# Analysis of Factors Influencing Nodal Status in Endometrial Carcinoma ; Our Experience

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DOI: 10.29322/IJSRP.9.03.2019.p8767
http://dx.doi.org/10.29322/IJSRP.9.03.2019.p8767

***Abstract-*** A retrospective analysis was of a total 170cases of patients who underwent systematic pelvic and para- aortic lymphadenectomy between 2011 - 2017 , at AHRCC. chi=square was used for univariate analysis of variables influencing the lymph node involvement in endometrial cancer, those with p value<.05 were included in multivariate logistic regression. The effect of variables on lymphnode involvement are reported using odds ratio and 95%confidence. chi=square was used for univariate analysis of variables influencing the lymph node involvement in endometrial cancer, those with p value<.05 were included in multivariate logistic regression. The effect of variables on lymphnode involvement are reported using odds ratio and 95%confidence intervals. The effects of variables on lymph node involvement are reported using adjusted odds ratios(Ors) and confidence interval (95%). The mean age at surgery was 56.6+/-9.014 yrs. In univariate analysis tumor size, hisological type,myo-invasion, lvsi and cervical extension had a significant association, with lymphnode involvement. On multivariate logistic regression tumor size,histological type and cervical extension was found to be most signicant, factor associated with nodal involvement.

***Index Terms***- EC- ENDOMETRIAL CANCER, USPIO—Ultrasmall –superparamagnatic iron oxide MRI ,MRI- magnetc resonance imaging,ROC- receptor operator analysis curve,lvsi-lymphovascular space invasion,HP-Histopathology

***Objective -*** Aim of our study is to analyse variables effecting the nodal status in endometrial cancer and to assess the need for systematic lymphadenectomy in low risk cases. This aim of the study was to determine the incidence of lymphnode metastasis in endometrial cancer based on the age, myoinvasion, lvsi, grade,cervical extention and histopathologic type.

## I. Introduction

Endometrial cancer the commonest malignancy in developed countries. Its incidence is on rise, probably due to increased life expectancy and obesity.Mortality rate has increased in past three decades. One explanation for this is patients being diagnosed at older ages, which leads to increase in high risk type and advanced stage cancer.

- Patients diagnosed in early stage disease i.e stage I A overall survival of 85%-91%(1).Nevertheless patient in advanced stage have guarded prognosis(2 The most significant prognostic factors are histological grade, depth of myometrial involvement, lymphovascular invasion and lymphnode status(3).20%of the patients with EC extending outside of the uterus (stage II AND IIA-B).and 10% with clinical stage I have lymph node metastasis(1).Therefore removal of the pelvic and para-aortic lymph node has been recommended as a part of comprehensive surgical staging including total hysterectomy and bilateral salpingoopherectomy.(3) Protocol of management of EC with regards to lymph nodes is varies in different countries and instituitions.Recently, the publication demonstrate that pelvic lymphadenectomy (4,5)did not improve the disease free and survival rates and therefore should not be recommened as a routine procedure.however there are several limitation of the above trials, (no randomisation for postoperative adjuvant therapy , no systematic para-aortic lymphadenectomy) Make there validity questionable.(6,7) Lymphnode dissection till date the only way to fully stage the disease and to determine patients likely to benefit from adjuvant therapy(8,9).There is lack of proper imaging procedures to determine the extent of extra uterine disease; USPIO enhanced MRI might improve the staging.,allowing detection metastasis in normal sized node.(10,11) Most of the predictors of lymphnode metastasis are histological type,tumor grade,lymphovascular space invasion and depyh of myometrial involvememt,age studies done by widschwendter et al.one hundred twenty five patients received pelvic lymphadenectomy, with a median of 25 removed nodes ,and 111 patients additionally received paraaotic lymhadenectomy with median removal of 12 nodes.metastastic lympnode positive found in 24.8%of the patients and a multivariate logistic regression showed that lympho-vascular space invasion,histological type,and tumor stage significantly and indepedently predicted lymphnode involvement. of 111 patients with both pelvic and para-aortic lymphadenectomy,18 patients(16.2%)had metastatic para –aortic nodes,and 3(2.7%) patients had isolated positive para-aortic lymphnodes, without involvementof pelvic lymphnodes

