

Prognostic Factors in Endometrial Carcinoma

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Abstract

Endometrial carcinoma is the third most common carcinoma of the female genital tract in Singapore. Although most endometrial carcinomas are detected while still at low stage, there is still a significant mortality from the disease. It is desirable that patients at high risk of relapse are identified early for consideration for additional treatment. Some information required for management can be obtained from clinical history, gross examination of the uterus and routine microscopy. These are age, stage of disease, histologic type of carcinoma (serous carcinoma and clear cell carcinomas are poor prognostic types), grade and lympho-vascular space involvement. Of less certain significance are tumour size, location and status of peritoneal cytology. Other factors currently being investigated are oestrogen and progesterone receptor status, p53 status, flow cytometric analysis for ploidy and S-phase fraction, and oncogenes such as HER-2/neu (c erbB-2). Although some of these show independent prognostic significance on multivariate analysis, it is still uncertain if the information adds significantly to the information available from routine evaluation.

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Introduction

In the United States of America, endometrial carcinoma is the most common cancer of the female genital tract and has an annual incidence of 72 per 100,000 women. In Singapore it is the third most common female genital tract cancer after cancer of the cervix and ovary. According to Trends in Cancer Incidence in Singapore 1968 to 1992 published by the Singapore Cancer Registry, the average annual incidence of uterine cancer from 1968 to 1992 was 6.7 per 100,000 women.¹ However, there is a slowly rising trend in the annual incidence, from about 4.1 per 100,000 women in 1975 to about 6.7 in 1990. Among the different races, it is the 6th most common cancer in Indians, 8th most common in Malays and 9th most common in Chinese.¹ Fortunately many endometrial carcinomas are detected while still in a low stage (75% are stage I and II at the time of diagnosis) and this is likely to be due to the fact that it becomes symptomatic early in its course, presenting with abnormal vaginal bleeding, thus prompting its sufferer to seek medical attention while the disease is still confined to the uterus. Despite this, the mortality is still significant. There is a continual search for factors which will help to identify the patient at high risk for disease relapse and for whom additional therapy may be helpful.

Non-Tumour Factors

Age

Some studies have found that age at diagnosis is an important non-tumour factor in prognosis.²⁻⁴ For example, Beckner et al² found that women older than 50 years and post-menopausal women of any age had lower survival, less favourable histological features and higher stage. A study from the Surveillance, Epidemiology and End Results Program in the United States of America found that the 5-year actuarial survival for white women with stage I disease was 94% for women under the age of 55 and 80% for women 55 years and older.³ The difference in survival may in part be related to the fact that tumours arising in younger women are of a lower grade, of a favourable histologic type and show no or only superficial myometrial invasion. This has led some authors to suggest that there may be 2 clinico-pathologic forms of endometrial carcinoma: one an oestrogen-related neoplasm that tends to be low-grade, associated with endometrial hyperplasia and seen in younger pre-menopausal women, and the other a more aggressive non-oestrogen related tumour arising in older post-menopausal women with atrophic endometrium.⁵ Some support for this postulate comes from Nyholm et al⁶ who found that women on oestrogen therapy were younger and had more superficially invasive, lower grade and

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lower stage tumours than non-oestrogen users, suggesting that cancers of oestrogen users may be less aggressive than cancer of non-users. Another reason for poorer survival in older women is that a higher proportion of them have tumours of unfavourable histologic type i.e. serous, clear cell and undifferentiated carcinoma.

Significance of Histological Factors

Stage of Disease

The stage of the tumour is the single most important prognostic factor in endometrial carcinoma. In patients presenting with stage I disease, substage of the disease by the degree of myometrial invasion is important. In one study, substage was found to be an independent prognostic indicator, more significant than tumour histologic type or grade.⁷ With increasing depth of myometrial invasion, the risk of lymph node metastases goes up. One of the problems of assessing myometrial invasion is that the normal endo-myometrial junction is irregular and the degree of irregularity varies from patient to patient. Hence the evaluation of depth of tumour invasion is difficult. A few authors have evaluated the significance of distance of tumour from the serosal surface of the uterus and found that it was not only easier to measure and more reproducible, but also gave good prognostic information.^{8,9} This however has not been adopted into the FIGO staging system.

Among patients with stage II disease, the survival is about 75%.¹⁰ Part of the decreased survival is attributed to the greater incidence of para-aortic lymph node involvement (12%) in this group of patients.

