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IMPACT OF TUMOR SITE ON LYMPH NODE METASTASIS AND SURVIVAL OUTCOMES IN CARCINOMA ENDOMETRIUM: A RETROSPECTIVE SINGLE- INSTITUTION STUDY

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ABSTRACT

Background: Tumor location within the uterus may influence lymphatic spread and prognosis in endometrial carcinoma. Understanding these patterns is essential for risk stratification and tailoring treatment strategies.

Objective: To evaluate the relationship between primary tumor site in the endometrial cavity and its association with lymph node metastasis, clinicopathological characteristics, and survival outcomes in patients undergoing curative-intent treatment.

Methods: This retrospective study included 156 patients with non-metastatic carcinoma endometrium who underwent curative surgery at a tertiary care center between January 2016 and December 2020. Clinicopathological features, tumor site, nodal status, and survival data were analyzed. Statistical analysis was performed using SPSS version 29.0.

Results: Mean patient age was 57.65±9.24 years. Most tumors (66%) were endometrioid histology. Tumors involving the lower uterine segment (LUS) were more common in younger, premenopausal women and were associated with high-grade histology, increased lymphovascular space invasion (LVSI), deep myometrial invasion, cervical involvement, and advanced FIGO stage. Lymph node

metastasis was observed in 14% of cases. Mean overall survival was highest in fundal tumors (94.6 months) and lowest in LUS tumors (74.3 months). Disease-free survival followed a similar trend.
Conclusion: Lower uterine segment involvement is associated with aggressive pathological features and poorer survival outcomes in endometrial cancer. Tumor location should be considered in prognostic evaluation and treatment planning.

Keywords: Endometrial carcinoma, tumor site, lower uterine segment, lymph node metastasis, survival, retrospective study

INTRODUCTION

Endometrial carcinoma is the most common gynecological malignancy in developed countries, with an incidence rate of 8.4 per 100,000 women annually【1】. In India, the incidence is relatively lower at 2.3 per 100,000 women; however, the rate is rising, likely due to changes in lifestyle, dietary habits, and reproductive patterns【2】. Most patients are diagnosed in their sixth or seventh decade of life, with a mean age of 60 years at diagnosis【2】.

The uterus has three main lymphatic drainage networks—endometrial, myometrial, and subperitoneal—which communicate and drain in a site-specific manner. Lymphatics from the fundus and upper uterine body primarily drain into para-aortic nodes via the infundibulopelvic ligament and partially into superficial inguinal nodes via the round ligament. The mid-body drains into external iliac nodes, while the lower uterine segment and cervix drain into the external iliac, internal iliac, and sacral nodes【3】.

Lymphatic dissemination is the principal metastatic route for uterine malignancies and is also a major contributor to recurrence. Key risk factors for nodal metastasis include deep myometrial invasion and high histological grade. The most commonly involved pelvic lymph nodes are the external iliac, internal iliac, and obturator groups【3】. However, few studies have assessed the relationship between the anatomical origin of the tumor within the endometrial cavity and patterns of lymph node involvement.

Approximately 14% of endometrial carcinomas arise in the lower uterine segment (LUS) or isthmus. These tumors have been found to occur more frequently in association with Lynch syndrome (hereditary non-polyposis colorectal cancer syndrome)【4】. Involvement of the LUS has also been identified as an independent prognostic factor, associated with increased risks of distant metastasis and mortality【5,6】.

Given the limited data on the impact of tumor site within the uterus, this study aims to evaluate the relationship between the primary tumor location and its association with various clinicopathological characteristics, lymphatic dissemination, and survival outcomes. This could guide more individualized clinical decision-making and enhance prognostic stratification.

MATERIALS AND METHODS

Study Design and Ethical Approval

This was a retrospective observational study conducted at a single tertiary care center. The study protocol received approval from the Institutional Review Board. Given the retrospective and non-interventional nature of the study, the requirement for informed consent was waived.

