Clinicopathological Analysis of Carcinoma Endometrium at a Tertiary Care Centre in Chennai – A Retrospective Study

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ABSTRACT

BACKGROUND

Endometrial carcinoma is a leading malignancy among females. Pre-operative imaging and biopsy are necessary to identify the disease. Clinicopathological analysis determines the extent of the disease. Complete surgical staging is advised for high-risk patients. The purpose of this study was to analyze the different clinical endpoints, prognostic factors and demographic details that will influence the survival patterns of the cases of carcinoma of endometrium who underwent surgery during the period from 2014 to 2017 at a tertiary care centre, Chennai, India.

METHODS

Patients diagnosed with operable endometrial carcinoma were surgically staged based on the surgical procedures performed namely, total abdominal hysterectomy (TAH) with bilateral salphingo-oophorectomy (BSO), bilateral pelvic lymph node dissection, and para-aortic lymphadenectomy (patients with high-risk features). Post-surgical staging specimens were histopathologically examined in the Department of Pathology. Adjuvant radiation was given to patients with stage IA grade II and above. Patients with stage III disease received adjuvant chemotherapy. Descriptive analysis was done to show the distributions of patients accordingly. Kaplan-Meier survival analysis was performed for the overall median survival of the patients.

RESULTS

The study consisted of a total of 35 patients with a mean age of 56 ± 8.64. Parameters such as age, clinicopathological features, stage (FIGO staging), tumor size, grade, lymphovascular invasion (LVI), myometrial invasion, cervical involvement, involvement of margins, lymph node ratio (LNR) and survival were studied. Tumor size and grade were found to be significant factors affecting the survival. Overall median survival period of patients who underwent surgery was found to be 31 months.

CONCLUSIONS

Tumor size and grade of the tumor are significant prognostic factors affecting the survival of the patients with carcinoma of endometrium. Lymph node ratio is a new concept in carcinoma endometrium to be pondered upon as a factor predicting survival in future studies thereby defining the role of lymph node dissection in surgical staging.

KEYWORDS

Endometrial Cancer, FIGO Staging, Lymph Node Ratio, Prognosis, Survival Analysis

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BACKGROUND

The second most common gynecological malignancy worldwide is endometrial carcinoma preceded by the breast.[1] The first symptom for the diagnosis of the disease is abnormal vaginal bleeding, usually in postmenopausal women. Endometrial carcinoma comprises a spectrum of neoplasms with variable histologic differentiation ranging from well-differentiated to poorly differentiated carcinomas originating from glandular epithelial cells.[2] The most common histological type of endometrial cancer is endometrioid carcinoma, estrogen-dependent grouped as type I having a better prognosis. Other histologic types include serous papillary carcinoma and mixed carcinoma (including clear cell carcinoma), being estrogen-independent grouped as type II having a poor prognosis.[3] Most of the endometrial cancers are diagnosed at an earlier stage resulting in a 5-year survival rate for more than 95 % of the patients.

However, the same is lower when there is a regional spread or distant metastasis. Long-term exposure to endogenous or exogenous estrogens is considered as one of the most critical risk factors for endometrial carcinoma.[4] Infertility, nulliparity, overweight, obesity, diabetes mellitus, hypertension, early menarche, late menopause and tamoxifen treatment are associated risk factors for the disease. Sporadic mutations increase the risk of endometrial cancer.

Lynch syndrome, a germline mutation caused in DNA mismatch repair gene *MSH6, BRCA1, β-catenin, PIK3CA, K-ras, p53* mutations, Peutz-Jeghers syndrome (PJS) – *STK11* gene mutation, Cowden syndrome (CS) contribute towards the disease. Physical activity, breastfeeding, multiparity, oral contraceptives are some of the known protective factors for endometrial carcinoma.[3,5,6] The incidence of endometrial carcinoma in India is 4.3 per 100,000, which is lower compared to western statistics.[7] Surgery for endometrial carcinoma includes a complete surgical staging procedure (staging laparotomy) with total abdominal hysterectomy and bilateral salphingo-oophorectomy (BSO) including pelvic and para-aortic lymphadenectomy (regional lymph nodes) based on the risk categories and extent of disease. It has been suggested that complete surgical staging may not be necessary for patients with low-risk endometrial carcinoma who have disease limited to the uterus.[8,9] Pre-operative imaging (transvaginal sonography and MRI Pelvis) and biopsy are essential to identify the disease. Parameters such as pathological staging namely the International Federation of Gynecology and Obstetrics (FIGO) and American Joint Committee on Cancer TNM staging (AJCC), histological grading, lymphovascular invasion (LVI), involvement of the margins (parametrial and vaginal cuff), cervical involvement, extent of myometrial invasion and lymph node ratio (LNR) are important for an expert pathological review to determine the extent of malignancy. Adjuvant therapy is guided for patients depending on the stage and variable risk groups suggested by the European Society for Medical Oncology (ESMO). Here we present a retrospective analysis of 35 consecutive cases operated in a tertiary care centre.

