM+HTN+DLDP	10 (18%)
HTN	1 (1.8%)
HTN+CAD	3 (5.4%)
High-Grade Histology	
Endometrioid grade 3	13 (23.4%)
Clear cell carcinoma	3 (5.8%)
Serous carcinoma	32 (57.6%)
Carcinosarcoma	2 (3.6%)
Endometrioid with squamous differentiation	3 (5.8%)
Mixed (serous endometrioid)	2 (3.6%)
Myometrial Infiltration	
<50%	22(39.3%)
>50%	34(60.7%)
Omental Disease	
Nil	55 (98.2%)
Yes	1 (1.8%)

DM-Diabetes Mellitus, HTN-Hypertension, DLDP-Dyslipidemia, CAD-Coronary Artery Disease

Table 2 displays histology type with nodal metastasis. Serous carcinoma was predominant (32/56) patients of which 34% and 9% had pelvic node metastasis and pelvic with paraaortic positivity. Among 13 patients with endometrioid grade 3, only 15% had pelvic node metastasis and only one (8%) patient had isolated para-aortic node metastasis.

All patients underwent total abdominal hysterectomy, bilateral salphingo oophorectomy, omentectomy, pelvic and para-aortic

lymphadenectomy and adjuvant chemo radiation. Mean pelvic lymph node yield was 16.92 ± 5.34 lymph nodes and mean para-aortic lymph node yield was 9.47 ± 3.78. The overall incidence of lymph node metastasis was 27% (15/56) in our study. 14 patients (25%) had pelvic lymph node metastasis, 6(11.6%) patients had para-aortic lymph node metastasis and 1(1.8%) patient had isolated para-aortic node metastasis.

Tab. 2. Frequency of lymph node metastasis and histological grade	Histology	Number of Patients (n)	Pelvic Node Metastasis n (%)	Pelvic + Para-aortic Node Metastasis n (%)	Isolated Para-Aortic Metastasis n (%)
	Serous carcinoma	32	11 (34%)	3 (9%)	0
	Endometrioid grade 3	13	2 (15%)	1 (8%)	1 (8%)
	Clear cell Ca	3	1 (33%)	1 (33%)	0

Among the patients with >50% myometrial invasion, lymph node involvement was noted in 14 (29.4%) and in patient with <50% myometrial infiltration, lymph node involvement was 7 (27.3%) patients (Table 3). Cervical stromal invasion seen in 14 pts (25%).

Tab. 3. Frequency of lymph node metastasis with respect to myometrial infiltration	Myometrial Infiltration (MI)	Pelvic Node Metastasis	Pelvic + Para-Aortic Node Metastasis	Isolated Para-Aortic Node Metastasis
	<50% (n=22)	6 (11.6%)	1 (1.8%)	0
	>50% (n=34)	9 (17.4%)	4 (7.2%)	1 (1.8%)

The median follows up period of the study population was 58.7 months (95% CI 54.5-84.6). The overall survival for one year -98%, 2 year -94%, 3 year -90% and 4 year 82.7% (Figure 1).

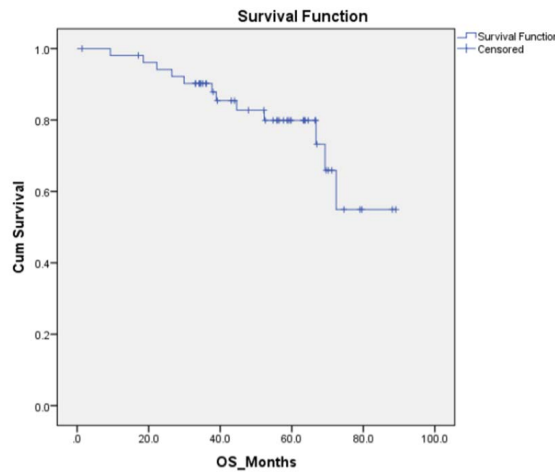


Fig. 1. Kaplan Meier curve displaying overall survival of patients with high grade endometrial carcinoma with staging laparotomy

Mean survival time of node positive patients was 69.6 months (95% CI 66.7-83.1) with no difference in survival (95%CI 54.5-84.6) and of node negative patients were 74.9 (p=0.41) (Figure 2).