Patient Selection

A total of 158 patients with non-metastatic endometrial carcinoma were treated with curative intent at our center between January 2016 and December 2020. Two patients were excluded due to the presence of synchronous malignancies (one with carcinoma breast and one with carcinoma thyroid). Of the remaining 156 eligible patients, 10 were excluded from survival analysis due to insufficient follow-up or the development of a second primary malignancy (carcinoma lung, carcinoma vulva, carcinoma thyroid, cholangiocarcinoma, and non-Hodgkin lymphoma). The follow-up period extended until December 31, 2024.

Data Collection
Clinical and pathological data were extracted from hospital records. Parameters collected included demographic details, clinical presentation, menopausal status, BMI, parity, staging, tumor location and size, histology, grade, lymphovascular space invasion (LVSI), perineural invasion (PNI), nodal status, and details of surgical and adjuvant treatments. Follow-up data regarding recurrence and survival were also recorded.

Inclusion Criteria
- Histologically confirmed carcinoma endometrium
- Non-metastatic at presentation
- Underwent curative-intent surgical management between January 2016 and December 2020

Exclusion Criteria
- Presence of synchronous malignancies
- Incomplete follow-up data
- Diagnosis of a second primary malignancy during the follow-up period

Treatment Details
All patients were evaluated by a gynecologic oncologist and treatment plans were discussed in a multidisciplinary tumor board. Surgical management consisted of staging laparotomy with total abdominal hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic lymphadenectomy, and para-aortic lymphadenectomy. Omentectomy was performed in cases with serous carcinoma, clear cell carcinoma, or carcinosarcoma.

Post-treatment follow-up included:
- Every 3 months for the first 2 years
- Every 6 months for the next 3 years
- Annually thereafter

At each visit, a thorough physical examination was conducted. Imaging studies were performed if patients reported concerning symptoms.

Outcome Measures
Overall Survival (OS): Time from completion of treatment to death from any cause.
Disease-Free Survival (DFS): Time from initiation of treatment to the first documented recurrence or death.

Statistical Analysis
Survival analysis was performed using the Kaplan-Meier method. Statistical testing and correlation analyses were conducted using IBM SPSS Statistics for Windows, Version 29.0 (IBM Corp., Armonk, NY, USA). A p-value < 0.05 was considered statistically significant.

RESULTS
Patient Demographics
The mean age of the cohort was 57.65 ± 9.24 years. Body mass index (BMI) distribution showed that 39.7% of patients had a normal BMI, 41% were overweight, and 13.5% were obese. Among the 156 patients, 84% were parous and 16% were nulliparous. The majority (81%) were postmenopausal, and 19% were premenopausal.
The most common presenting complaint was postmenopausal bleeding (76.9%), followed by abnormal uterine bleeding (AUB) in 16%, vaginal discharge in 5.8%, and abdominal pain in 1.2%. These findings are summarized in Table 1.

Table 1. Patient Characteristics

Characteristic	No. of Patients (%)
BMI	
Underweight	9 (5.8)
Normal	62 (39.7)
Overweight	64 (41.0)
Moderately Obese	16 (10.3)
Severely Obese	4 (2.6)
Morbidly Obese	1 (0.6)
Parity	
Nullipara	25 (16.0)
Para 1	14 (9.0)
Parity ≥2	117 (75.0)
Menopausal Status	
Premenopausal	29 (19.0)
Postmenopausal	127 (81.0)
Presenting Complaints	
Postmenopausal Bleeding	120 (76.9)
AUB	25 (16.0)
Vaginal Discharge	9 (5.8)
Abdominal Pain	2 (1.2)

Histopathological Characteristics

The site of tumor origin was identified as follows: 9.6% from the fundus, 17.3% from the body, 17.3% from both fundus and body, 4.5% from the lower uterine segment (LUS), 5.8% from both body and LUS, and 26.3% involved the entire endometrial cavity including fundus, body, and LUS. In 19.2% of cases, the tumor site was not clearly specified in the pathology report and was simply documented as arising from the endometrium.

Endometrioid carcinoma was the most common histological type, observed in 66% of patients. Serous carcinoma was found in 19.2%, mixed endometrioid and serous histology in 8.3%, malignant mixed Müllerian tumors (MMMT) in 3.8%, and clear cell carcinoma in 1.3%. In terms of tumor size, 91.7% of cases had tumors larger than 2 cm. High-grade tumors (including Grade 3 endometrioid, serous, and clear cell histologies) were seen in 44.9% of patients, while Grade 1 and Grade 2 tumors were present in 23.7% and 31.4% respectively.

