

Prognostic factors in endometrial cancer

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Abstract

Introduction: Endometrial cancer (EC) is the most common malignancy of the female genital tract. It is now the fourth most common gynecological cancer among women and the sixth worldwide cancer in Western countries. It is the most curable of the 10 most common cancers in women and the most frequent and curable of the gynecologic cancers. The incidence is increasing when life expectancy rise. This study was carried out to evaluate the prognostic factors of Endometrial Cancer.

Methods: Clinico-pathological characteristics and follow-up cases of endometrial cancer were analysed retrospectively between January 2000 to December 2007 with its prognostic factors influence were statistically analysed.

Results: During the study period total 180 patients were taken. Univariate model revealed that the menopausal status, the FIGO stage, grade, histological type, myometrial invasion, ER, PR, peritoneal cytology, lymph node metastases, adjuvant therapy, and the method of operation were related with the prognosis significantly. The multivariate analysis Cox proportion hazards regression model showed that the ER ($P=0.004$), PR ($P=0.000$), myometrial invasion ($P=0.006$) and lymph node metastases ($P=0.049$) were related with the prognosis significantly.

Conclusion: The clinico- pathological character of endometrial cancer is responsible for patient's better survival. If the patients had early detection and treated in proper modalities, this might improve the good prognosis.

Keywords: endometrial cancer, prognosis, prognostic factors

Introduction

Endometrial Cancer (EC) is one of the three malignant tumours of the female reproductive system. The incidence increases steadily with the age and peaks between the age 70-74 years. Fortunately, the prognosis for survival is high: the 5 year survival in Sweden is over 80%.^{1, 2} Ninety Percentage of all cancers of the uterus arise from the glands of the endometrium so called as endometrial adenocarcinoma.³⁻⁶ Type I EC is hormone dependent, about 80% is characterized by well to moderately differentiated tumors that present at diagnosis and therefore the overall prognosis is optimistic. Excessive estrogen is associated with most of the risk factors that is linked to endometrial carcinoma. Patients with atypical endometrial hyperplasia have a 23 % of risk of endometrial carcinoma over ten years. The Type II is non hormone dependent, about 23% characterized by more aggressive tumours usually

not associated with unopposed estrogens or hyperplasia and shows a high mortality rate with poorer prognosis. During the past two decades, there are improvements in treatment and its follow-up of endometrial carcinoma patients, the importance of various prognostic factors has been extensively studied and published the prognostic parameters of endometrial cancer. These factors are important in tailoring proper adjuvant therapy consisting of modalities such as radiation, chemotherapy and hormonal therapy. Over the past few decades, several studies have demonstrated the prognostic importance of different parameters including lymph node status, histological type of carcinoma, histological grade and stage of disease, depth of myometrial invasion, lympho-vascular space involvement and cervical involvement.

This study aims to review the Clinical pathological materials as prognostic factors of endometrial cancer.

This will enable the high risk patients to obtain suitable moderate treatment and avoid recurrence and metastasis and improve disease free survival rate and quality of life of women.

Methods

This was a retrospective study of patients admitted from Jan 2000 to Dec 2007 in the gynecological department of Guangxi Medical University with the diagnosis of Endometrial Carcinoma who underwent primary surgical procedure. Hospital charts records of these cases were reviewed and updated by use of modified 2000 FIGO criteria for Endometrial Carcinoma. These patients were followed up till Dec 2008.

The follow up was done by telephone inquiry and letter correspondence. If there was no follow up for up to four times, and no reply by telephone calls, then the information of the local police station or local administration for death records were checked. If there was no information, the patients were taken as lost to follow up. SPSS 13.0 software was used for analysis of prognostic factors of endometrial cancer. Univariate analysis was estimated by Log-rank test, and the multivariate analysis was assessed by Cox proportion hazards regression model. P value <0.05 was taken as significant.

