

A profile of endometrioid adenocarcinoma of uterus in a tertiary centre

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Abstract

Aims: To evaluate the clinicopathological features and relationship of tumor grade, myometrial invasion and lymph node metastasis.

Settings and Design: Retrospective analysis.

Materials and Methods: The medical records of patients with endometrioid adenocarcinoma of the endometrium treated between January 2013 and January 2016 were reviewed retrospectively.

Statistical Analysis Used: The continuous variables were reported using mean \pm SD and the categorical variables were reported using number and percentages. The pre and post operative grades were compared using Wilcoxon Sign Rank Test. All the analyses were done using SPSS version 18.0.

Results: A total number of 40 patients were included in the analysis. The mean age was 58.65 years (range- 39 to 71). While 29 (72.5%) were post menopausal, 28 (70%) patients presented with PMB. metastases was detected in 12.5% patients.

Conclusions: Complete surgical staging is the precise way of determining stage and requirement of adjuvant treatment as it defines prognosis and survival. Studies including large number of patients with complete surgical staging done is required to define the surgical management of patients with endometrial carcinoma.

Keywords: Tumor grade, Myometrial invasion, Lymphnode metastases.

Introduction

Endometrial carcinoma (EC) is the fourth most common malignancy in women and is the most common gynaecologic malignancy worldwide. Almost 75% of women present in early stages of the disease.¹⁻³ The incidence of EC is around 4.2 to 4.3 per 10,000 in India.⁴ Abnormal vaginal bleeding is seen in 90% of women with endometrial carcinoma and postmenopausal bleeding (PMB) is the commonest symptom at presentation. Endometrioid tumors account for 80% of EC. Prolonged estrogen action unopposed by progesterone is considered the mechanistic factor in the pathogenesis of endometrioid carcinoma and it evolves from the premalignant condition complex atypical endometrial hyperplasia. Thus, the risk factors include late menopause, obesity, nulliparity, diabetes mellitus, estrogen secreting ovarian tumors, polycystic ovarian disease, anovulation and tamoxifen administration.^{5,6} The initial histopathological evaluation of the endometrium is by endometrial biopsy (office biopsy or dilatation and curettage). Surgery is the primary modality of treatment. The standard of treatment in the management of endometrial carcinoma almost worldwide is total hysterectomy (TH) with bilateral salpingo-oophorectomy (BSO). Complete surgical staging including pelvic lymphadenectomy (PLND) and para-aortic lymphadenectomy (PALND) aids in guiding post operative adjuvant treatment, survival and prognosis. However, this approach is debatable since most of the cases are early stage and adjuvant therapy is not warranted. Current practice is to perform removal of enlarged pelvic lymph nodes for intraoperative detection of metastasis. Complete PLND is done in patients who have gross tumor of more than 2cm, grade 3 tumors, more than

50% myometrial invasion (MI) and cervical extension with resection of any enlarged para aortic lymph nodes.

Adjuvant treatment is tailored according to histology and stage. Women with early stage disease have a favourable prognosis overall, hence adjuvant treatment recommendations are challenging. Women with advanced disease - high grade tumors and MI of > 50% receive adjuvant radiotherapy (RT)+/- chemotherapy (CT). Hence assessment of various clinico-pathological variables are essential to determine the postoperative management of these patients. This study attempts to assess clinico-pathological variables like tumor grade, MI and lymph node (LN) metastases.

Materials and Methods

The medical and histopathological records of patients with endometrioid adenocarcinoma of the endometrium treated between January 2013 and January 2016 were reviewed retrospectively. The primary line of treatment was surgery – TAH + BSO with omental biopsy (OB), peritoneal cytology (PC), PLND and PALND. Surgical staging was done according to FIGO-2009. Depending upon the grade, MI, presence of lymphovascular space invasion (LVSI) and stage patients were stratified into two categories (low risk and high risk). The low risk patients were offered observation.

The high risk patients received RT (brachytherapy / External beam radiotherapy/ extended field radiotherapy) with or without platinum based chemotherapy. The pre-operative histopathological diagnosis, post operative tumor grade, MI and LN metastases were recorded.

The continuous variables were reported using mean \pm SD and the categorical variables were reported using number and percentages. The pre and post operative grades were compared using Wilcoxon Sign Rank Test. All the analyses were done using SPSS version 18.0.