Aim

The aim of this study was to analyze different clinicopathological parameters of carcinoma of endometrium at a tertiary care centre.

Objectives

Primary Objective

The retrospective study primarily aimed to analyze different clinical endpoints that will influence the overall median survival patterns of the cases of carcinoma endometrium who underwent surgery during the period 2014 - 2017 at a tertiary care centre, Chennai, India using Kaplan-Meier survival analysis.

Secondary Objective

The study also aimed at descriptive analysis to show the distributions of patients according to various prognostic factors and demographic details.

METHODS

The study was approved by the institutional ethics committee (Reference Number: IEC-NI/19/NOV/71/93) and was carried out as per the ethical principles. Confidentiality and patient anonymity were maintained and informed consent was obtained.

This hospital-based study was carried out based on the descriptive statistical analysis, and median survival of patients who were operated from January 2014 to December 2017 at the Department of Surgical Oncology. Histologically confirmed patients with carcinoma of endometrium suitable for primary surgery were included in the study (stages I to IVA). All the samples collected were studied/observed to confirm with endometrial carcinoma, at the department of pathology. Patients with advanced stage IVB disease requiring neo-adjuvant or palliative therapy were excluded. Other types of malignancies including sarcomas were also excluded. Thus, a total of 35 consecutive patients who found to be satisfying the above criteria were included in the study.

The computerized hospital database helped in a thorough investigation of every particular case with respect to its clinical setting, medical history, prior investigations, diagnoses, treatments, last follow-up, and survival status of the subjects.

A follow-up protocol to update on the present status of the individual was followed. The patients were reviewed once in 3 months for the first three years, once in 6 months for the next two years and then annually in the forthcoming years. Clinical examination was done every visit and radiological imaging of the abdomen and pelvis was done annually. Computed tomography (CT) of whole abdomen and pelvis or positron emission tomography (PET-CT) for the whole body was done for patients with suspected recurrence or metastasis.

The medical records of 35 patients were reviewed, and parameters such as histopathological findings (tumor size, histology, type, grade, stage, myometrial invasion, lymphovascular invasion, the involvement of the cervix, and

involvement of the margins, ESMO risk, and nodal status), age, parity, menopausal status, underlying co-morbidities, and clinical indications were recorded. Date of diagnosis, date of surgery, the last follow-up date, and the present status of the patient was also recorded.

Patients diagnosed with endometrial carcinoma were surgically staged. Total abdominal hysterectomy, bilateral salphingo-oophorectomy, staging laparotomy, including pelvic (external iliac, internal iliac, obturator and common iliac nodes) and para-aortic lymphadenectomy based on the risk categories and extent of disease was performed.

Para-aortic lymphnode dissection was done in patients with more than 50 % of myometrial invasion, tumor more than 2 cm with poorly differentiated histology, high grade lesions, clear cell and serous histology. Omentectomy was performed on serous and papillary tumor histology cases. Biological samples obtained from these specimens have been processed using the conventional method of paraffin embedding and hematoxylin and eosin staining was performed on three-micron thick sections cut from these blocks.

The histopathological findings were classified according to the world health organization (WHO), FIGO and ESMO classification.

Statistical Analysis

Statistical analysis was carried out using statistical package for social sciences (SPSS) software version 16.0. Descriptive and overall survival analysis was done.

RESULTS

Clinical Factors

We analyzed 35 cases of carcinoma of endometrium, who underwent surgery from 2014 to 2017 in our tertiary cancer care centre. The mean age of the patients was 56 ± 8.64 years (range 40 to 71 years).

Out of the total 35 patients, 21 (60 %) patients were postmenopausal. Co-morbid illness included diabetes mellitus in 21 (60 %) patients, systemic hypertension in 11 (31.4 %) cases and hypothyroidism in 8 (22.9 %) patients (Table 1).

