

Endometrial carcinoma: a South African perspective

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Introduction

Endometrial carcinoma is a less common gynaecological malignancy in the developing world, yet a significant number of individuals are diagnosed each year in South Africa. The relative frequency of endometrial carcinomas has increased over the last years in developing economies due to an increase in obesity and a decrease in fertility rate. In South Africa endometrial carcinoma is more common in certain subpopulations. Asian women have a life time risk of 1 in 106 to develop endometrial carcinoma. The overall risk for women of all races in South Africa is 1 in 146.¹ The most common histological type is endometrioid-type adenocarcinoma but other histological types include mucinous adenocarcinoma, clear cell carcinoma, uterine papillary serous carcinoma (UPSC), squamous carcinoma and also carcinosarcoma.

The endometrium represents a specialised tissue in the uterine cavity which, during the reproductive years, undergoes profound histological changes during each menstrual cycle. The endometrium is stimulated by trophic hormones during each cycle to undergo normal growth and eventually be transformed into a secretory endometrium with active mucin production. The two hormones controlling the endometrial cycle are oestrogen and progesterone. Oestrogen causes growth (proliferative phase) and progesterone causes luteinisation and mucin secretion (secretory phase). It is clearly established that excessive oestrogen production will lead to over stimulation of the endometrial stratum functionalis and if normal secretory phase endometrial changes do not occur under the influence of progesterone regular shedding of the endometrium is absent which may eventually lead to hyperplastic and malignant changes.

Symptomatology

Hyperplasia and carcinoma of the endometrial cavity often lead to early symptoms related to abnormal vaginal bleeding. In the peri-menopausal period the patient may experience bleeding with an acyclical pattern and in the post-menopausal woman bleeding is often the first sign of an endometrial carcinoma. Investigation of this abnormal bleeding usually consists of a cytological smear of the cervix to exclude cervical pathology followed by imaging of the endometrial cavity for endometrial thickness and endometrial sampling; whether it is by endometrial sampling device or hysteroscopy.

In patients with post menopausal bleeding a transvaginal ultrasound to measure the endometrial lining is now standard practice.² In the event of a thickened lining, histology is obtained. Information gained from the pre-operative histology specimen can be used to determine the need for additional surgical dissection of lymph nodes. Endometrial sampling with a simple outpatient sampling device has shown good accuracy and predictive value.³ The safety of hysteroscopy in the presence of endometrial

carcinoma has been investigated in the literature and there is a theoretical concern that seeding of endometrial cells into the abdominal cavity may lead to a poorer prognosis.^{4,5} The fact that spilling occurs is supported by scientific evidence but the clinical importance remains unclear.⁶

Aetiological factors

Excess oestrogen is associated with the biggest group of adenocarcinomas of the endometrium and may be due to endogenous over-production of oestrogen or exogenous ingestion of unopposed oestrogen compounds.^{7,8} Endogenous production may arise from ovarian pathology including conditions such as polycystic ovarian syndrome and more infrequently oestrogen producing tumours of the ovary. Other endogenous sources of oestrogen may include adipose tissue particularly in patients with high body mass index. In South Africa obesity is a major health risk among women and may lead to higher rates of oestrogen related malignancies.⁹ Medical conditions associated with high body mass include diabetes and hypertension (syndrome X or Metabolic Syndrome) which is often associated with endometrial carcinoma. Exogenous ingestion of unopposed oestrogen occurs when hormone therapy is prescribed injudiciously. In the presence of endometrial tissue (i.e. patients with intact uteri) oestrogen therapy should always be countered with progesterone.