Results

A total number of 40 patients were included in the analysis. The mean age was 58.65 years (range- 39 to 71). While 29 (72.5%) were post menopausal, 28 (70%) patients presented with PMB, the median duration of menopause was 10 years. Most of the patients were multiparous with a mean parity of 3. Hypertension (HTN) was present in 26 (65%) and diabetes mellitus in 22 (55%). A family history of malignancy was present in 7 patients. Atypical glandular cells were noted in 11 (27.5%) patients on cervical cytology. The clinic-pathological profile of the patients is summarised in Table 1

As indicated in Table 1, all 40 patients underwent preoperative EB and the HPR in 28/40 patients was endometrioid adenocarcinoma (10/28 grade 1, 11/28 grade 2 and 7/28 grade 3), 11/40 was complex hyperplasia (CH) with atypia with suspicion of invasion and 1/40 was atrophic endometrium.

The surgical management is described in table 2 and indicates that the surgical procedure undertaken in 28/40 (70%) was TAH+BSO+OB+PC+ PLND+PALND, 4/40 (10%) was TAH+BSO+OB+PC+ PLND and in 8/40 (20%) was restricted to TAH+BSO+OB+PC because of high risk medical co morbid conditions.

While, 5 (12.5%) of 10 (25%) that were preoperatively diagnosed as grade 1 tumors were upgraded to grade 2 tumors, 2 (5%) of 11 (27.5%) grade 2 were downgraded to grade 1 and 2 (5%) of 7 (17.5%) grade 3 were downgraded to grade 2 in the post operative specimen. The 'p' value when pre-operative and post-operative grades were compared was found to be 0.193. The agreement between pre-operative and post-operative grades were found to be weak using Kappa statistic ($k=0.5$, $p < 0.001$ which is significant). The final postoperative histopathological grade

in the 12 with a preoperative non malignant HPR was grade 1 in 10/12, grade 2 in 1/12 and grade 3 in 1/12. The 'p' value when pre-operative and post-operative histopathology were compared was found to be 0.004. The LVSI was present in 2/40 (5%) patients and PC was negative in all the patients.

Table 2 indicates the stage distribution according to FIGO 2009: 22 patients stage Ia, 4 stage Ib, 1 stage IIIa, 1 stage IIIc1, 4 stage IIIc2, 1 stage IVb and 7 were classified as stage unknown since complete surgical staging was not performed.

Table 3 indicates the extent of MI and the tumour grade. The disease was confined only to the polyp in 1/40 (2.5%) - grade 3, only to the endometrium in 2 /40 (5%) - grade 1, <50% MI in 28/40 (70%) - 11 grade 1, 14 grade 2 and 3 grade 3 and >50% MI in 9/40 (22.5%)- 4 grade 1, 3 grade 2 and 2 grade 3.

Intraoperatively no LN were palpable in 32 patients who underwent lymphadenectomy. LN metastases was detected in 5/32 (12.5%) patients of which pelvic LN metastases was observed in 1/5(2.5%), only para-aortic LN metastases in 2/5 and 2/5 were found to have both pelvic and para-aortic LN metastases. While 3 /5(7.5%) patients with LN metastases, had <50% MI, 2/5 (5%) had >50% MI, 2/5 (5%) had grade 1 tumor, 2/5 (5%) had grade 2 tumor and 1/5(2.5%) had grade 3 tumor which is described in table 4.

Continuous variables were reported using mean \pm SD (standard deviation) for the normally distributed variables otherwise median and inter-quartile range were used. Categorical variables were reported using number and percentages. The proportions of the positive and negative lymph nodes were compared using Z test. Pre and post operative grades were compared using McNemar Test. Agreement between pre-operative and post-operative grade was found using kappa statistic. Pre and post operative histopathology were compared using Wilcoxon Sign Rank test. All the analysis were done using SPSS version 18.0. All the analysis were considered statistically significant at 5% level (p value <0.05).