9 (26.1 %) patients had other co-morbid illnesses such as asthma, anemia, depression disorder, bronchiectasis, tubal block, fibroid uterus, skin allergy, goiter, seizures, TB lymphadenitis, and H1N1 sepsis.

Characteristic n (%)	
Parity	• Nulliparous 5 (14.3) • Parous 21 (60.0) • Missing 9 (25.7)
Menopausal status	• Pre-menopausal 5 (14.3) • Post-menopausal 21 (60.0) • Missing 9 (25.7)
Diabetes mellitus	• Yes 21 (60.0) • No 14 (40.0)
Hypertension	• Yes 11 (31.4) • No 24 (68.6)
Hypothyroid	• Yes 8 (22.9) • No 27 (77.1)

Table 1. Demographic Characteristics

Surgical Factors

Based on the risk categories and extent of disease, different surgical procedures were opted. Total abdominal hysterectomy and bilateral salphingo-oophorectomy were performed on all 35 (100 %) patients, pelvic and para-aortic (Figure 1a & 1b) lymphadenectomy (regional lymph nodes) for 34 (97.1 %) patients and omentectomy for 4 (11.5 %) patients.

Figure 1a. Completed Right Pelvic Lymph Nodal Dissection Exposing the Right External Iliac Vessels and Right Obturator Nerve

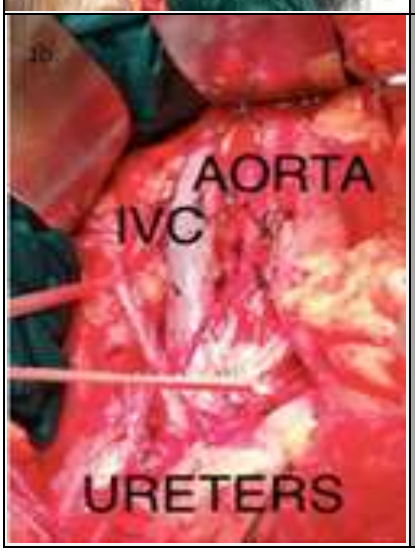


Figure 1b. Completed Para-Aortic Lymph Node Dissection Showing the IVC, Aorta and Ureters

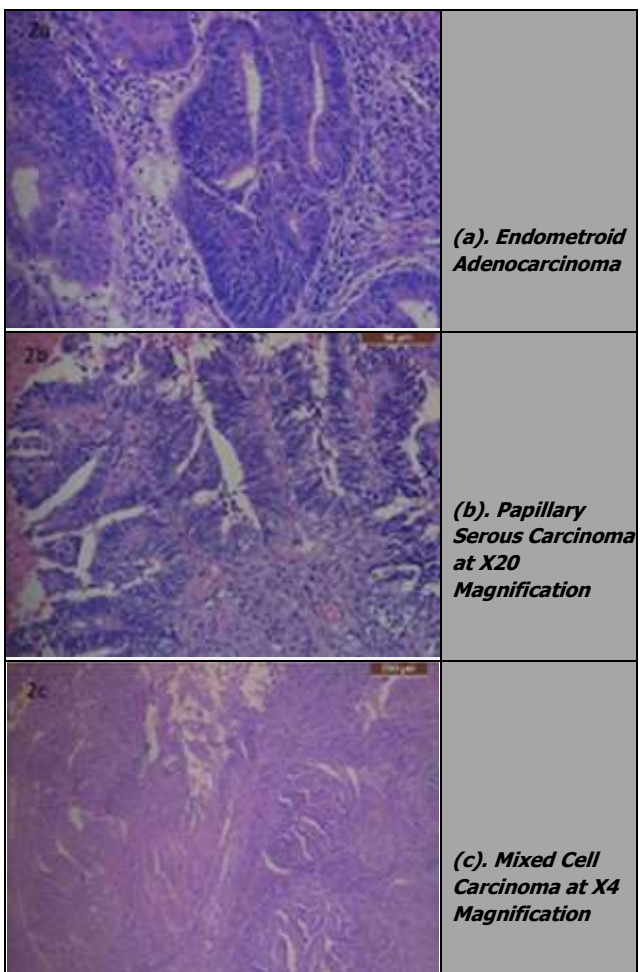
Pathological Factors

The average size of the tumor was calculated to be 3.79 cm. The predominant histology was endometrioid adenocarcinoma in 30 (85.7 %) cases. 4 (11.4 %) patients had papillary serous carcinoma. Mixed carcinoma histology was present in 1 (2.9 %) patient (Figure 2a, 2b & 2c). In other words, 30 (85.7 %) patients had type 1 endometrial carcinoma (Endometrioid Adenocarcinoma), while 5 (14.3 %) patients had type 2 (inclusive of papillary serous and mixed carcinoma).