Patients who had breast carcinoma are often treated with tamoxifen to reduce the risk of recurrence. Tamoxifen acts as an anti-oestrogen in breast tissue, but it has an oestrogenic effect in the uterus and can cause endometrial hyperplasia which has the potential for malignant change.¹⁰

In patients on tamoxifen endometrial surveillance may be done with:

- Transvaginal ultrasound to measure the thickness and evenness of the endometrium lining¹¹
- Regular endometrial sampling

Endometrial measurements of post menopausal patients on tamoxifen are often increased, and efforts to determine the threshold for endometrial sampling have been published. Franchi et al conclude that an endometrial thickness of more than 8 mm and a report of vaginal bleeding are independent predictors of endometrial pathology in patients treated with tamoxifen.¹² Patients who have bleeding, discharge, abnormal glandular cells on Papanicolaou smear or an endometrial measurement on ultrasonography of more than 8 mm should undergo sampling of the endometrium.¹¹ In future the use of tamoxifen could be substituted with another selective oestrogen receptor modulator to reduce the potential problems associated with endometrial stimulation.¹⁰

A small number of women may develop endometrial carcinoma in the presence of an atrophic endometrial background. These tumours, sometimes referred to as Bokhman type II, occur in older, lean women and often carry a poorer prognosis.¹³

Familial disorders like Lynch syndrome (hereditary nonpolyposis colon carcinoma, HNPCC) increase the risk for the development of colon, ovarian, endometrial and breast carcinomas. The risk for endometrial carcinoma in Lynch families is similar to that of colon carcinoma and endometrial monitoring is essential.¹⁴

Histology

The diagnosis of endometrial carcinoma should be confirmed before surgery on endometrial tissue samples. It is important to get as much information as possible about the architecture of the tissue pre-operatively in order to plan subsequent surgery. Grading of endometrial carcinoma may be very difficult on small samples but good communication with the pathologist about the degree of differentiation is essential if it is not clear from the biopsy report. Poorly differentiated tumours (grade II and III), UPSC, clear cell and carcinosarcomas have a poorer prognosis and may need more exact surgical staging.

Preoperative investigations

Careful preoperative staging investigations should include a chest x-ray to exclude metastases. An ultrasound of the abdomen (or CT scan when available) may illustrate metastases to the liver and possibly pathological lymph nodes. Routine blood examinations including a full blood count, liver and renal function tests and a random glucose test should be standard practice before surgery. In certain centres a preoperative Ca125 level is done as a baseline reference and is used in follow-up where the presence or absence of recurrent tumour is sought.¹⁵

A hysteroscopy, despite the safety concerns outlined earlier, may improve pre-operative diagnosis because the tumour volume can be assessed and cervical involvement can be diagnosed pre-operatively. Ultrasound is a reliable method to assess myometrial invasion, cervical involvement and adnexal metastases and may be a safer option.¹⁶ This information may alter the extent of the surgery. The use of MRI is standard practice internationally and should be considered if resources are available.

Staging of endometrial carcinoma (See Table I)

Endometrial carcinoma is surgically staged and includes information about lymph node status. However, information about lymph nodes is not always available which makes the staging incomplete and less reliable.

Table I: FIGO staging for endometrial carcinoma¹⁷

Stage Ia:	Tumour limited to the endometrial cavity
Stage Ib:	Invasion to the inner half of the myometrium
Stage Ic:	Invasion to the outer half of the myometrium
Stage IIa:	Endocervical glandular involvement only
Stage IIb:	Cervical stromal invasion
Stage IIIa:	Tumour invades the serosal surface of the uterus and/or the adnexae and/or positive peritoneal cytology
Stage IIIb:	Vaginal metastases
Stage IIIc:	Metastases to the pelvic and/or para-aortic lymph nodes
Stage IVa:	Tumour invasion of the bladder and/or bowel
Stage IVb:	Distant metastases including intra-abdominal nodules and/or inguinal lymph nodes

The FIGO staging includes not only the extent of the disease as described earlier but also pathological grading. The grading is done according to the degree of differentiation of the adenocarcinoma. (See Table II)

Table II: Grading of endometrial carcinoma

Grade I:	5% or less is of a non-squamous or non-morular solid growth pattern (most of the endometriod part of the tumour is in a glandular pattern)
Grade II:	Between 5 and 50% of a non-squamous or non-morular growth is solid
Grade III:	More than 50% of a non-squamous or non-morular growth is of a solid pattern

The grading of tumour may be altered where significant nuclear atypia or inappropriate architecture raises the grade by one. Serous adenocarcinoma, clear cell adenocarcinoma and squamous cell carcinoma are graded according to nuclear characteristics. Adenocarcinoma with squamous differentiation is graded according to the nuclear grade of the glandular component. In the absence of a surgical specimen (where the patient is unsuitable for surgery) the old FIGO 1971 clinical staging may still be used.