Table 1: Clinico-pathological profile

Variable	Frequency (%)	
Age in years	mean- 58.65 (39 to 71)	
Postmenopausal status	72.5	
Post menopausal bleeding	70	
Parity	Mean - 3	
Multiparous	82.5	
Feature	Pre-operative	Post-operative
Atrophic endometrium	1(2.5%)	0
CH	11 (27.5%)	0
Endometrioid	28 (71.8%)	40 (100%)
Grade 1	10/ 28 (35.7%)	5/ 28 (17.9%)
Grade 2	11/ 28 (39.3%)	14/ 28 (50%)
Grade 3	7/ 28 (25%)	5/ 28 (17.8%)
Non-malignant HPR	12	Grade 1 – 10 Grade 2- 1 Grade 3- 1

Table 2: Surgical profile

Surgery	Frequency
TAH + BSO	8 (20%)
TAH + BSO+ OB + PC+ PLND	4 (10%)
TAH + BSO+ OB + PC+ PLND+ PALND	28 (70%)
Stage	Frequency
Unknown	7(17.5%)
Ia	22(55%)
Ib	4(10%)
IIa	1(2.5%)
IIc1	1(2.5%)
IIc2	4(10%)
IVb	1(2.5%)

Table 3: Depth of MI versus post operative tumor grade

Depth of MI	Grade			Total
	Grade 1	Grade 2	Grade 3	
Confined to Polyp	-	-	1	1
Confined to endometrium	2	-	-	2
< 50%	11	14	3	28
>50%	4	3	2	9
Total	17	17	6	40

Table 4: LN metastases with grade and MI

Myometrium	Pelvic	Para-aortic	Pelvic + para-aortic	Total
< 50%	1	2	0	3
>50%	0	0	2	2
Grades				
1	1	0	1	2
2	0	2	0	2
3	0	0	1	1

Discussion

The commonest complaint is PMB and this contributes to the early diagnosis of EC. PMB was the commonest complaint of 70% of patients in this study. Stage Ia was seen in 55% of patients. The age ranged between 39 to 71 years with a mean of 58.65. Parity ranged between with a mean of 3. Thus, multiparity was not a rare event.

A poor correlation has been observed between pre-operative and post-operative tumor grades^{3,8,9} and this study also observe the same which is in agreement with Behiye Pinar et al and L Helpman et al. Around 40 to 45% of patients with complex hyperplasia in the pre-operative endometrial biopsy will have endometrial carcinoma which will be missed. The observations of this study indicated that the 12 patients who had a non malignant HPR in pre-operative endometrial biopsy actually had endometrioid adenocarcinoma in post-operative specimen.

Pre-operative evaluation by MRI / PET are expensive and are unable to pick up microscopic abdominal and LN metastases. Hence, to categorise a patient as low risk or high risk depending upon the preoperative grade and MRI report remains a dilemma.

Even after many decades of debate no convincing data demonstrating a therapeutic role of lymphadenectomy in EC is available. The criteria for the selection of patients for

lymphadenectomy, the extent of lymphadenectomy (pelvic and/or aortic), and whether a minimum number of nodes are required to define the lymphadenectomy as adequate remains a topic of continuing debate. Some authors have proposed that systematic lymphadenectomy including pelvic and para-aortic be performed only in high grade tumors and also suggest that complete surgical staging is not indicated in low risk endometrial carcinoma with grade 1/2 tumors and no deep MI.¹⁰⁻¹³ However other studies have suggested that lymphadenectomy should be performed in all patients except when major morbidity is anticipated.^{14,15} Others have concluded that lymphadenectomy not only provides accurate surgical staging but also has therapeutic benefit.^{16,17}

According to this study 3/ 5 (7.5%) patients who had lymph node metastases had <50% MI and 3/5 (7.5%) had grade 1 and 2 tumors suggesting that they would be considered as low risk did not require lymphadenectomy.

Isolated paraaortic lymphnode metastases with negative pelvic nodes is usually <5% however, in patients with deeply invasive endometrioid grade 2 and 3 cancer, it can be noted in higher than 10%.¹⁸ In our study, two patients had isolated paraaortic lymphnode metastases, both patients had grade 2 tumors with less than 50% myometrial invasion. If lymphadenectomy is done only for diagnostic purpose to identify those patients with extrauterine disease, pelvic

lymphadenectomy is sufficient, but if lymphadenectomy is therapeutic, as suggested by the SEPAL trial, the para-aortic lymphadenectomy needs to be done in patients with documented lymphatic dissemination in the pelvis.^{19,20} In these cases, we need also to be aware that para aortic disease is usually present in the anatomical area above the IMA.¹⁸

Though the total number of patients enrolled in this study were small, LN involvement were noted in 12.5% of our patients which is a significant number. Hence complete surgical staging is necessary to rule out micro metastases in LN in all the cases of EC.

Conclusion

Complete surgical staging is the most precise way of determining stage and requirement of adjuvant treatment and it defines the prognosis and survival in a better way. Studies including large number of patients with complete surgical staging done is required to define the surgical management of patients with EC.

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