- Kadir Cetinkaya et al (12),lymph node metastasis was observed in22out of 247(8.9%), of the factors with potential effects on LNM was analysed using the fisher exact test :age, grade,histological type,myometrial invasion, tumor size and malignant peritoneal cytology.lymphnode involvement was significantly more common in higher grades, deep myometrial invasion, cervical stromal involvement and positive peritoneal cytology.
- Factors with level of significance was put to logistic regression analysis.Myometrial invasion of more ½,was identified as a independent prognostic factor with a increase lymphnode risk of 8.5 fold. The clinical data help us in defining the low and high risk patients based on pre and post operative findings, that will help us categorise the patients and their need for lymphadenectomy.More recently sentinel lymphnode mapping has been a useful alternative to complete lymphadenectomy.

## II. MATERIAL METHODS

A analysis was conducted on a total of cases with EC who underwent systemic pelvic and combined pelvic and paraaortic lymphadenectomy inclusion and exclusion criteria –

- INCLUSION CRITERIA- The study included patients of only endometrial cancer, proved by preoperatively and those who underwent complete surgical staging at AHRCC.
- EXCLUSION CRITERIA-1. all other corpus cancers i.e sarcomas 2. all the cervical cancers3 sychronous malignancy 4.did not undergo lymphadenectomy

**Table-1: Clinical and pathologic characteristics of Patients**

| Variables | | | Values |
|---|---|---|---|
| **Age(in years), mean ± SD** | | | **56.86±9.01** |
| | Categories, n(%) | 25≤age≤55 | **69 (40.6)** |
| | | +node | 16 |
| | | -node | 53 |
| | | 55<age≤60 | **48 (28.2)** |
| | | +node | 14 |
| | | -node | 34 |
| | | 60<age≤80 | **53 (31.2)** |
| | | +node | 19 |
| | | -node | 34 |
| **Surgery, n (%)** | | | |
| | Laparotomy | | **160 (94.1)** |
| | | +node | 46 |
| | | -node | 114 |
| | Laparoscopy | | **10 (5.9)** |
| | | +node | 3 |
| | | -node | 7 |
| **Histologic type, n (%)** | | | |
| | Non-endometrioid | | **26 (15.3)** |
| | | Clear Cell | **17** |
| | | +node | 11 |
| | | -node | 6 |
| | | Pappillary Serous | **9** |
| | | +node | 6 |
| | | -node | 3 |
| | Endometrioid | | **144 (84.7)** |
| | | +node | 32 |
| | | -node | 112 |

| | | |
|---|---|---|
| **Grade, n(%)** | | |
| Grade-1 | | **26 (15.3)** |
| | +node | 7 |
| | -node | 19 |
| Grade-2 | | **106 (62.35)** |
| | +node | 23 |
| | -node | 83 |
| Grade-3 | | **38 (22.35)** |
| | +node | 19 |
| | -node | 19 |
| **Tumor size(in cm), n(%)** | | |
| <2 | | **58 (34.1)** |
| | +node | 7 |
| | -node | 51 |
| ≥2 | | **112 (65.9)** |
| | +node | 42 |
| | -node | 70 |
| **Myometrial invasion, n(%)** | | |
| <50% | | **138 (81.2)** |
| | +node | 33 |
| | -node | 105 |
| ≥50% | | **32 (18.8)** |
| | +node | 16 |
| | -node | 16 |
| **Lymphovascular invasion. n(%)** | | |
| No | | **152 (89.4)** |
| | +node | 37 |
| | -node | 115 |
| Yes | | **18(10.6)** |
| | +node | 12 |
| | -node | 6 |
| **Cervical extention, n(%)** | | |
| No | | **147 (86.5)** |
| | +node | 34 |
| | -node | 113 |
| Yes | | **23 (13.5)** |
| | +node | 15 |
| | -node | 8 |
| **Bplnd, n(%)** | | **170 (100)** |
| | +node | 49 |
| | -node | 121 |
| **Bplnd+bpand, n(%)** | | **85 (50)** |
| | +node | 32 |
| | -node | 53 |