Surgical procedures

Some controversy exists about the appropriate skin incision. Many gynaecologic oncologists feel that the abdominal cavity should be accessed using a vertical abdominal incision for cases of endometrial carcinoma. However, others feel that patients with low-risk tumours may safely have a Pfannenstiel skin incision.¹⁸ In general the principle should be to get good exposure of all the tissues that may be involved by disease. In the case of poorly differentiated tumours or non-endometriod type histology the best approach would be a vertical skin incision in order to allow the surgeon to carefully assess the para-aortic lymph nodes and the omentum. On opening the peritoneal cavity a little bit of fluid (normal saline) should be instilled in the pelvis around the uterus. This fluid should then be aspirated before contamination by blood and sent for cytological diagnosis. The rest of the standard surgical procedures include total abdominal hysterectomy, bilateral salpingo-oophorectomy and possible lymph node dissection. In the presence of uterine papillary serous and clear cell histology an infracolic omentectomy should also be performed in order to exclude micro-metastases.¹⁹ These tumours often behave in a way similar to that of ovarian malignancy.

Endometrial carcinoma surgery including lymphadenectomy

The extent of surgical staging has been controversial for a long time. The potential benefits of a lymphadenectomy include:

- Possible therapeutic benefit
- Diagnostic accuracy and careful staging
- Ability to plan for adjuvant treatment

Possible therapeutic benefit

An initial non-randomised retrospective study by Kilgore suggested that there may be a survival benefit from systematic lymphadenectomy.²⁰ Other studies on the potential benefit of lymphadenectomy also suggested a possible survival advantage.²¹ However, this information has not been confirmed for early, low-risk disease by well designed recent work.²² Pelvic lymphadenectomy may statistically significantly improve surgical staging, but it did not improve disease-free or overall survival. Lymph node metastases to pelvic nodes occur in about 10% of women with clinical stage I that is confined to the corpus.^{23,24} The incidence of lymph node metastases increases with increasing depth of myometrial invasion and increasing de-differentiation of the tumour. A large prospective,

randomised study conducted with funding from the Medical Research Council and National Cancer Research network in the United Kingdom recently published data about systemic pelvic lymphadenectomy in early stage endometrial carcinoma (the so-called ASTEC trial).²⁵ This well designed study showed no evidence of benefit in terms of overall or disease-free survival for pelvic lymphadenectomy in women with early endometrial carcinoma. The authors suggest that “unless surgical staging will directly affect adjuvant therapy, routine systematic pelvic lymphadenectomy cannot be recommended in women undergoing primary surgery for stage I endometrial carcinoma outside of clinical trials”. The ASTEC trial provides convincing evidence that there is no therapeutic benefit of lymphadenectomy in early disease. However, it is important to remember that lymph node status may provide very important information for the planning of adjuvant treatment.

Diagnostic accuracy and careful staging

Pelvic lymphadenectomy, with or without para-aortic lymphadenectomy, gives valuable information for accurate surgical staging. Even though lymphadenectomy is not universally performed, the FIGO staging increase in the presence of microscopic node metastases.¹⁷

Better ability to plan for adjuvant treatment

If lymph nodes are negative, brachytherapy only instead of external beam therapy may save time, money and side effects.²⁶

Potential problems associated with lymph node dissection

Lymph is a proteinaceous fluid similar to blood plasma and enters the lymph capillaries throughout the body. These capillaries enter into specialised filters (lymph nodes) and, in solid malignant tumours, cells that escape from the primary tumour into the interstitial fluid may be transported and collected in lymph nodes. Removal of lymph nodes and careful histological examination may identify apparent localised tumours with a poor prognosis because of systemic spread. Lymph nodes in the abdomen and pelvis are mostly found in close relation to large blood vessels.