18 (51.4 %) patients had grade I tumors, 10 (28.6 %) patients had grade II tumors, and grade III tumors in 6 (17.1 %) patients. The stage distribution was stage IA in 22 (62.9 %) patients, stage IB in 3 (8.6 %) patients, stage II in 3 (8.6 %) patients, stage III A in 2 (5.7 %) patients, 4 (11.3 %) patients in stage IIIC1 and stage IVA in 1 (2.9 %) patient. Based on the ESMO risk classification, 19 (54.2 %) patients had low risk, 2 (5.7 %) patients had intermediate and 3 (8.6 %) high-intermediate, 10 (28.6 %) patients were at high risk, and 1 (2.9 %) in the advanced risk category.

27 (77.1 %) patients had less than 50 % myometrial invasion, while 8 (22.9 %) patients had more than 50 % invasion. 1 (2.9 %) patient had lymphovascular space

invasion. Cervical stromal involvement was present in 4 (11.4 %) patients. Margins were free of tumor in all (100 %) patients. The total nodes examined ranged from 7 to 42. The number of nodes examined differed with respect to each patient. 5 (14.7 %) patients had their nodes examined in the range 0 - 10, 17 (49.9 %) patients in the range 11 - 20, 5 (14.7 %) patients in the range 21 - 30, 6 (17.6 %) patients in 31 - 40 and 1 (2.9 %) patient in the range 41 - 50. 30 (85.7 %) patients had node-negative disease, and 4 (11.4 %) patients had node-positive disease. The nodal percentage was calculated based on the lymph node ratio, that is, the ratio of the total nodes involved (positive) to the total number of nodes examined. The highest nodal percentage in the study was 25, while the lowest was 0.



(a). Endometroid Adenocarcinoma

(b). Papillary Serous Carcinoma at X20 Magnification

(c). Mixed Cell Carcinoma at X4 Magnification

Figure 2. Photomicrograph Showing Haematoxylin and Eosin Staining

Follow Up Status

26 (74.3 %) patients were free of disease (normal), while 3 (8.6 %) patients were dead at the time of analysis. The patients with advance staged disease died. 6 (17.1 %) patients were lost to follow-up (Table 2).

Survival Analysis

Kaplan-Meier survival analysis was performed. Figure 3 shows the overall survival rate of the 35 selected patients in months. The median period of survival of the patients from surgery was calculated to be 31 months. Figure 4 shows the survival patterns of the selected 35 patients who underwent surgery with respect to the size of the tumor, which was measured in centimeters. Patients with tumor size more than 3 cm have a median period survival of 25 months while those having less than 3 cm have a median period survival of 31 months. Figure 5 shows the survival patterns of the selected 35 patients who underwent surgery with different grades of cancer. Of the three grades, grade 3 has the least median period of survival of 11 months, followed by grade 2 with 28 months and grade 1 with the highest median period survival of 33 months, respectively.

Characteristic n (%)	
Histology	• Endometroid adenocarcinoma 30 (85.7) • Papillary serous carcinoma 4 (11.4) • Mixed carcinoma 1 (2.9)
Histological type	• Type 1 30 (85.7) • Type 2 5 (14.3)
Grade	• Grade I 18 (51.4) • Grade II 10 (28.6) • Grade III 6 (17.1)
FIGO staging	• IA 22 (62.9) • IB 3 (8.6) • II 3 (8.6) • IIIA 2 (5.7) • IIIC1 4 (11.3) • IVA 1 (2.9)
ESMO risk	• Low 19 (54.2) • Intermediate 2 (5.7) • High-Intermediate 3 (8.6) • High 10 (28.6) • Advanced 1 (2.9)
Myometrial Invasion	• <50 % invasion 27 (77.1) • ≥50 % invasion 8 (22.9)
Lympho-vascular invasion (LVI)	• Present 1(2.9) • Absent 34 (97.1)
Involvement of the cervix	• Involved 4 (11.4) • Not involved 31 (88.6)
Involvement of the margins	• Involved 0 (0) • Margins Free 35 (100)
Nodal status	• Positive 4 (11.4) • Negative 30 (85.7)
Follow-up status	• Free of Disease 26 (74.3) • Died 3 (8.6) • Unable to contact 6 (17.1)