Lymphovascular space invasion (LVSI) was observed in 15.4% of cases, and perineural invasion (PNI) in 0.6% (only one patient). Lymph node metastasis was detected in 14% of cases. Among these, 8.9% had pelvic nodal involvement only, 4.5% had both pelvic and para-aortic involvement, and 0.6% had isolated para-aortic node involvement. Overall, para-aortic lymph node metastasis was present in 5.1% of all patients. Stage distribution was as follows: 58.3% were Stage I, 16% Stage II, 21.8% Stage III, and 3.8% Stage IV disease.

Table 2 - Histopathological characteristics

Histological characteristics	No.of patients (%)
Site of tumor	
Fundus	15 (9.6)
Body	27 (17.3)
Fundus + Body	27 (17.3)
LUS	7 (4.5)
Body + LUS	9 (5.8)
Fundus + Body + LUS	41 (26.3)
Not specified	30 (19.2)
Histology	
Endometrioid	103 (66)
Serous	30 (19.2)
Clear cell	2 (1.3)
Mixed (Endometrioid + serous)	13 (8.3)
MMMT	6 (3.8)
Others	2 (1.3)
Tumor size	
≤ 2cm	13 (8.3)
> 2cm	143 (91.7)
Grade of tumor	
Grade 1	37 (23.7)
Grade 2	49 (31.4)
Grade 3	70 (44.9)
LVSI	
Present	24 (15.4)
Absent	132(84.6)
PNI	
Present	1 (0.6)
Absent	155 (99.4)
Lymph node metastasis	
No nodal mets	134 (85.9)
Pelvic nodal mets	14 (8.9)
Para aortic node	1 (0.6)
Both pelvic and paraaortic node	7 (4.5)

Survival Outcomes

The mean overall survival (OS) was estimated to be 90.2 months, with a 95% confidence interval (CI) of 85.6–94.8 months. A total of 13 patients experienced disease recurrence during the follow-up period. The most common sites of recurrence were the lungs (five cases), liver (five cases), vaginal vault (four cases), and lymph nodes (four cases), including inguinal, common iliac, para-aortic, and mediastinal nodes. Additional recurrence sites included the abdominal wall in two cases and peritoneum in one case. The mean disease-free survival (DFS) was 94.9 months (95% CI: 91.0–98.8 months).

