The survival outcome and patterns of failure in node positive endometrial cancer patients treated with surgery and adjuvant radiotherapy with curative intent

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Objective: The purpose of this study was to evaluate the patterns of failure, overall survival (OS), disease-free survival (DFS) and factors influencing outcome in endometrial cancer patients who presented with metastatic lymph nodes and were treated with curative intent.

Methods: One hundred and twenty-six patients treated between January 1996 to December 2008 with surgery and adjuvant radiotherapy were identified from our service's prospective database. Radiotherapy consisted of 45 Gy in 1.8 Gy fractions to the whole pelvis. The involved nodal sites were boosted to a total dose of 50.4 to 54 Gy.

Results: The 5-year OS rate was 61% and the 5-year DFS rate was 59%. Grade 3 endometrioid, serous, and clear cell histologies and involvement of upper para-aortic nodes had lower OS and DFS. The number of positive nodes did not influence survival. Among the histological groups, serous histology had the worst survival. Among the 54 patients relapsed, only three (6%) failed exclusively in the pelvis and the rest of the 94% failed in extrapelvic nodal or distant sites. Patients with grade 3 endometrioid, serous and clear cell histologies did not influence pelvic failure but had significant extrapelvic failures (p<0.001).

Conclusion: Majority of node positive endometrial cancer patients fail at extrapelvic sites. The most important factors influencing survival and extrapelvic failure are grade 3 endometrioid, clear cell and serous histologies and involvement of upper para-aortic nodes.

Keywords: Endometrial neoplasms, Lymph nodes, Prospective studies, Radiotherapy, Survival rate

INTRODUCTION

More than 80% of endometrial cancer patients present with disease confined to the uterus and have a 5-year survival higher than 80% [1]. Five to twenty percent of endometrial cancer patients are found to have lymph node metastases and are designated as stage IIIC. Unlike, early stage patients, these patients are at a high risk of recurrence and death. The optimal adjuvant management of these patients is unclear and currently they are variably treated with, postoperative radiotherapy with or without chemotherapy.

The purpose of this study was to look at survival, patterns of failure, and prognostic factors for outcome of node positive endometrial cancer patients treated with curative intent using surgery and post-operative radiotherapy with or without chemotherapy.

MATERIALS AND METHODS

1. Patient selection criteria

All patients who referred to Peter MacCallum Cancer Centre with node positive carcinoma of the endometrium for adjuvant radiotherapy were entered into an ethics-approved database prospectively. Patients eligible for this study were diagnosed between January 1996 and December 2008, and had endometrioid/mucinous, serous papillary or clear cell histology; with evidence of metastasis in pelvic, common iliac, or para-aortic nodes on either surgical staging or imaging and were treated with curative intent with surgery and adjuvant radiotherapy.

2. Staging

All patients underwent total abdominal hysterectomy, bilateral salphingo-oophorectomy with or without pelvic nodal sampling or lymph node resection. Positive pelvic, common iliac, and para-aortic nodal involvement was confirmed by surgery or positron emission tomography. Ninety-three percent of patients were staged surgically according to the 1988 the International Federation of Gynecology and Obstetrics staging system. Lymph nodes were detected on positron emission tomography (PET) scan in 7% of patients.

3. Treatment policy

All patients with confirmed positive pelvic, common iliac, or para-aortic nodes with no other evidence of metastatic disease elsewhere were treated with adjuvant radiotherapy.

External beam radiotherapy was delivered to the pelvis in all patients and to the para-aortic nodal strip when there was common iliac or para-aortic nodal involvement, employing 4-fields technique using 18 MV photons. The upper border of the pelvic field was at the L5–S1 intersection and those patients with common iliac nodes and above received radiation to the next echelon of nodes in the para-aortic strip. The lateral borders were 2 cm outside the true pelvis and the lower border was kept at the inferior margin of obturator foramina. In lateral projection, the anterior field was set at 1 cm anterior to the symphysis pubis and the posterior margin at the S2–S3 intersection. A dose of 45 Gy was given to the whole pelvis and the para-aortic strip. A 3 cm margin around the vaginal vault, in all axes was boosted to a dose of 50.4 to 54 Gy in 28 to 30 fractions. All positive nodal sites were boosted to 50.4 to 54 Gy. Vaginal vault brachytherapy was used in patients with close or positive vaginal margin. Concurrent chemotherapy and systemic chemotherapy was given to selected patients assessed as being particularly high-risk for recurrence by the multidisciplinary team. This treatment involved weekly cispla-tin (40 mg/m^2) or carboplatin (AUC 2) during radiotherapy, followed by four cycles of carboplatin (AUC 5) and paclitaxel (175 mg/m^2) 3 weekly.