SD: Standard deviation, n(%): Total number of cases (percentage involvement), Total no of cases = 170

**Table-2: Univariate analysis**

| Variables | $\chi^2$-value | p-value |
|---|---|---|
| Age (in years) | 2.346 | .309 |
| Histologic type | 19.999 | .001 |
| Grade | 10.975 | .004 |
| Tumor size | 12.046 | .001 |
| Myometrial invasion | 8.617 | .003 |
| Lymphovascular invasion | 14.053 | .001 |
| Cervical extention | 17.172 | .001 |

Statistical significance ($p<0.05$) i.e, 5% level of significance, $^2$: chi-square, Total no of cases = 170.

**Interpretation of table-2**

In table-2; Since p value for age is 0.309 ($\geq 0.05$) which means it is not statistically significant, thus we accept null hypothesis (Ho) i.e., there is no significant association between lymph node involvement and ages of the patients under study.

Similarly p value for Histological type is 0.001 ($<0.05$) which means it is statistically significant, thus we reject null hypothesis (Ho) and accept alternative hypothesis (H1) i.e., there is a significant association between lymph node involvement and Histological type of the patients under study.

And so on …

Thus, in the univariate analysis Histological type, Grade, Tumor size, Myometrial invasion, Lymphovascular invasion and Cervical extention were found significantly associated with lymph node involvement of the patients under study.

**Table-3: Multivariate analysis**

| Variables | OR | 95% CI | | p-value |
|---|---|---|---|---|
| | | Lower | Upper | |
| Age (in years) | | | | |
| 25≤age≤55 | 1 | | | |
| 55<age≤60 | 1.043 | .396 | 2.745 | .932 |
| 60<age≤80 | 1.475 | .584 | 3.725 | .411 |
| Histologic type | | | | |
| Non-endometrioid | 1 | | | |
| Endometrioid | .216 | .081 | .571 | .002 |
| Grade | | | | |
| Grade-1 | 1 | | | |
| Grade-2 | .437 | .151 | 1.264 | .126 |
| Grade-3 | .851 | .244 | 2.971 | .801 |
| Tumor size (in c.m.) | | | | |
| <2 | 1 | | | |
| ≥2 | 3.573 | 1.401 | 8.930 | .008 |
| Myometrial invasion | | | | |
| <50% | 1 | | | |
| ≥50% | 1.590 | .608 | 4.158 | .344 |
| Lymphovascular invasion | | | | |
| no | 1 | | | |
| yes | 2.308 | .652 | 8.166 | .195 |
| Cervical extention | | | | |
| no | 1 | | | |
| yes | 3.630 | 1.330 | 10.133 | .014 |

Statistical significance ($p<0.05$), OR: Odds ratio, CI: Confidence interval, Total no of cases = 170.

**Interpretation of table-3**

In this case the dependent variable is categorical in nature and divided into two categories i.e., positive node and negative node. Hence here, multivariate analysis is done through binary logistic regression model using SPSS software.

As shown in the above table-3; only 3 independent effects ( Histologic type, Tumor size and Cervical extention) were statistically significant in nature by showing p-value < 0.05; whereas the other 4 independent effects (Age, Grade, Myometrial invasion and Lymphovascular invasion) were not statistically significant as they have p-value ≥ 0.05 at 5% level of significance.