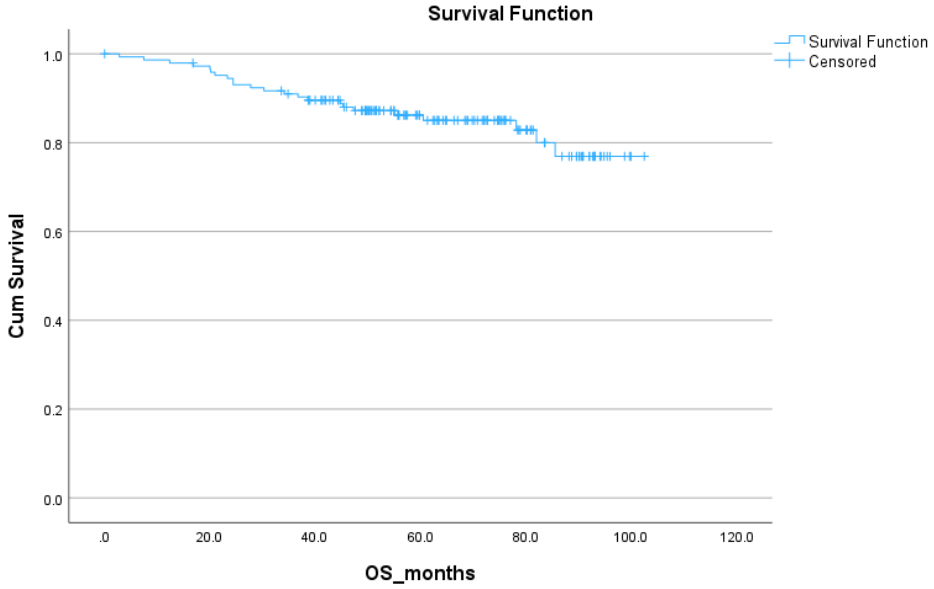

Figure 1. Overall survival

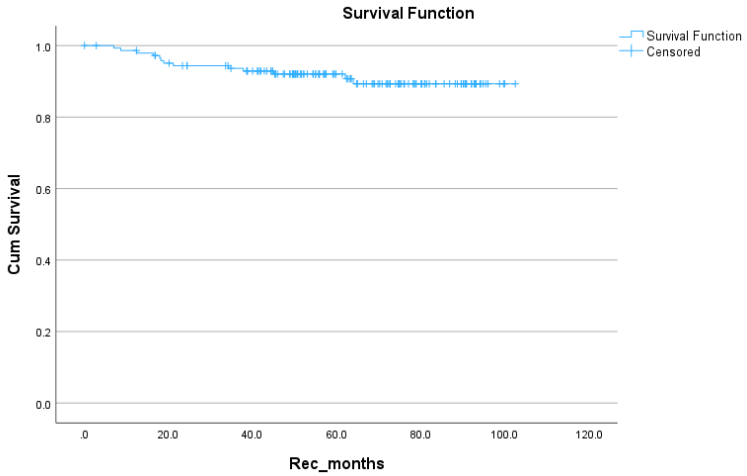

Figure 2: Disease free survival

Tumor Site Associations

Lymph Node Metastasis and Stage

Tumors limited to the fundus and body were mostly early-stage with no nodal metastasis. Among fundus + body tumors, 7.4% had pelvic node involvement and 3.7% had both pelvic and para-aortic involvement. Pelvic nodal metastasis was seen in 14.3% of LUS tumors, while 11.1% of LUS + body tumors had para-aortic involvement. Among tumors involving all uterine segments, 14.6% had pelvic node metastasis, 2.4% had isolated para-aortic involvement, and 4.9% had both.

Stage I tumors were observed in 100% of fundal tumors and 96.3% of body tumors. In tumors involving both fundus and body, 66.6% were Stage I, 18.2% were Stage II, and 14.8% were Stage III. Most LUS tumors were diagnosed at higher stages: 57.1% Stage II and 14.3% Stage III. LUS + body tumors had more advanced stage distribution, including 22.2% Stage IV disease. Tumors involving all segments also had high rates of advanced-stage disease.

SITE (n= 156)		FUNDUS	BODY	FUNDUS + BODY	LUS	BODY + LUS	ALL	NS
SIZE >2cm(%)		53.3	88.9	96.3	100	88.9	100	93.3
Histology (%)	Endometrioid	66.7	48.1	70.4	71.4	77.8	63.4	76.7
	Serous	33.3	18.5	18.5	28.6	11.1	17.1	16.7
	Clear cell	-	3.7	–	-	11.1	-	-
	Mixed	-	18.5	3.7	-	-	14.6	3.3
	MMMT	-	7.5	7.4	-	-	2.4	3.3
Grade (%)	1	46.7	23.1	34.6	14.3	-	10	33.3
	2	20	19.2	34.6	57.1	50	40	26.7
	3	33.3	57.7	30.8	28.6	50	50	40
LVSI Present (%)		13.3	11.1	7.4	28.6	22.2	19.5	16.7
PNI Present (%)		0	0	0	0	0	0	3.3
Myometrial involvement > 50 % (%)		26.7	33.3	70.4	85.7	88.9	85.4	70
Cervical stromal involvement (%)		-	3.7	18.5	71.4	66.7	43.9	16.7

Table 4 - Association between tumor site and histopathological characteristics

Survival Outcomes by Tumor Site

Fundal tumors were associated with the best overall survival, with a mean OS of 94.6 months (95% CI: 86.8–102). Tumors involving the body and fundus had an OS of 82.6 months, while LUS tumors had the poorest OS at 74.3 months (95% CI: 55.3–93.3). Tumors involving all parts of the endometrium had a mean OS of 79.1 months.

Disease-free survival followed a similar trend. DFS was highest in fundal tumors (93.2 months) and lowest in LUS tumors (75.0 months). DFS for tumors involving the body, fundus + body, and all segments were 89.7, 86.9, and 86.5 months, respectively. Fundal tumors had the longest survival and lowest recurrence. LUS tumors had the shortest OS and DFS, correlating with more aggressive disease features.