Tumour Location

The significance of tumour location in the uterus is still uncertain. Creasman et al¹¹ found in their study that patients with tumours extending to the lower uterine segment had a 2 to 3 times risk of lymph node metastases compared with those whose tumours were in the fundus only. Tumours that arise in the lower uterine segment are rare but reported cases have been found to have a worse prognosis than those that arise higher in the corpus. However, many of these have also been found to be of higher grade, of poorer prognostic type or deeply invasive and so the effect of isthmic origin alone is uncertain.

Tumour Size

Schink et al¹² found that increasing tumour size was associated with an increased risk of lymph node metastases and decreased survival. The risk of lymph node metastases was 4% for tumours with a maximum dimension less than 2 cm, 15% for tumours more than 2 cm, and 35% for tumours involving the whole cavity. The corresponding 5-year survival rates were 98%, 84%, and 64%.

Histologic Type

Certain histologic types of endometrial carcinomas, notably serous and clear cell carcinomas are associated with a worse prognosis than typical endometrioid carcinomas. Accurate histologic typing of endometrial carcinomas hence becomes important for subsequent management, especially for diagnoses made on uterine curettings.

Serous Carcinoma (Uterine Papillary Serous Carcinoma): Serous carcinoma accounts for 1% to 10% of all endometrial carcinomas. Most patients are post menopausal. This tumour does not appear to be related to a hyperoestrogenic state, oestrogen therapy, endometrial hyperplasia or obesity. In many cases the uterus is not even enlarged. However a greater proportion present with extrauterine disease (stages 3 and 4) compared with endometrioid carcinoma. Histologically, the formation of papillae is a prominent feature in serous carcinoma although cases with predominant glandular and solid patterns are also sometimes seen. In view of the latter, some authors favour dropping the adjective "papillary" from the tumour to de-emphasize the importance of papillae in making the diagnosis. On the other hand, cytologic features are important in diagnosis. The nuclei are usually large, pleomorphic and vesicular with prominent, sometimes "cherry-red" nucleoli. Loss of polarity is present and often bizarre hyperchromatic nuclei, some with "smudged" chromatin, are seen. Some cases arise in or are confined to an endometrial polyp where it may be a focal lesion. In papillary areas of the tumour, the papillae may be short and broad or long and thin with fibrovascular cores lined by cuboidal, low columnar or "hobnail" cells. In glandular areas, the glands tend to be jagged and gaping in contrast to the more tubular appearance of endometrioid carcinoma. Nuclear grade of the cells is also worse than expected for the architectural grade. Psammoma bodies are identified in about one third of cases. The tumour is often deeply myoinvasive and vascular invasion and cervical involvement are common. This contrasts with the villoglandular variant of endometrioid carcinoma which is a tumour also associated with papillary formation. In this lesion, the lining cells are usually pseudostratified columnar with nuclei showing grade I or II nuclear atypia. The prognosis of villoglandular endometrioid carcinomas is good, the behaviour being very similar to the usual endometrioid carcinoma of the same grade.

The 5-year survival rate of serous carcinoma varies from 27% to 36% and lo-year survival from 14% to 18%. In the series reported by Hendrickson et al,¹³ 50% of recurrences in stage I endometrial carcinomas were serous carcinomas and 50% of patients with surgical stage I serous carcinoma had a relapse. The aggressive behaviour of the tumour is also evidenced by the fact that extrauterine disease, recurrence and metastases

may occur even if the tumour is confined to a polyp or limited to the endometrium.^{14,15} Some authors have raised the possibility that extrauterine disease in such cases may be a manifestation of multifocal tumorigenesis (multiple primary tumours) rather than metastatic disease from a uterine primary, but the answer to this question is as yet unknown.

The presence of a serous component in a mixed endometrial carcinoma worsens the prognosis although what minimum proportion of serous carcinoma is necessary for this is as yet undetermined. In one study, mixed serous-endometrioid carcinomas in which 25% of the tumour was composed of serous carcinoma showed similar prognosis as pure serous carcinoma.¹⁶ Others have noted cases with only a small component of serous carcinoma, but in which the serous component showed extensive invasion of myometrial lymphatics.¹⁷ The presence of any quantity of serous carcinoma in a uterine curetting must be reported for planning of the subsequent surgical management.

Clear Cell Carcinoma: Clear cell carcinoma has been reported to represent about 5% of endometrial carcinomas although it appears to be uncommon in our population. Similar to serous carcinoma, most patients are postmenopausal and the tumour is not associated with oestrogen therapy or endometrial hyperplasia.