Table-4

| | | +ve node | %ge contribution | -ve node | %ge contribution |
|---|---|---|---|---|---|
| age | 25≤age≤55 | 16 | 9.411764706 | 53 | 31.17647059 |
| | 55<age≤60 | 14 | 8.235294118 | 34 | 20 |
| | 60<age≤80 | 19 | 11.17647059 | 34 | 20 |
| Surgery | laparotomies | 46 | 27.05882353 | 114 | 67.05882353 |
| | laparoscopy | 3 | 1.764705882 | 7 | 4.117647059 |
| Histologic type | Non-endometrioid | 17 | 10 | 9 | 5.294117647 |
| | Endometrioid | 32 | 18.82352941 | 112 | 65.88235294 |
| Grade | G1 | 7 | 4.117647059 | 19 | 11.17647059 |
| | G2 | 23 | 13.52941176 | 83 | 48.82352941 |
| | G3 | 19 | 11.17647059 | 19 | 11.17647059 |
| Tumor size | <2 | 7 | 4.117647059 | 51 | 30 |
| | ≥2 | 42 | 24.70588235 | 70 | 41.17647059 |
| Myometrial invasion | <50% | 33 | 19.41176471 | 105 | 61.76470588 |
| | ≥50% | 16 | 9.411764706 | 16 | 9.411764706 |
| Lymphovascular invasion | no | 37 | 21.76470588 | 115 | 67.64705882 |
| | yes | 12 | 7.058823529 | 6 | 3.529411765 |
| Cervical extention | no | 34 | 20 | 113 | 66.47058824 |
| | yes | 15 | 8.823529412 | 8 | 4.705882353 |
| Bplnd | | 49 | | 121 | |
| Bplnd+bpand | | 32 | | 53 | |

## III. RESULTS

The mean age at surgery 56+/- 8.8 yrs, and the majority of patients ( 96% ) had open surgery. 170 patients ( 100 % ) had pelvic lymphadenectomy alone, and 85 ( 50%) pelvic and para aortic lymphadenectomy . Most patients were of endometroid histology 144(84.7%) and non endometroid 26(15.3%). Of the 170 cases of bplnd 49(28.8%) was lymphnode positive , and of the 85 cases of bplnd+bpand ,(37.64%) was positive for lymph node. Of 146 cases of endometroid (21.9%),of 26 cases of non endometroid 17 cases+ve(65%). Of the total nos of grade 1 cases i.e 26, positive were7 (26%). of 23 g2 cases((21.7%) positive, of 38 case g3 (50%) were positive. Of the 112 cases of tumor size>2cm 42 were positive(38%), of the 58 cases with tumor size < 2cm , 12% were positive. Of 152 cases of lvsi negative ,37 cases(24%) were positive and 18 cases lvsi +ve12 cases(66%) were positive for lymphnode.of the 147 case of cervical extension negative 34 cases (24% )positive and of 23 cases of cervical extension negative (45%) was positive.

- On multivariate logistic regression analysis tumor size , cervical extension and histologic type were found to significantly influence the nodal status, with a p value of .008, .014,.002 respectively . with cut off value of tumor size being 2cm

Here, in the binary logistic regression analysis we have the predicted probability is of membership for positive node.