Result

There were 190 patients admitted in the gynecological department of Guangxi Medical University with the diagnosis of Endometrial Carcinoma. During the study period 180 patients underwent primary surgical procedure. Ten patients were excluded as four refused for primary surgical procedure and six patients did not undergo the surgical procedure, as four were of late stage, one of which had heart disease and the other had surgically not fit due to old age.

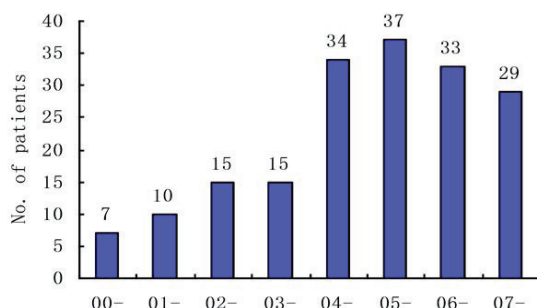


Figure 1 Distribution of total no of endometrial cancer patient admitted in each year

Figure 1 shows distribution of Endometrial Carcinoma in

each year. There were more patients from 2004 onwards. The median age of the patients was 53 yrs (30-71 years), and average age of menopause was 50.6 yrs (41-59 yrs).

Table 1: Univariate prognostic factors analysis of endometrial cancer patients according to demographic profile.

Factors	No. of cases (X2)	Chi-Square	(P value)
Age		2.483	0.117
<50 yrs	60		
>50 yrs	120		
Parity		0.998	0.318v
Nulliparous	14		
Parous	166		
Menopause		4.025	0.045
Pre-menopause	85		
Post-menopause	95		
BMI		1.691	0.429
<25kg/m2	124		
>=25 <30kg/m2	38		
>=30kg/m2	10		

Table 1 shows Univariate prognostic factors analysis of endometrial cancer patients according to demographic profile where menopausal status was significant (P< 0.05) for the prognosis of the endometrial cancer, whereas parity, age and BMI were not significant.

Table 2: Univariate prognostic factors analysis of endometrial cancer patients according to Associate medical disorder.

Factors	No. of cases	Chi-Square	Sig. (P value)
		(X2)	
Associate diseases		2.431	0.488
No diseases	143		
Diabetes Mellitus(DM)	11		
Hypertension (HTN)	20		
DM+HTN	6		

Table 2 shows Univariate prognostic factors analysis of endometrial cancer patients according to associate medical disorder which was not significant $P > 0.05$ for the prognosis of the endometrial cancer.

Table 3: Univariate prognostic factors analysis of endometrial cancer patients according to Surgical stage.

Factors	No. of cases	Chi-Square (X2)	Sig. (P value)
Surgical Stage		14.516	0.000
Stage I	112		
Stage II	18		
Stage III	49		
Stage IV	1		

Table 3 shows Univariate prognostic factors analysis of endometrial cancer patients according to surgical stage which was significant ($P < 0.05$) for the prognosis of the endometrial cancer.

Table 4: Univariate prognostic factors analysis of endometrial cancer patients according to Treatment.

Factors	No. of cases	Chi-Square (X2)	Sig. (P value)
Surgical Procedure		7.906	0.045
TAH+/-BSO	74		
TAH+/-BSO & Pelvic Lymphadenectomy	33		
RH+/-BSO & pelvic Lymphadenectomy	50		
Semi RH+/- BSO & Pelvic Lymphadenectomy	23		
Adjuvant Therapy		1.028	0.905
No therapy	74		
Radiotherapy(RT)	14		
Chemotherapy(CT)	62		
Both(RT+CT)	18		
Hormonal Therapy	12		

Table 4 shows Univariate prognostic factors analysis of endometrial cancer patients according to treatment procedure where surgical procedure was significant ($P < 0.05$) for the prognosis of the endometrial cancer.