The tumour resembles clear cell carcinoma in the ovary. Papillary, tubulocystic and solid patterns are seen and most tumours show an admixture of the three. The cells may have clear or eosinophilic cytoplasm and nuclei are usually large, pleomorphic and vesicular with prominent nucleoli. Psammoma bodies may be seen, though less frequently than in serous carcinoma. The tumour may be mixed with serous or endometrioid carcinoma. FIGO recommends grading by nuclear grade only. Deep myometrial invasion has been reported in 30% of cases and lympho-vascular space invasion in 40%. There is conflicting data as to the prognostic importance of these features but in one large study, depth of invasion and a papillary or tubulocystic pattern were of prognostic significance.¹⁸ Unlike serous carcinoma, recurrence or metastases are uncommon in patients whose tumours are confined to a polyp or to the endometrium, and the tumour does not seem to show a propensity to spread to the peritoneum. Survival is worse than in endometrioid carcinoma, but one study showed that stage I and II tumours show similar survival to grade III endometrioid carcinoma.¹⁹

Grade

Most studies show that grade correlates with depth of myometrial invasion and incidence of lymph node metastases. In one study, a higher percentage of pelvic and para-aortic lymph node metastases was observed with increasing stage and grade but the largest percent-

age increase occurred between grade II and grade III tumours.¹¹ Several studies showed that in stage I disease, grade III vs grade I and II was the most significant independent variable for survival and recurrence.^{20,21} One study of surgical stage I patients reported a 5-year survival of 92% for grade I tumours and 78% for grade III tumours.⁴ Another showed that grade III tumours were 5 times as likely to develop recurrence as grade I or II tumours.²² In contrast, one study showed that when age and depth of myometrial invasion were taken into account in multivariate analysis, grade lost much of its importance as a prognostic factor.⁷

Lympho-vascular Space Invasion

Lympho-vascular space invasion (LVSI) is not very common in endometrial carcinomas, being reported in 15% to 25% of all cases of endometrial carcinomas. There is some relation to depth of myometrial invasion, with a reported frequency in stage IA being 2%, stage IB 14% and stage IC 50%. High tumour grade and adverse histologic types are also more likely to show LVSI. One study showed that the 5-year survival decreased from 88% to 66% with LVSI⁴ while another showed that this was the only prognostic indicator present in all patients who died from endometrial carcinoma.²³ Another study found that patients with LVSI had pelvic lymph node involvement 4 times and para-aortic lymph node involvement 6 times more often than patients without LVSI.¹¹ In terms of prognosis, it does not appear to be important to differentiate between lymphatic and venous involvement. Immunohistochemical studies are not necessary to identify LVSI; in one study, immunohistochemistry did not identify additional foci of LVSI compared with routine H&E sections.²⁴

Peritoneal Cytology

Five per cent to 15% of clinical stage I patients with endometrial carcinoma have a positive peritoneal cytology. In older studies using clinical staging, positive cytology was found to be a significant prognostic factor. The newer surgico-pathologic staging of FIGO (1988) now includes positive peritoneal cytology as a feature for assignment to stage III (III A). One study found that in 32 patients with positive peritoneal washings as the only positive risk factor, recurrence occurred in 18.8% of patients. Others have found that prognosis is worse in surgical stage I patients with positive cytology.²⁵ On the other hand, other studies found that positive cytology is not a prognostically significant factor in surgical stage I patients²⁶ and is only significant in patients with extrauterine disease,²⁷ and therefore should not be used to determine treatment.²⁸

Simultaneous Endometrial and Ovarian Carcinomas

It has been reported that up to 8% of endometrial carcinomas are accompanied by simultaneous ovarian

carcinomas which may or may not be of the same histologic type. These scenarios may represent:

- 1) metastases from an endometrial primary to the ovary(ies),
- 2) metastases from an ovarian primary to the endometrium, or
- 3) independent primary tumours.

In most cases, the 2 tumours are of the same histologic type. Ulbright et al²⁹ have classified the ovarian tumour as metastatic if there is multinodular ovarian involvement or at least 2 of the following features are present:

- 1) small ovaries less than 5 cm,
- 2) bilateral ovarian involvement,
- 3) deep myometrial invasion,
- 4) vascular invasion and
- 5) fallopian tube lumen involvement.