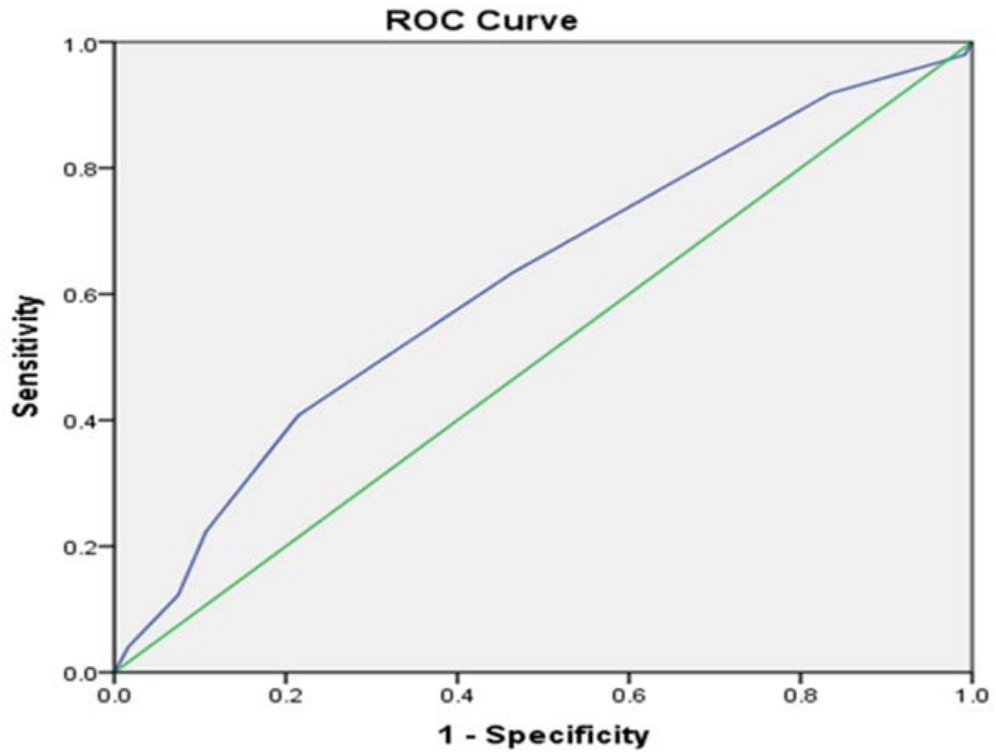
In the above table-3;

i) Histologic type (p=0.002) is found to be significantly associated with prevalence of positive node. The odds in favors of having positive node in case of Endometrioid cases are 0.216 times lesser than that in case of Non-endometrioid .

ii) Tumor size (p=0.008) is also found to be significantly associated with prevalence of positive node. The odds in favors of having positive node in case of Tumor size ≥2c.m are 3.573 times higher than that of Tumor size <2c.m .

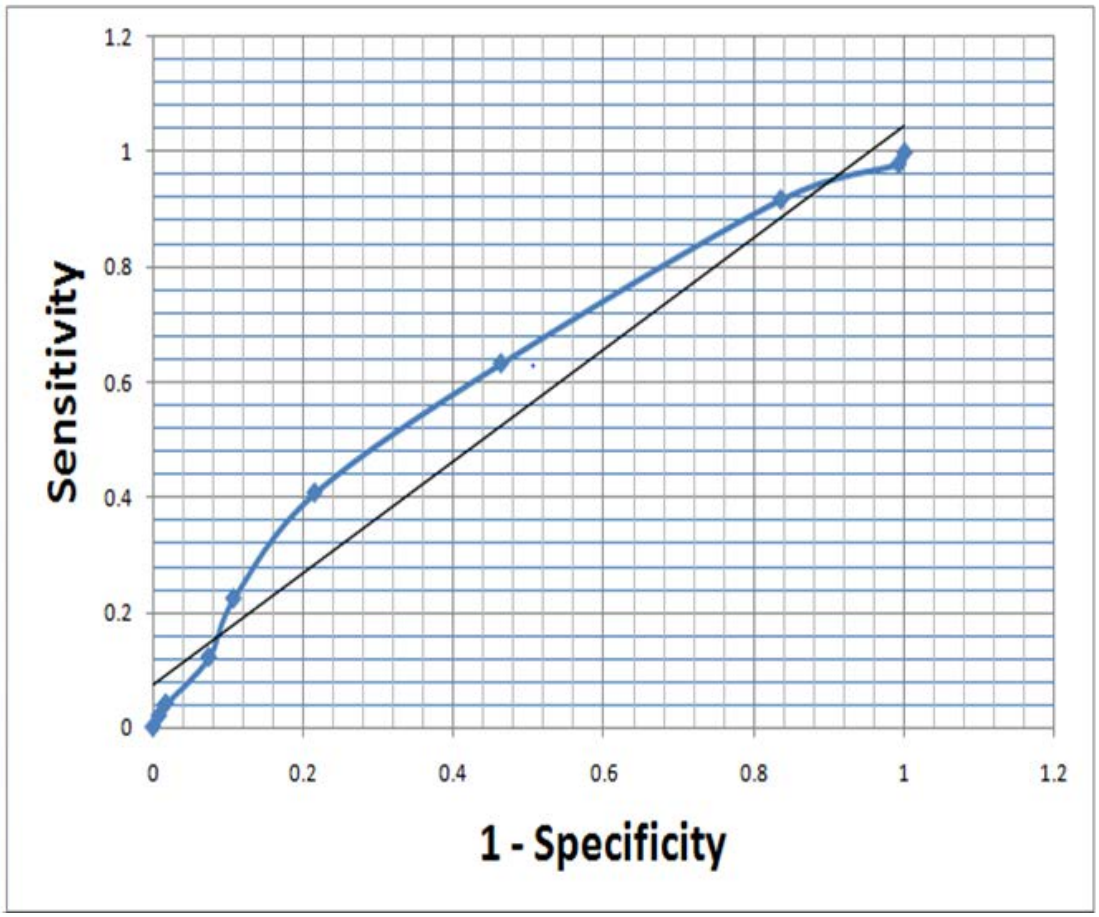
iii) Cervical extention (p=0.014) is also found to be significantly associated with prevalence of positive node. The odds in favors of having positive node in case of yes category are 3.630 times higher than that of no category.