1) Prognostic factor grouping

The grade and histology were combined and grouped as follows for analysis. Group 1 included grade 1 and 2 endometrioid/mucinous types, group 2, grade 3 endometrioid/mucinous, group 3, clear cell and group 4, serous histology. Group 1 was considered as the 'low risk' group and the rest of the groups together as the 'high risk' group.

2) Follow-up and salvage

All patients were examined at 4 to 6 weeks postradiotherapy and thereafter every 3 months during the 1st year, every 4 months in the 2nd and 3rd years and 6 monthly in the 4th and 5th years. After 5 years patients were reviewed once per year, indefinitely. No routine investigations were carried out during the follow-up period in asymptomatic patients. Symptomatic patients were investigated thoroughly and if found to have salvageable disease, were treated either by radiotherapy, surgery, or both.

4. Criteria for assessing outcomes

Failure was defined as recurrence of disease following radiotherapy. The date of failure was taken as the date of any of these types of failure either on clinical examination or imaging.

Sites of failure were recorded as pelvic failure (recurrent disease at vaginal vault or pelvic nodes), extrapelvic nodal failure (abdominal, mediastinal, supraclavicular, or inguinal nodes) or distant parenchymal failure. For analysis, extrapelvic nodal failure and distant failures together were considered as extrapelvic failure.

When patients first failed at multiple sites, the dominant site of failure was determined according to the hierarchy, in descending order: distant, inguinal, supraclavicular, mediastinal, abdominal, pelvic, and local.

5. Statistical methods

Overall survival (OS) was defined as the time difference between the date of diagnosis or treatment to date of death irrespective of the cause of death. Disease-specific survival (DSS) excluded deaths not related to this disease. Disease-free survival (DFS) was defined as the time difference between date of diagnosis or treatment and date of first failure. Kaplan-Meier curves for OS and DFS were calculated from which 5-year event-free rates were determined. Prognostic factors were evaluated using the Cox proportional hazards model. The impact of prognostic factors on OS and DFS were sum-

marised using hazard ratios (HRs) along with 95% confidence intervals and also as 5-year event-free rates. The closeout date for the follow-up was 06/09/2011. The data was analysed using Stata ver. 12.1 (StataCorp, College Station, TX, USA).

RESULTS

1. Characteristics of the patients

There were 126 patients eligible for the study. The median (interquartile range) follow-up was 52.6 months (32.7 to 92.9). The characteristics of patient and tumour-related factors are presented in **Table 1**. Their age ranged from 32 to 88 years (median, 61 years).

One hundred and seventeen patients (93%) had nodes detected on nodal sampling or lymph node resection and nine (7%) on PET. Ninety-four patients (75%) had pelvic, 9 (7%)

Table 1. Patient and tumour characteristics (n=126)

Variable	No. of patients (%)
Age (yr), median (range)	61 (32–88)
Histology	
Endometroid/mucinous	93 (74)
Serous	23 (18)
Clear cell	10 (8)
Tumor grade	
1	27 (21)
2	38 (30)
3	61 (48)
Lymphovascular space invasion	
Present	108 (86)
Absent	18 (14)
Lymph node detected on	
Lymphadenectomy	117 (93)
Positron emission tomography	9 (7)
Maximum site of nodal involvement	
Pelvic	94 (75)
Common iliac	9 (07)
Para-aortic	23 (18)
No. of nodes removed, median (range)	11 (1–36)
No. of positive nodes, median (range)	
Nodal sampling or lymph node resection	2 (1–17)
Positron emission tomography	2 (1–6)
Concurrent chemotherapy	
Given	48 (38)
Not given	78 (62)

common iliac, and 23 (18%) para-aortic nodal involvement as the highest echelon of involved nodes. The median number of nodes involved was 2 (range, 1 to 17). Forty-eight patients (38%) received concurrent chemotherapy with weekly carboplatin (34%) or cisplatin (4%). Systemic chemotherapy was given to 21 patients (17%).