Table 5: Survival by Tumor Site

Tumor Site	Mean OS (months)	DFS (months)
Fundus	94.6	93.2
Body	92.2	89.7
Fundus + Body	82.6	86.9
LUS	74.3	75.0
Entire cavity	79.1	86.5
Not specified	91.1	95.7

DISCUSSION

This retrospective study assessed the impact of tumor site within the endometrial cavity on lymph node metastasis and survival outcomes in 156 patients treated with curative intent. Our findings demonstrate that tumors involving the lower uterine segment (LUS) are associated with more aggressive clinicopathological features and poorer prognoses compared to tumors originating in the fundus or body of the uterus.

Demographic and Clinical Characteristics

The mean age of patients in our cohort was 57.65 years, consistent with previous Indian studies such as Gouthaman et al., which reported a comparable age distribution among endometrial carcinoma patients【7】. In our study, 81% of women were postmenopausal, aligning with data from Kumar et al., where 80.9% of patients were postmenopausal【8】. Known risk factors such as obesity, nulliparity, and metabolic syndrome were prevalent, with more than half (54.5%) of patients being overweight or obese.

Most patients (76.9%) presented with postmenopausal bleeding, which concurs with findings from Yixuan Zhen et al., where abnormal bleeding was the most frequent presenting symptom in early-stage disease【10】.

Tumor Location and Distribution

Approximately 44.2% of tumors in our study were located in the upper uterine segment (fundus, body, or both), while 10.3% were located in the LUS. This distribution is in line with the findings of Kemi et al., who reported 18.6% of tumors in the lower segment and 64.9% in the upper segments【11】.

Histopathology and Tumor Grade

Endometrioid adenocarcinoma was the predominant histological type (66%), followed by serous carcinoma (19.2%), mirroring trends seen in other Indian cohorts【7】. However, a greater proportion of high-grade tumors was observed in the LUS group, with significant associations between tumor site and grade ($p = 0.042$).

LVSI was more common in LUS tumors (28.6%) compared to fundal (13.3%) and body tumors (11.1%), although this was not statistically significant. Deep myometrial invasion was also more prevalent in LUS and LUS + body tumors, suggesting a more invasive phenotype. These findings support the observations of Kemi et al., who noted increased rates of LVSI, deep invasion, and adnexal involvement in lower segment tumors【11】.

Cervical Involvement and Lymph Node Metastasis

Cervical stromal involvement was significantly higher in LUS (71.4%) and LUS + body (66.7%) tumors, compared to fundal tumors (0%). This emphasizes the aggressive behavior of LUS tumors and their tendency to extend beyond the endometrial cavity.

Although nodal metastasis was not significantly associated with tumor site ($p = 0.181$), LUS and LUS + body tumors exhibited higher rates of pelvic and para-aortic involvement compared to fundus- and

body-only tumors. This aligns with findings from Suchetha et al., who documented pelvic and para-aortic nodal spread in 13.5% and 5.8% of patients, respectively【12】.

Stage Distribution and Tumor Progression

Tumors confined to the fundus and body were generally diagnosed at earlier stages (Stage I), while LUS and LUS + body tumors were more likely to be diagnosed at advanced stages (Stage II–IV). These findings were consistent with Wang et al., who reported that LUS tumors were more frequently associated with advanced disease and higher tumor grades【13】.

Survival and Recurrence

Fundal tumors exhibited the best overall and disease-free survival, with mean OS of 94.6 months and DFS of 93.2 months. Conversely, LUS tumors had the poorest outcomes, with mean OS and DFS of 74.3 and 75 months, respectively. The higher recurrence and mortality associated with LUS tumors further highlight their aggressive nature and poorer prognosis.

Our results support prior evidence that tumor site is a significant prognostic marker. Kemi et al. reported similar associations between lower uterine segment involvement and reduced progression-free and overall survival【11】. Additionally, our findings reinforce the concept that LUS tumors should not be regarded as biologically equivalent to upper uterine tumors and may warrant a distinct clinical approach.