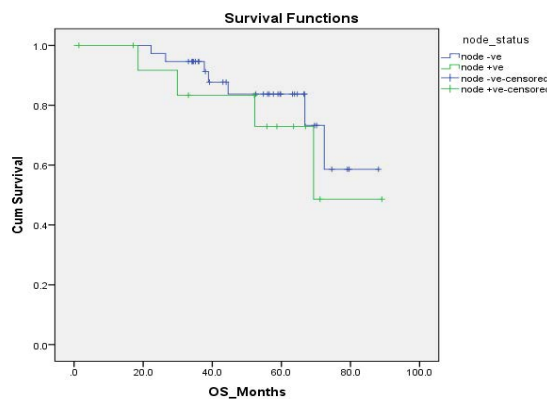


Fig. 2. Kaplan Meier curve comparing overall survival in node positive and negative patients with high grade ca endometrium (p=0.41)

DISCUSSION

Therapeutic benefit of lymph node dissection in early endometrial cancer remains controversial. Assessment of nodal involvement helps in accurate staging and to decide on adjuvant treatment. The overall incidence of lymph node metastasis was 27% (15/56) in our study. The incidence of isolated para-aortic metastasis was 1.8% while in other studies it ranged between 2%-6% (7). Mari-

ani et al., from Mayo clinic demonstrated favourable endometrial cancer characteristics included three low risk features involving tumour size <2 cm, grade 1 tumours or 2 tumours and depth of invasion <50%. They also demonstrated 5% risk for nodal metastasis and 97% cancer specific survival in this low-risk group [6-8]. MRC ASTEC trial randomised 1408 women with clinical stage I or II endometrial cancer to either systematic pelvic lymphadenectomy or no lymphadenectomy. and observed no difference in re-

currence free survival or overall survival between these groups [9]. In the present study, with high-risk endometrial carcinoma, the nodal positivity was higher (27%) with no differences in overall survival between the patients with nodal status.

Many of the centres practice selective lymph node dissection in endometrial cancer by risk stratification. Preoperative tumour grade in endometrial biopsy and myometrial infiltration by imaging are being used for risk stratification, and lymphadenectomy is done only in high-risk groups (patients with >50% myometrial infiltration and high-grade disease). This practice can cause missing of lymph node metastasis in some patients with low-risk disease though it is rare. GOG-33 study demonstrated that the probability of finding metastatic disease was strongly correlated with final tumour grade. The risk of nodal spread in clinical stage I with grade 1 disease was 3% for pelvic and 2% for para-aortic nodes, while the risk of nodal spread for grade 3 disease in the same stage was 18% for pelvic and 11% for para-aortic nodes [10]. Creasman et al demonstrated that risk of lymph node involvement is increased in patients with deep myometrial invasion and high grade disease, they reported up to 34% pelvic lymph node metastasis in this group of patients [10]. In the present study, 38% (13/34) patients with deep myometrial invasion had nodal positivity while in 31% (7/22) patients reported nodal positivity in patients with myometrial infiltration <50%.

The concept of Sentinel Lymph Node Mapping (SLNM) is the

upcoming approach for lymph node evaluation to decrease the morbidities associated with lymphadenectomy. In SLNM, cervical injection alone may be associated with chance of missing the para-aortic node metastasis. Studies have shown that injecting dye into cervix and fundus improves detection rate of sentinel para-aortic nodes [11]. But at centres where sentinel lymph node mapping is not available, omitting lymphadenectomy by risk stratification should be done carefully. Even in low-risk patients, nodal basins should be evaluated intraoperative and any suspicious nodes should be biopsied.

The result of Selective Targeting of Adjuvant Therapy for Endometrial Cancer (STATEC) may give a final answer regarding therapeutic benefit of lymphadenectomy in early endometrial cancer [12]. Till further developments in preoperative assessment of the lymph node status based on biological factors, it is better to have an assessment of the lymph nodes for all patients with endometrial cancer depending on the available resources to prevent understating and under treatment.

CONCLUSION

Node positivity in high grade endometrial carcinoma was 27% and there were no differences in overall survival among the patients with nodal positivity. Routine assessment of nodal status for all patients with endometrial cancer shall guide in optimal staging and management.

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