2. Overall and disease-free survival

Of the 126 patients included in this study, 54 (43%) died, out of which 44 (35%) died due to endometrial cancer. The 5-year OS was 61%. DSS at 5 years was 67%. The 5-year DFS was 59%. Fifty-six patients (44%) were free of disease at last follow-up. Adding chemotherapy to radiation did not improve OS (p=0.589) or DFS (p=0.643).

3. Prognostic factor analyses

Age >60 years had significant negative impact (p=0.001) on OS and DSS (p=0.021) but not on DFS (p=0.172). Group 1 (grade 1 and 2 endometrioid/mucinous) included 52% (n=65), group 2 (grade 3 endometrioid/mucinous), 22% (n=28), group 3 (clear cell), 8% (n=10) and group 4 (serous histology), 18% (n=23) of patients.

Each high risk group was compared with the low risk group and found to have significant negative impact on OS (group 2, p=0.003; group 3, p=0.002; and group 4, p<0.001); DSS (group 2, p=0.001; group 3, p<0.001; and group 4, p=0.001); and DFS (group 2, p=0.002; group 3, p=0.023; and group 4, p<0.001). A comparison between the low risk vs. high risk groups (groups 2, 3, and 4 combined together) revealed that at 5 years, 78% were alive among the low risk group compared to 43% among high risk group. Similarly, 76% were without relapse at 5 years among the low risk group compared to 40% among high risk groups. The 5-year OS, DSS, and DFS among the low and high risk groups are shown in **Fig. 1**.

As serous histology had very significant impact on survival, we analysed the OS, DSS, DFS of group 1 vs. groups 2 and 3 vs. group 4 (**Fig. 2**) and found that serous histology appeared to have the worst outcome.

There was no significant difference in OS (HR, 1.44; p=0.208) or DFS (HR, 1.48; p=0.185) when patients with positive pelvic nodes were compared with those with positive common iliac, lower para-aortic (nodes below coeliac axis), and upper para-aortic nodes (nodes below renal vessels) together as one group. However, involvement of upper para-aortic nodes had a negative impact on both OS (p=0.002) and DFS (p=0.003). The number of involved nodes did not have any significant impact on OS (p=0.131) or DFS (p=0.304).