Table 5: Univariate prognostic factors analysis of endometrial cancer patients according to Pathological findings,

Factors	No. of cases	Chi-Square (X ²)	Sig. (P value)
Histopathological Grade		6.269	0.044
G1	84		
G2	72		
G3	24		
Myometrial Invasion		11.874	0.000
<1/2	139		
>1/2	41		
Steroid Hormone Receptor			
ER		4.901	0.002
Positive	119		
Negative	61		
PR		20.046	0.000
Positive	129		
Negative	51		
Histological Type		9.662	0.022
Endometrial adenocarcinoma(EA)	135		
EA with squamous adenocarcinoma	19		
Papillary serous carcinam	25		
Squamous carcinaoma	1		
Peritoneal cytology		5.554	0.000
Positive	29		
Negative/Not sample	151		
Lymphnode metastases		6.852	0.033
Metastases	7		
No metastases	102		
Not sampled	71		

Table 5 shows Univariate prognostic factors analysis of endometrial cancer patients according to treatment procedure where histopathological grade, myometrial invasion, ER, PR ,histological type, peritoneal cytology and lymphnode metastases were significant ($P < 0.05$) for the prognosis of the endometrial cancer.

Table 6: Cox proportional hazard regression model for multivariate prognostic factors of endometrial cancer

	B	SE	Wald	df	Sig.	OR	OR 95.0% CI	
							Lower	Upper
ER	1.130	.387	8.518	1	.004	3.096	1.449	6.611
PR	-1.610	.312	26.649	1	.000	.200	.108	.368
Myometrial Invasion	.852	.308	7.671	1	.006	2.345	1.283	4.285
Surgical Stage(FIGO)	.061	.237	0.66	1	.797	1.063	1.691	1.691
Lymphnode metastasis	-.582	.309	3.547	1	.049	1.853	.953	3.605
Menopause	.268	.341	.619	1	.432	1.307	.671	2.549
Surgical Procedure	.026	.191	.019	1	.891	1.027	.706	1.493
Surgical grade	.151	.173	.757	1	.384	1.163	.828	1.633
Peritoneal cytology	.141	.424	.110	1	.740	1.151	.502	2.641
Pathological stage	.220	.221	.992	1	.319	1.246	.808	1.920
Adjuvant therapy	.115	.111	1.078	1	.299	1.122	.903	1.393

Table 6 shows multivariate prognostic factors of survival analysis in endometrial cancer. For Independent prognostic factors of endometrial cancer, which are comparatively significant with survival curve, we further analysis it by using Cox proportional hazard regression model which demonstrated ER, PR, myometrial invasion and lymphnode metastases has the remarkably significant for the prognosis of endometrial cancer.

Discussion

The prognosis of patients with endometrial carcinoma is well known to be related to histological grade and stage of tumor. According to the GOG⁷⁻¹⁰ the prognostic parameters for Endometrial Carcinoma of the uterine factors include histological type, histological grade and depth of myometrial invasion, vascular invasion, presence of atypical endometrial hyperplasia, cervical involvement, DNA ploidy and S-shape fraction and hormone receptor status. The extra-uterine factors include positive peritoneal cytology, adnexal involvement, pelvic and para-aortic lymph node metastasis and peritoneal metastasis. Patients with extra-uterine disease along with cervical involvement and vascular invasion comprise a high risk group in which approximately 65% will experience recurrence¹⁰ and those patients with tumour con-fined to the uterus without evidence of vascular invasion have a decreased risk of recurrence.⁸⁻¹⁰

In this study, age less than 50 yrs and more than 50 yrs

had no significant difference, though older age had a poor prognostic variable in endometrial cancer. Many authors have reported an inverse relationship between advancing age and outcome.¹¹ More recently, Farley et al,¹² demonstrated that endometrial cancer survival decreases significantly in older patients, with the 5 year survival falling below 80% after age 50. If a patient nulliparous and obese reaches menopause at age 52 or later, she appears to have a five-fold increase in the risk of developing endometrial cancer. Reduced 5-year survival of 57% among nulliparous women in comparison with 81% for patients with one or more deliveries has been reported¹³ but there are no other studies to support this data. Though nulliparity is a risk factor for endometrial cancer, parity did not show effect in our study.