ROC CURVE:




Diagonal segments are produced by ties.

Figure 1:ROC CURVE



| Test Result Variable(s): tumor size | | | | |
|---|---|---|---|---|
| Area | Std. Error | Asymptotic Sig. P-value | Asymptotic 95% Confidence Interval | |
| | | | Lower Bound | Upper Bound |
| .619 | .048 | .015 | .525 | .714 |

| Coordinates of the Curve | | |
|---|---|---|
| Test Result Variable(s): tumor size | | |
| Positive if Greater Than or Equal To | Sensitivity | 1 - Specificity |
| -1.00 | 1.000 | 1.000 |
| .50 | .980 | .992 |
| 1.50 | .918 | .835 |
| 2.50 | .633 | .463 |
| 3.50 | .408 | .215 |
| 4.50 | .224 | .107 |
| 5.50 | .122 | .074 |
| 6.50 | .041 | .017 |
| 7.50 | .020 | .008 |
| 9.00 | .000 | .000 |
| The test result variable(s): tumor size has at least one tie between the positive actual state group and the negative actual state group. | | |
| The smallest cutoff value is the minimum observed test value minus 1, and the largest cutoff value is the maximum observed test value plus 1. All the other cutoff values are the averages of two consecutive ordered observed test values. | | |

## IV. DISCUSSION

This study has analysed the factors influencing the the lympnode involvement.

The analysis of low risk group i.e tumor size <2 cm, grade 1, negative cervical extension lvsi negative,<50% myo-invasion has( 4% -21.76%)risk of lymphatic disseminiation. However from multivariate analysis analysis the three most important factors influencing the positive nodal status are the cervical extention,tumor size and histogic type. Considering the above three factors only i.e cxextension –ve, tumor size <2cm and endometroid histology and the risk of lymphatic dissemination ranges from( 18%- 24%, ) we cannot omit lymphadenectomy in cases with above factors involvement in the patients, with proper co-relation of the three factors with maximum consideration to tumor size followed by cervical extension and endometroid histology

It is difficult to identify low risk patients preoperatively because of variability of tumor grade and myo-invasion, for which preoperative mri ,hp co-relation becomes essential.

## V. PURPOSE OF STUDY

This study, will be of help to all instituitions,in proper management and staging of patients of endometrial cancer , with respect to prediction of lymphnode involvement considering tumor size, cx extension, grade, lvsi, myo invasion into consideration

## VI. STUDY LIMITATIONS

This study susceptibility to selection bias ans referral bias. The strength of study is the clinicopathological factors that impact lymph node metastasis and perfomance of uniform surgical staging procedures

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