Eighty-six percent of patients in this cohort had lymphovascular space invasion (LVSI). LVSI was associated with a margin-
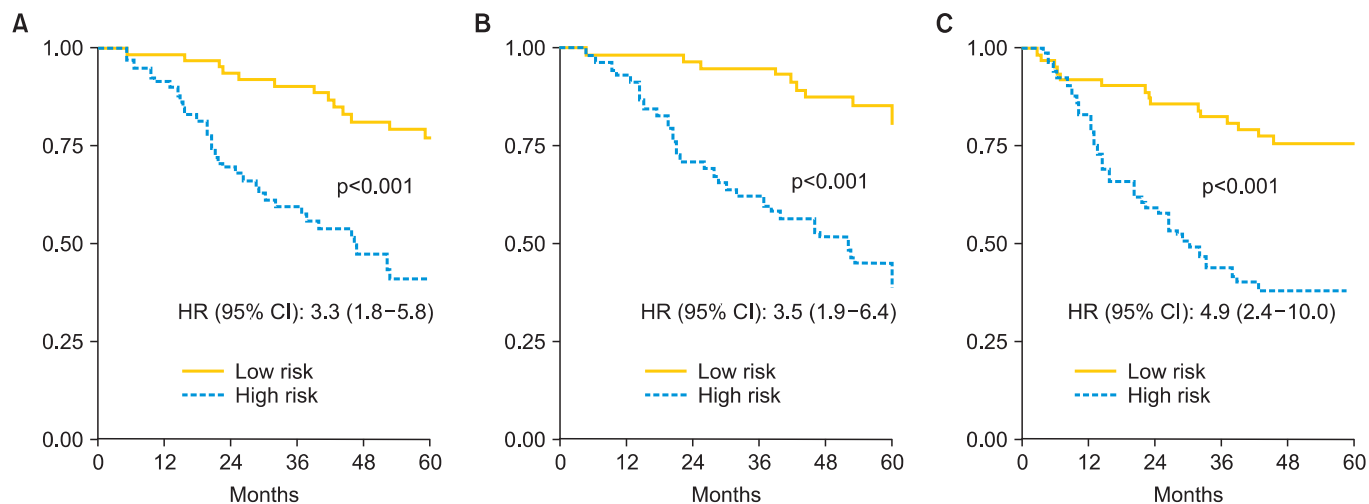
Fig. 1. (A) Overall survival, (B) disease-specific survival, and (C) disease-free survival estimates of high risk and low risk node positive endometrial cancer patients. CI, confidence interval; HR, hazard ratios.
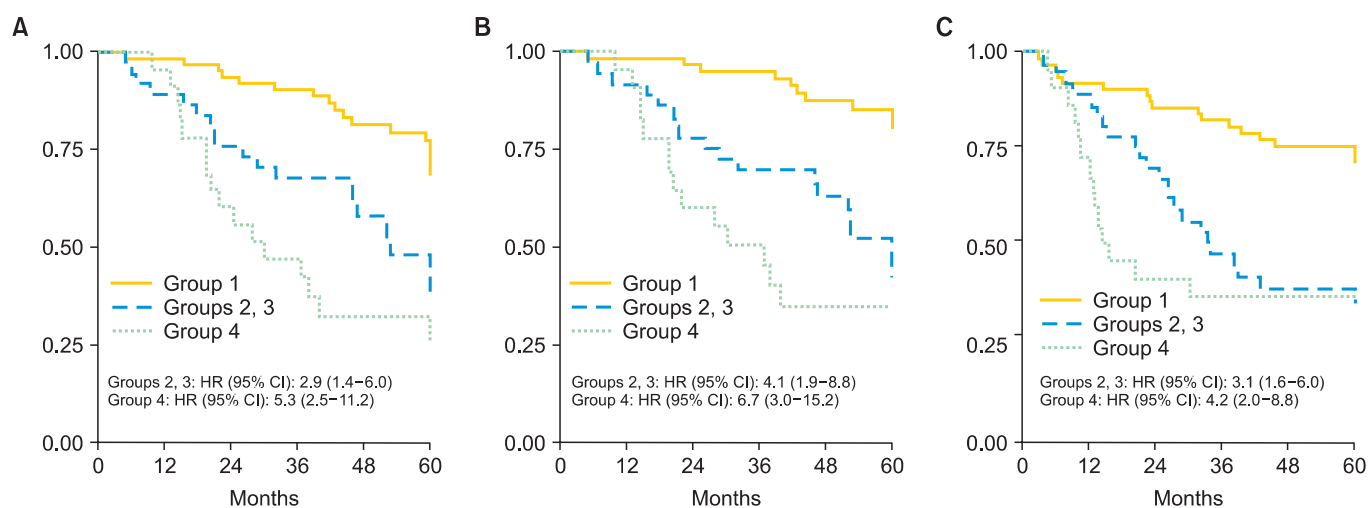

Fig. 2. (A) Overall survival, (B) disease-specific survival, and (C) disease-free survival estimates of grade 1 & 2 endometroid (group 1) vs. grade 3 endometroid (group 2) and clear cell (group 3) vs. serous histology (group 4). CI, confidence interval; HR, hazard ratios.

ally worse OS (HR, 2.67; p=0.058) but not with DFS (HR, 2.3; p=0.12), the fractional myometrial invasion did not influence OS (HR, 0.95; p=0.064) or DFS (HR, 0.96; p=0.164).

4. Patterns of failure

Fifty-four patients (43%) relapsed either at pelvic, extrapelvic nodal, or distant parenchymal sites. Among those relapsed, 23 patients (18%) failed in the pelvis. The pelvic control rate was 82%. However, only three patients (6%) failed exclusively in pelvis. The rest of the 51 (94%) failed at extrapelvic nodal or distant parenchymal sites either initially or subsequently. The three patients who had failure limited to pelvis had only pelvic nodal disease at presentation. One had vault recurrence and

was treated with interstitial implant brachytherapy and remains disease free. The 2nd patient had a massive pre-sacral recurrence and died of disease. The 3rd patient had vault recurrence and was treated surgically and was alive at last contact. Hence only two patients had salvageable disease at recurrence.

In the low risk group, 14% (9/65) failed in the pelvis compared to 23% (14/61) in high risk group. At 5 years, 88% in the low risk and 79% in the high risk group did not relapse in pelvis. This difference was not statistically significant (p=0.201).

The extrapelvic failure in the low risk group was 23% (15/65) and 59% (36/61) in the high risk group. Eighty percent of the low risk group and 42% of the high risk group were relapse free at 5 years. This difference in extrapelvic failure was statisti-

cally significant (p<0.001).