Table 2. Summary of Clinicopathological Features and Follow-Up Status Studied

DISCUSSION

Endometrial carcinoma attributes to one of the most common gynecological cancers worldwide. Obesity, diabetes, hypertension, early age at menarche, nulliparity, late age at menopause, Lynch syndrome, older age (≥ 55 years), and tamoxifen use contribute towards the risk factors for uterine neoplasms.[10-13] The mean incidence age of the disease is 60 years.[14] Endometrial cancer is generally seen among postmenopausal women, and only 25 % of the patients are seen in the premenopausal period. In our study population, the mean age of the patients was 56 years, which is younger than other studies. 60 % of the patients were postmenopausal, and 60 % of patients were diabetic, which is in concordance with the risks given in the literature. Associated risk factors such as nulliparity, hypertension, hypothyroidism were also analyzed in the study.

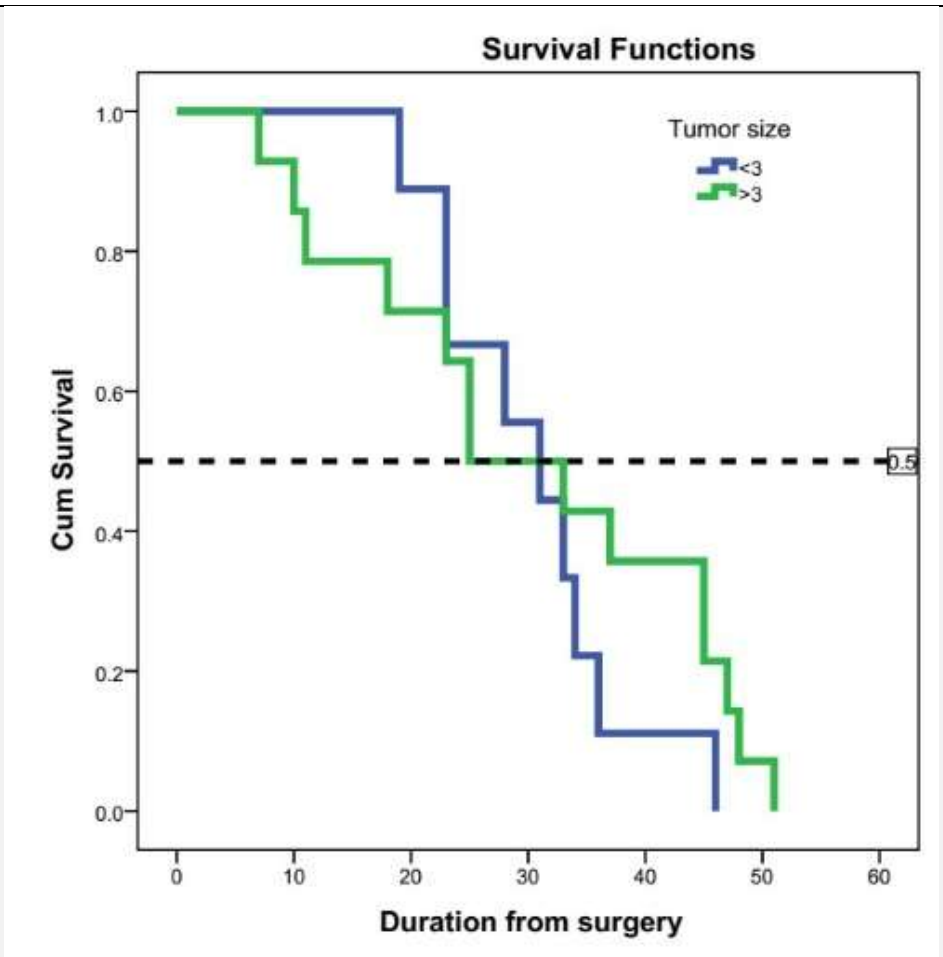


Figure 3. Overall Survival of Patients from Surgery

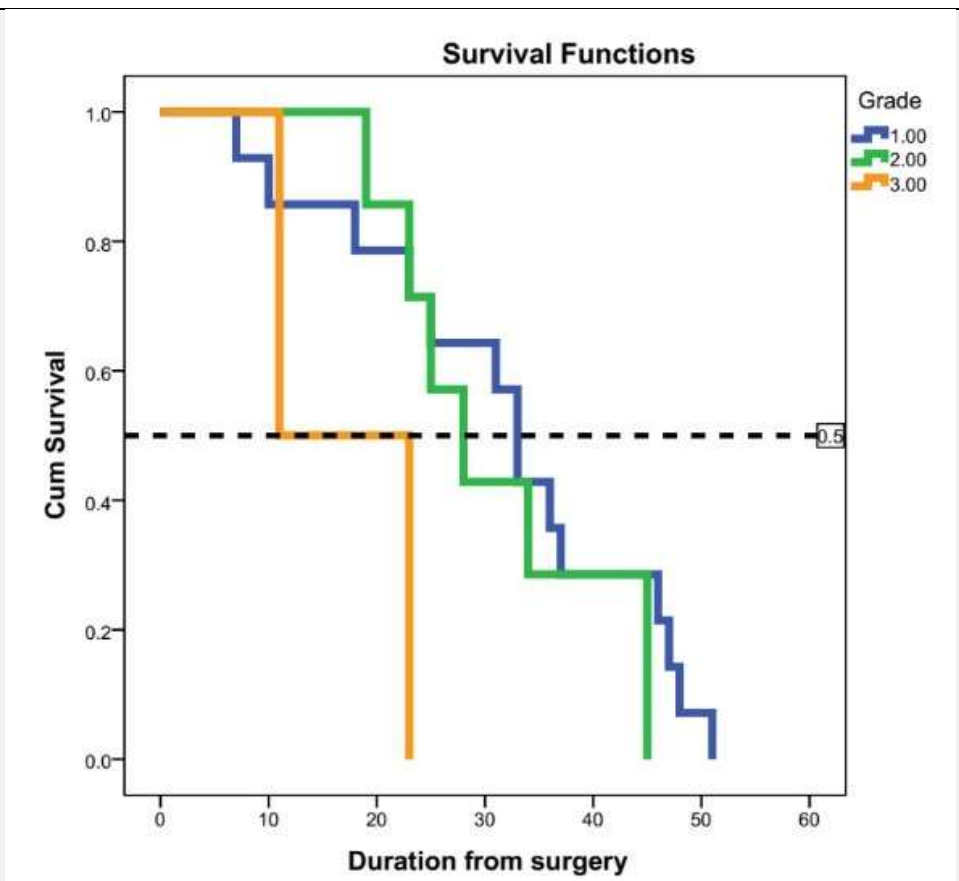


Figure 4. Overall Survival of Patients Who Underwent Surgery w.r.t. the Size of Tumour (cm)