The degree of obesity generally has a proportional effect on a women's risk of endometrial cancer but BMI was not prognostic factor in this study. Epidemiological studies indicate that increased waist circumference and/or BMI are positively correlated with the development endometrial cancer (postmenopausal).^{14,15} Furthermore, a large prospective study by Calle and colleagues¹⁶ demonstrated that increasing BMI is associated with increased mortality from many types of cancer. The authors suggest that increased BMI (> 25 kg/m²) contributes to 90,000 cancer-related deaths per year in the US.

Endometrial Carcinoma is often associated with medical disorders such as hypertension, diabetes mellitus, obesity, PCOS, and infertility.^{17,18} Steiner et al,¹⁹ found 21.8% of

patients with diabetes mellitus in endometrial carcinoma had a significantly deeper infiltration of the myometrium and were more likely to have lymph node metastasis. In this study, the effect of obesity, hypertension diabetes mellitus on endometrial carcinoma prognosis was not remarkable.

Both univariate and multivariate analysis showed a strong significant correlation between surgicopathological stages as prognostic factors for endometrial cancer. The FIGO staging system which is a surgical-pathological staging system.²⁰ Carol²¹ reported 5 year disease free survival for stages I, II, III, IV, are 93.9%, 72.9%, 48.1% and 25.4%. that conventional pathologic features do not lose their prognostic significance in pathologic stage I-II endometrial adenocarcinoma patients following Post-operative adjuvant radiation therapy, and 5 year disease free survival as 91.5% for stage IA / IB, 85.5% for stage IC, and 75.8% for stage IIA / IIB.

In this study, univariate analysis showed histological grade had significant prognostic effect but in multivariate analysis, difference was not significant. Large number of patients had low histological grade and few numbers with high grade. Histologically, high grade with lymph node metastasis and myometrial invasion has influence on the survival rate of endo-metrial cancer. Five-year survival rates of 94% in patients with grade 1 tumors, 84% in those with grade 2 tumors and 72% in those with grade 3 tumors has been reported.²²

Both univariate and multivariate analysis showed there was a significant correlation between myometrial invasion as prognostic factors. In endometrial carcinomas the depth of myometrial invasion has been shown to be an independent predictor of outcome.^{7,10,23} Depth of myometrial invasion of tumor is correlated with a risk of lymph node metastases and an independent risk factor for risk of death and recurrence.^{9,24} Patients with tumours that are less than 5mm from the serosal surface are at much higher risk for recurrence and death than those with tumours greater than 5 mm from the serosal surface.^{5,6} In GOG Study 33, recurrence developed in only 1% of patients with no myometrial invasion. 7.7% had invasion of the inner one-third of the myometrium, 14.5% had invasion of the middle-third of the myometrium, and 15% had invasion of the outer-third of the myometrium.¹⁰

Univariate and multivariate analysis showed there was a significant correlation between steroid hormone receptor ER and PR as prognostic factors for endometrial cancer. Steroid hormones, especially estrogen, play an important role in the pathogenesis of endometrial cancer. The presence and quantity of steroid receptors have been correlated with stage, histological grade and survival in several studies

and several authors have reported that receptor status constitutes an independent prognostic factor.^{25,26} The United States National Cancer Institute recommended that steroid receptors should be included whenever possible in the evaluation of stage I and II patients.²⁵

Only univariate analysis showed significance in histological types. This may be because there were large number of patients with low grade adenocarcinoma and minimally invasive with few numbers having serous cell and squamous cell carcinoma. The type I usually have a favorable outcome; stage I disease carries a 5 year survival rate of 86%.²⁷ The Type II is aggressive tumor usually not associated with unopposed estrogen or hyperplasia, early invading myometrium and lympho-vascular spaces with associated advanced-stage disease and higher tumor grade non-endometrioid histology; and shows a high mortality rate with poorer prognosis.²⁸ The GOG study group reported its statistically result in large cohort of endometrial cancer patients, the clear cell carcinoma and papillary serous carcinoma has the worst prognosis, the 5 year disease free survival is 25% and 18%.²⁴