Using these criteria, they showed a significant difference in frequency of distant metastases in the group classified as metastatic compared with that classified as independent primary tumours. Other features that have been used in support of ovarian lesions being metastatic include the presence of multiple surface implants on the ovary, extensive lymphatic or vascular invasion in the ovarian stroma, and involvement also of other pelvic tissues. Tumours are thought to be independent primaries if both tumours are of low grade, low stage, of different histologic type, and the endometrial tumour is small. Poorly differentiated endometrioid, serous and clear cell carcinomas, and malignant mixed Mullerian tumours are generally metastatic to the ovary.^{29,30} There is no one diagnostic feature to separate the 2 groups but all clinical and pathologic information available should be evaluated and the patient treated accordingly.

Significance of Biochemical and Immunohistochemical Studies

Oestrogen and Progesterone Receptor Status

Oestrogen receptors (ERs) and progesterone receptors (PRs) are present in the majority of endometrial carcinomas and 'are found in both epithelial and stromal cells. The proportion of positive cells depends on the histologic type, being 70% for endometrioid carcinoma and its variants, and negative for most serous and clear cell carcinomas. Since most endometrioid carcinomas are usually receptor positive, simple reporting of positive or negative is of little prognostic value. Different methodologies varying from biochemical to the use of polyclonal and monoclonal antibodies have been used to determine receptor positivity. Methods using cytosol receptor assays may give rise to a falsely higher proportion of positivity because receptors are also found in normal stromal cells and myometrium which may be present in the material submitted for analysis. Data as to which receptor is most predictive of prognosis are also conflict-

ing; some studies find this to be ER³¹ while others find it to be PR.^{32,33} Some studies find no difference between positive and negative patients in surgical stage I and II, but significant in patients with extrauterine disease.³² Tumour response to progestin treatment was reported to be 60% in PR positive patients and 19% in PR negative patients.³⁴

p53 Status

Tumour suppressor gene p53, located on the short arm of chromosome 17, is one of the most extensively investigated genes in human cancers. The p53 protein regulates transition of cells from G1 to the S phase in cell division and has a role in apoptosis in the presence of excessive DNA damage. If DNA repair is unsuccessful, p53 protein has a role in inducing apoptosis. Mutation in the p53 gene is one of the commonest genetic defects in human tumours. p53 positivity on immunohistochemistry is seen in 20% to 30% of endometrioid carcinomas and 70% to 85% of serous carcinomas.^{35,36} p53 positivity is equally likely in early and late stage serous carcinomas but in endometrioid carcinomas are more prevalent in higher grade or higher stage tumours. Some studies have found p53 positivity to be a significant negative prognostic factor by univariate or multivariate analysis^{37,38} but uniform evidence for it to be an independent predictor of survival is lacking.³⁹

Ploidy Status

Flow cytometry can be used to determine the ploidy and S-phase fraction of tumours. In most studies, aneuploidy, high S-phase fraction or both are poor prognostic factors.⁴⁰⁻⁴³ Overall 67% to 78% of all endometrial carcinomas are diploid. One study found that ploidy was a strong prognostic factor that covaried with nuclear grade and that addition of ploidy to a multivariate analysis resulted in nuclear grade losing much of its impact.⁴⁰ The same study found that age, stage and aneuploidy were the most important predictors of outcome in multivariate analysis. Another study on both DNA ploidy and steroid receptors found that in multivariate analysis, ploidy was the most important prognostic factor and surgical stage the next.⁴⁴ Britton et al⁴¹ found that in low grade tumours, 5-year survival was significantly different between diploid (94%) and aneuploid (64%) tumours. Xue et al⁴⁵ on the other hand reported that DNA ploidy and high S-phase fraction were associated with high grade, high stage and deep myometrial invasion and were not independent prognostic factors.

HER-2/neu (c-erb B2)

This gene encodes a protein (p185) which is a transmembrane tyrosine kinase receptor. Overexpression can induce a malignant phenotype *in vitro* and the protein expression can be measured by immunohistochemistry. Reports of HER-2/neu detection rate range from almost

0% to 50% positivity, overall it is about 10% to 20 %. Positive tumours appear to have a worse prognosis.⁴⁶⁻⁴⁸ However comparison between studies has been difficult because of different methodologies.

Conclusion

Endometrial carcinoma is a common gynaecological tumour that often presents in early stage and is amenable to curative treatment. Factors important in prognosis can be obtained from clinical history and routine histological examination. The value of steroid receptor analysis, ploidy, tumour suppressor gene and oncogene studies is still being evaluated. These tests are often costly, time consuming to perform or labour intensive and should be viewed as research tools only until further validation.

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