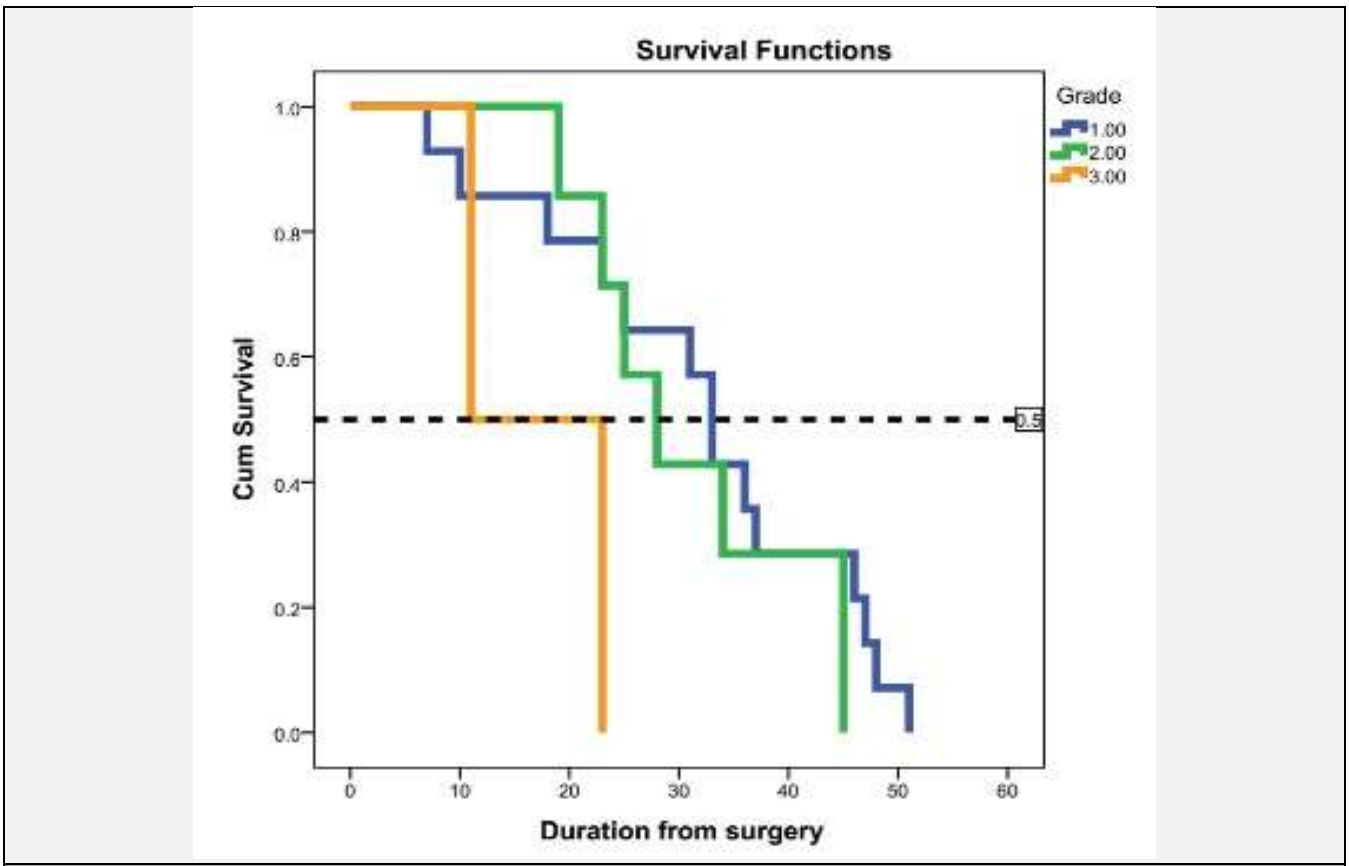


Figure 5. Overall Survival of Patients Who Underwent Surgery w.r.t. the Grade of the Cancer

The disease is usually diagnosed using two procedures namely endometrial aspiration and endometrial curettage. The recommended protocol for medically operable endometrioid histologies confined to the uterus includes surgical staging with total abdominal hysterectomy with bilateral salphingo-oophorectomy and lymph node assessment.[15]

Surgical staging was done in all patients suitable for primary surgery (stages I to IVA). Omentectomy was performed on certain patients (11.5 %) based on the extent of the disease and tumor histology. Patients with serous and papillary histology underwent omentectomy. In a recent study by Samoon et al. in Pakistan, the overall median survival of patients who underwent complete debulking of the tumor was 27.34 months, while in our study the overall median survival of patients from surgery was found to be 31 months, which is comparatively higher.[16]

The overall median survival of patients with primary tumor size less than 3 cm was higher than those who had huge tumors. This is similar to that of the results by Mariani et al. and Ozgul et al. where the study considered a cut-off of 2 cm primary tumor size.[17,18] In a study by Şık et al. the most frequently encountered histopathological type of endometrial cancer was endometrioid carcinoma, followed by clear cell carcinoma, papillary serous, and mucinous carcinoma.[19] Endometrioid adenocarcinoma (85.7 %) was the predominant histology in our study followed by serous papillary carcinoma (11.4 %) and mixed carcinoma (2.9 %), ultimately type 1 being more prevalent than type 2 similar to a study by Wei et al.[20]

Grade of the tumor is one of the significant predictors of survival.[21] Most of the patients had grade I histology (51.4 %) in our study. In a study by Ates Karateke et al. the five-year survival rate for patients with grade 1 tumors was 93.3 % with a decrease in those with grade 2 and the least in grade 3.[22] A similar pattern is observed in the present study where the patients with grade 1 tumors had the highest overall median survival period of 33 months, grade 2 with 28 months and grade 3 having the least of 11 months.