There was a significant correlation between peritoneal cytology as prognostic factor in univariate analysis. In the past 20 years, over 50 reports on the significance of positive peritoneal cytology in endometrial carcinoma have been published and many conflicting results have appeared in the literature several reports in the literature have noted increased recurrence rates and decreased survival rates and, on this basis, have recommended treatment for positive cytology.^{10, 29-36} Positive peritoneal cytology was found to be associated with deep myometrial invasion, cervical involvement, adnexal spread, and lymph node metastasis as well as propensity for intra abdominal disease recurrence. Kadar et al,³⁴ demonstrated that positive cytology did not influence survival if the disease was confined to the uterus using Cox's proportional hazards model.

Univariate and multivariate analysis showed there was a significant correlation between lymph node metastases as prognostic factors in this study. Lymph node spread represents the most common site of extrauterine disease in endometrial cancer. Reports show that 5 year survival for patients with stage I and II disease ranges from 80% to 91%, and those patients with nodal metastases have a survival of only 44–52%.^{36, 37}

In univariate analysis there was a significant role between surgical procedure in prognosis but in multivariate Cox regression analysis it could be entered as it is decided by the stage, type and depth of myometrial invasion and lymph node metastases. The choice of treatment method depends upon patient's willful demand and condition

and current economic condition etc. Many studies have demonstrated that the survival rate does not vary between simple total hysterectomy and radical hysterectomy and thus the type of hysterectomy is not a dependent prognostic factor.^{9,38} It has been reported that radical hysterectomy should be considered when gross cervical involvement is encountered.^{20,39} The subsequent change in the FIGO staging system in 1988⁴⁰ recognizes that pelvic lymph node metastasis may be present in approximately 8%–10% of apparent stage I tumors and reflects the influence of depth of myometrial invasion on this risk. Omentectomy does not form part of the FIGO staging for endometrial cancer, yet omental biopsy or full omentectomy is frequently performed in cases of uterine serous carcinoma.

This study did not show a strong association between adjuvant therapy and improved survival. The evidence continues to support a role for adjuvant radiotherapy in the treatment of early endometrial cancer for women at high risk of loco-regional recurrence but not for intermediate risk and distant recurrences are not prevented by this strategy and there may be a future role for adjuvant chemotherapy. Currently there is insufficient evidence of a survival benefit to support the routine use of adjuvant therapy. Data from adequate randomized trials are needed to determine the benefit of chemo-radiation and chemotherapy either prior to or following radiation. In endometrial cancer, there is currently no proof that adjuvant hormone therapy or chemotherapy results in better outcome. Adjuvant radiotherapy, while effective at reducing rates of loco-regional recurrence, does not alter survival.⁴¹ Radiotherapy has been widely used as adjuvant treatment following surgery in women at increased risk of disease recurrence. The results from Post-Operative Radiotherapy in Endometrial Cancer (PORTEC 1), one of a number one completed randomized trials addressing the survival, showed that post-operative radiotherapy in stage I endometrial cancer reduced locoregional recurrence from 14% to 10% but had no impact on overall survival.⁴²

Conclusion

In this study univariate model revealed menopausal status, the FIGO stage, grade, histological type, myometrial invasion, ER, PR, peritoneal cytology, lymph node metastases, adjuvant therapy, and the method of operation were related with the prognosis significantly. The multivariate analysis Cox proportion hazards regression model showed that the ER ($P=0.004$), PR ($P=0.000$), myometrial invasion ($P=0.006$) and lymph node metastases ($P=0.049$) were related with the prognosis significantly. The clinicopathological character of endometrial cancer is responsible for patient's better survival. If the patients had early

detection, and treated in proper modalities, this might improve the prognosis.

Conflict of interest: The authors declare that they have no conflict of interests.

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