DISCUSSION

Lymph node positivity is an important prognostic factor in endometrial cancer [2]. In the present study, the survival, patterns of failure, and factors influencing outcome of the node positive high risk group were analyzed.

To our knowledge, this is the largest single institution series of node positive endometrial cancer published in the literature. The 5-year OS and DFS of node positive endometrial cancer ranges widely between 60% to 84% and 34% to 81% respectively as shown in **Table 2**. In 2012, Lee and Viswanathan [3] had reported a 5-year OS rate of 81% and DFS of 71% among node positive patients. These survival figures are higher compared to the OS of 61% and DFS of 59% reported in the present study. This difference in survival is likely to be due to exclusion of serous and clear cell histology in Lee's study. In the present series, 26% of patients had serous and clear cell histology.

A similar study published by Klopp et al. [4] reported an OS rate of 73% in similar patient group. This study too had excluded serous and clear cell adenocarcinoma resulting in better survival compared to the present series.

Patel et al. [5] published their results on stage III endometrial cancer that had included patients with serous and clear cell histology. A subgroup analysis of node positive patients treated with adjuvant radiotherapy revealed a 5-year actuarial OS of 60%, which is comparable to results reported in the current study. Similarly, McMeekin et al. [6] had reported 5-year OS of 65% in a cohort of patients that included serous and clear cell types.

In the present report, age >60 years had negative impact on OS but not on DFS. Lee and Viswanathan [3] reported a strong negative association between survival and advancing age though, the cut off for advanced age was not defined. Patel et al. [5] too has reported significant negative association between age >70 years and OS among stage III endometrial cancer patients.

Histology and grade of tumor are closely related prognostic factors influencing survival in endometrial cancer. The impact of these two variables on survival is not uniform throughout literature. In a previous paper by Narayan et al. [7] it was shown that tumor histology such as clear cell and serous papillary are the most important factor for DFS and OS in intermediate and high risk endometrial cancer. However, the correlation between tumor grade and survival was not analyzed in this report. Klopp et al. [4] have shown a significant association between DSS and grade 3 endometroid histology. However, Lee and Viswanathan [3] and Mundt et al. [8] have reported that tumor grade was not significantly associated with survival in node positive patients. Steiner et al. [9] has reported tumor grade and histology as independent prognostic factors for OS and tumor grade for DFS. From the above evidences, we understand that grade 3 endometroid, serous and clear cell histologies have a negative impact on OS and DFS. Hence we categorized grade 1 and 2 endometroid as low risk group and compared with high risk histological types such as grade 3 endometroid, serous and clear cell. Our results revealed a significant negative impact of high risk histology on OS and DFS compared to the low risk group. Among the high risk histologies, serous had the worst survival, in keeping with other results in the published literature [10].

Lack of any significant difference in OS and DFS between patients with involved pelvic vs. para-aortic nodes compares favorably with results published in the literature [3,4,8]. The present study has revealed significantly worse outcome in patients with upper para-aortic nodes compared to pelvic nodes. This finding needs further evaluation in future studies.

The number of positive nodes did not have a negative impact on survival which is similar to results published by Lee and Viswanathan [3] and Secord et al. [11] has reported a significant negative correlation between OS, DFS and three or more positive nodes. A Gynecologic Oncologic Group (GOG) study published last year revealed a 7% increase in the risk of progression or death in patients with 2 or more positive nodes compared to a single positive node [12]. However, this association was not statistically significant.

In the present study, chemotherapy was administered only to 38% of patients and failed to show improvement in DFS. This may well be due to the limited number of patients receiving chemotherapy limiting the power of the study. The role of systemic therapy on survival on node positive endometrial

Table 2. Five-year survival results of node positive endometrial cancer treated surgically and with adjuvant radiotherapy

Author (year)	No. of patients	Overall survival (%)	Disease-free survival (%)
Onda et al. (1997) [13]	30/173	84	NA
Nelson et al. (1999) [14]	17	72	81
Mundt et al. (2001) [8]	30	NA	34
Patel et al. (2007) [5]	23/107	60	NA
Klopp et al. (2009) [4]	50/71	73	NA
Lee et al. (2012) [3]	62/66	81	71
Current study (2014)	126	61	59

NA, not available.

cancer patients published in the literature has been conflicting. Highest 5-year OS rates of more than 80% have been reported by Lee and Viswanathan [3] and Onda et al. [13] in single-arm retrospective studies where 73% and 77% of the cohort have received systemic therapy. Nelson et al. [14] has reported the highest DFS of 81% but only 12% of this retrospective cohort has received systemic therapy.