In a study by Kars et al. it was observed that 82 % of the patients were in stage 1, 8 % were in stage 2, 8 % were in stage 3, 2 % were in stage 4.[23] Stage IA was the most common in our series contributing to 62.9 % followed by stage IB in 3 (8.6 %) patients, stage II in 3 (8.6 %) patients stage III A in 2 (5.7 %) patients, 4 (11.3 %) patients stage IIIC1 and stage IVA in 1 (2.9 %) patient. Advanced FIGO staging affects the overall survival of the patients.[24]

New risk groups were identified according to the European Society for Medical Oncology known as ESMO risk, the most recent classification.[25] The patients in the study were classified into different risk groups based on ESMO namely as low, intermediate, high-intermediate, high, advanced.[26] The present study had 54.2 % patients under low-risk category, 5.7 % in intermediate and 8.6 % high-intermediate, 28.6 % in high-risk category and 2.9 % in the advanced.

The depth of myometrial invasion is one of the attributable risk factors.[27] 77.1 % of the patients had < 50 % myometrial invasion, while the remaining 22.9 % had ≥ 50 % invasion. This is correlated with the fact that most of the type I endometrial carcinomas (Endometrioid type) are usually without deep myometrial invasion while type II, non-endometrioid carcinomas are comparatively aggressive and higher depth of invasion.[28,29]

Lymphovascular invasion is the depth of invasion when the tumor cells are present in the wall of the blood vessel or lymphatic region. LVI is a strong predictor of lymph node positivity and ultimately affects the overall survival.[17] However, in our study, only one patient had LVI. 11.4 % of the patients had cervical involvement. Cervical involvement is an important prognostication in patients with endometrial carcinoma.[27] Vaginal cuff and parametrium are the most common sites for tumor recurrence. The involvement of margins is one of the predictive factors for recurrence.[30] The study had all patients margins free of tumor. This ultimately reflects that most of the patients in the study who were followed up did not show any recurrence and are free of disease.

Lymphadenectomy is an important component of surgical staging for endometrial carcinoma. Decisions about whether to perform lymphadenectomy can be made based on certain pre-operative and intraoperative findings indicative of low-risk features such as less than 50 % myometrial invasion, tumor less than 2 cm, and well or moderately differentiated histology.[31,32] However, it is difficult to accurately determine before the final pathology results are available. Hence, bilateral pelvic lymph node dissection and para-aortic nodal dissection in patients with high-risk features are done usually. Lymphadenectomy has helped to upstage the disease to plan appropriate adjuvant therapy.[21] Lymphadenectomy was performed in 97.1 % of the patients in the study. Our nodal count ranged from 7 to 42, the median lymph node count being 24.5 as compared to 10 lymph nodes in a study by Suchetha S et al.[21] Only four patients had node-positive disease in our study. Adjuvant radiation with vaginal brachytherapy with or without external beam radiation therapy was provided to patients with stage 1A grade II and above. Stage III patients received taxol and carboplatin-based chemotherapy.

A new concept of lymph node ratio (LNR) in patients who underwent surgical staging for carcinoma endometrium is introduced. The lymph node ratio is defined as the ratio of the total number of positive lymph nodes to the total number of lymph nodes examined. LNR is an important prognosis factor for overall survival (OS) and locoregional failure-free survival (LFFS) in head and neck cancer patients.[33] The prognostic value of lymph node ratio in breast cancer has been established by a Dutch study.[34] Even though LNR can be adopted in the follow-up of various cancers, well-recognized and unified optimal cut-point for LNR is not yet determined.[35] This can be obtained by expressing the LNR in percentage known as nodal percentage. The highest nodal percentage in the study was 25, while the lowest was 0. The prognostic significance of nodal percentage (LNR) would be known once when the survival analysis with a significant number of lymph node-positive patients is done as an extension of this study. Therefore, an optimal cut-off for LNR in carcinoma endometrium cases will be obtained. LNR may rejuvenate the concept of complete pelvic and para-aortic lymph node dissection in patients with carcinoma of endometrium once the survival advantage is established with further randomized trials.

Lymph node dissection has not shown any survival advantage as per the current evidence. Lymph node ratio is a new concept to be pondered upon in carcinoma endometrium. Further studies are needed to establish its prognostic significance and survival advantage in carcinoma endometrium encouraging aggressive nodal dissection by the gynecologic oncologist.

CONCLUSIONS

Tumor size and grade of the tumor are significant prognostic factors affecting the survival of the patients with carcinoma of endometrium. Lymph node ratio is a new concept in carcinoma of endometrium to be pondered upon as a factor predicting survival in future studies thereby defining the role of lymph node dissection in surgical staging.

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