CONCLUSION

This study highlights the prognostic relevance of tumor location in endometrial carcinoma. Tumors involving the lower uterine segment (LUS) are more frequently observed in younger, premenopausal women and are associated with adverse histopathological features, including high-grade histology, deep myometrial invasion, lymphovascular space invasion, and cervical stromal involvement. These tumors tend to present at more advanced stages and are linked to poorer overall and disease-free survival outcomes compared to tumors in the upper uterine segment (fundus and body).

Our findings suggest that tumor site within the endometrial cavity is an important factor influencing prognosis and should be considered during staging, risk stratification, and treatment planning.

RECOMMENDATIONS

- Tumor location should be routinely documented in pathology reports of surgical specimens in endometrial carcinoma.
- Consideration of tumor site is warranted when tailoring treatment strategies, particularly in patients with low- or intermediate-risk disease, to better individualize care.
- Future prospective studies are needed to validate the prognostic significance of tumor site and explore its utility in risk-based treatment algorithms.

LIMITATIONS

- In a subset of cases, the pathology reports did not clearly specify the primary tumor site; these were classified as "not specified" and included in the analysis, which may have diluted site-specific associations.
- Some tumors involved the entire endometrial cavity, making it difficult to determine the precise site of origin, especially in advanced-stage disease.
- This was a retrospective study from a single institution; prospective multi-center studies are needed to corroborate these findings.

REFERENCES

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74:229–63. doi:10.3322/caac.21834

2. Indian Council of Medical Research. Consensus Document for Management of Uterine Cancer. ICMR, 2019.
3. Chaurasia B. *Human Anatomy*, 5th ed., Volume 2. CBS Publishers; 392.
4. Koskas M, Amant F, Mirza MR, et al. FIGO Cancer Report 2021. *Int J Obstet Gynecol*. 2021;20 Oct.
5. Masuda K, Banno K, Yanokura M, et al. Carcinoma of the Lower Uterine Segment (LUS): Clinicopathological Characteristics and Association with Lynch Syndrome. *Curr Genomics*. 2011;12(1):25–9.
6. Bartosch C, Pires-Luís AS, Meireles C, et al. Pathologic Findings in Prophylactic and Nonprophylactic Hysterectomy Specimens of Patients With Lynch Syndrome. *Am J Surg Pathol*. 2016;40:1177–91.
7. Gouthaman S, Saravanan R, Maharajan S, et al. Clinicopathological analysis of carcinoma endometrium at a tertiary care centre in Chennai – a retrospective study. *J Evid Based Med Healthc*. 2021;8(29):2625–32. doi:10.18410/jebmh/2021/484
8. Kumar D, Noushad N, Viswanathan M, Sharma A. Endometrial Carcinoma: Survival Analysis at a Tertiary Care Center in India. *Indian J Gynecol Oncol*. 2022;20:69. doi:10.1007/s40944-022-00672-7
9. Salehiniya H, Allahqoli L, Momenimovahed Z. Risk Factors for Endometrial Cancer in the World: A Narrative Review. *Clin Exp Obstet Gynecol*. 2024;51(7):169.
10. Zhen Y, Zhang X. Clinicopathological Features, Molecular Mechanisms, and Prognosis of Microcystic, Elongated, and Fragmented (MELF) Pattern in Endometrial Carcinoma: A Review. *Gynecol Obstet Clin Med*. 2024.
11. Doll KM, Tseng J, Denslow SA, Fader AN, Gehrig PA. High-grade endometrial cancer: Revisiting the impact of tumor size and location on outcomes. *Gynecol Oncol*. 2014;132(1):44–49. doi:10.1016/j.ygyno.2013.10.023
12. Suchetha S, Mathew AP, Rema P, Thomas S. Pattern of Lymph Node Metastasis in Endometrial Cancer: A Single Institution Experience. *Indian J Surg Oncol*. 2021;12(1):73–77. doi:10.1007/s13193-020-01227-y
13. Wang H, Xiao Y, Cai Y, Zhou Y, et al. Clinicopathological Features and Prognoses of Lower Uterine Segment Cancer: A Retrospective, Single-Center Cohort Study. *Int J Womens Health*. 2024;16:1401–1411.