The GOG 122 study comparing whole abdominal radiotherapy to cisplatin and doxorubicin chemotherapy suggested a survival advantage from chemotherapy in stage III and IV patients [15]. However, the study is difficult to interpret because of the use of a nonstandard radiotherapy regimen. The Hogberg combined analysis of the Nordic Society of Gynecologic Oncology/The European Organisation for Research and Treatment of Cancer and The Mario Negri Gynecologic Oncology group studies of adjuvant chemotherapy in high-risk endometrial cancer suggested an improvement in progression free survival but not OS [16]. Of note, in the small subsets of patients with serous and clear cell histologies in both the GOG 122 and Hogberg analysis, no clear improvement in survival with adjuvant chemotherapy was identified, with the benefit predominantly seen in those with endometroid histologies [15,16]. In addition, the impact on quality of life of chemotherapy in this group of women who are often elderly and with comorbidities has not been reported. Unfortunately, the combination of drugs, the timing and the number of cycles used are different in each study making it difficult to have a uniform recommendation for practice. It is not clear if systemic therapy has a beneficial effect on OS of node positive patients with endometrial cancer. We need to await the results of ongoing randomized controlled trials such as the Post Operative Radiation Therapy in Endometrial Cancer (PORTEC) 3 and GOG 258.

In the present report, for both OS and DFS, LVSI seems to increase the risk. The fractional myometrial invasion did not influence OS or DFS. In a previous paper by Narayan et al. [7], it has been shown that LVSI and fractional myometrial invasion were shown to be significant predictors of DFS when nodal status was not considered. In the present study, among node positive patients, these two prognostic factors failed to show statistically significant impact on survival. Similar results had been reported by Lee and Viswanathan [3] where LVSI and deep myometrial invasion were not prognostic for outcome. Klopp et al. [4] too had reported lack of correlation between LVSI and DSS.

The failure rate of the present study was 43% at a median follow up of 52.6 months which is similar to 44% reported by Klopp et al. [4]. Lee and Viswanathan [3] has reported failure

rate of 26% at a median follow-up was 21 months. The lower failure rate may be due to exclusion of clear cell and serous types and short median follow-up. Secord et al. [11] has recently reported a failure rate of 29% among node positive patients in a multicentre evaluation at a median follow up of 42 months.

Among the 23 patients who relapsed in the pelvis, only three (2%) had isolated pelvic failure and two had salvageable disease. The rest of the 20 patients failed also at extrapelvic sites. In the present series, 82% of patients achieved pelvic control. Lee and Viswanathan [3] has reported a pelvic control rate of 95%. This difference in pelvic control rate could be due to exclusion of serous papillary and clear cell types and shorter follow-up time. Patel et al. [5] has reported pelvic control rates of 78% in node positive patients treated with adjuvant radiotherapy. Good pelvic control can be achieved with adjuvant radiotherapy. Ongoing randomized studies such as PORTEC 3 and GOG 258 will help to determine if adding concurrent chemotherapy to radiotherapy will impact the risk of pelvic relapse.

In the present study, among those failed, 94% failed at extrapelvic sites. Klopp et al. [4] and Secord et al. [11] have reported extrapelvic failure rates of 70% and 68% respectively among those failed. However, whether this was the first site of failure or subsequent failure was not recorded clearly. It is obvious that majority of node positive patients fail at extrapelvic sites. To improve survival in this high risk group, the focus should be on developing novel approaches for controlling extrapelvic failure.

In conclusion, in node positive endometrial cancer patients, tumor grade and histology are the most important prognostic factors influencing extrapelvic failure, hence survival. Among these patients, grade 1 and 2 endometroid histology behaves less aggressively compared to grade 3 endometrioid, clear cell and serous types. Though it is clear that some form of systemic treatment is mandatory in node positive patients to control extrapelvic failure, the less aggressive low risk node positive group may not benefit from systemic therapy. Future research should focus on selecting the right patients with nodal involvement for systemic therapy so that unwanted morbidity and mortality of systemic treatment in low risk node positive endometrial cancer could be avoided.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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