When surgical removal of lymph nodes is performed it may lead to long-term serious morbidity in the form of lymph oedema; in the case of endometrial carcinoma mainly of the lower limbs.²⁷ This lymph oedema is often severe with swelling of the extremities that makes mobility very difficult. Lymph oedema is not amenable to treatment and is often of a chronic incapacitating nature. The exact incidence of lymph oedema in surgically staged endometrial carcinoma is unknown but is substantially increased.²⁵

Because of the anatomical location of the lymph node chains the surgery for removal of lymph nodes may be hazardous and blood loss due to vascular injury, nerve damage (for instance in the obturator fossa) and increased operative time are the most important factors to take into consideration. Considering all these potential side-effects, the clinician should carefully plan and select those patients with the highest likelihood of benefit from a lymphadenectomy. The extent of the surgical removal of lymph nodes in endometrial carcinoma has been discussed extensively in the literature; however, there is no universally accepted consensus.^{28,29,30} The endometrial cavity has extensive lymph drainage to the obturator fossa, the internal and external iliac groups, the common iliac groups and also to the para-aortic lymph nodes up to the renal vessels. When the data from the Mayo clinic is considered, 16% of patients with lymph node metastases (which is only 10% of clinical stage I disease) will have metastases to the *para-aortic area only* and 77% of these patients had metastases above the inferior mesenteric artery.²⁸ Another finding from this study was that in those patients with excision of gonadal veins, 28% had documented metastatic involvement of the gonadal veins or surrounding

soft tissue. The authors conclude that the high rate of lymphatic metastases above the inferior mesenteric artery indicates a need for systemic pelvic and para-aortic lymph adenopathy up to the renal vessels and should include consideration of excision of the gonadal vein.²⁸ This represents rather extensive surgical dissection and the editorial in the same issue rightly comments that the safety and value of the procedure of high para-aortic lymphadenectomy should include discussion of the risks involved in this procedure and also take into consideration the skill of the surgeon.³¹ “We conclude that the data as presented in this article does not provide either the evidence for or the direction of a ‘paradigm’ shift in the surgical assessment and treatment of women whose endometrial carcinoma appears confined to the uterus at exploration.”³¹

The more extensive the surgery the higher the likelihood of complications and many gynaecologic surgeons may feel uncertain about para-aortic lymphadenectomy particular above the level of the inferior mesenteric artery. In any discussion about lymphadenectomy one should be practical about the generally available surgical skill before making blanket recommendations to do para-aortic lymphadenectomy.

Developing guidance for SA on lymphadenectomy

Evidence from the literature suggests that:

- The likelihood of nodal metastases increases with clinical extent of the disease³¹
- The risk and pattern of recurrence and long-term survival differ between women with node positive and node negative disease
- The probability and patterns of treatment failure as well as survival differ in comparison of outcomes of women with endometrioid and those with non-endometrioid histology

It is still to be answered exactly which individual patients would have *therapeutic benefit* from more extensive surgical staging but there is evidence that lymphadenectomy may have a survival benefit in tumours greater than stage IG3.^{29,28} However, it is clear that lymphadenectomy does not have a *therapeutic advantage* for groups for women with low-risk disease.^{28,25}

The surgical skill required for lymphadenectomy is available in most metropolitan centres throughout South Africa. Recently the Health Professions Council of South Africa introduced a sub-speciality registration for gynaecologic oncologists. These sub-specialists are adequately trained to safely perform lymphadenectomy for accurate surgical staging. Radiotherapy is a relatively scarce resource particularly in public sector hospitals and there are often long waiting lists for this limited resource. If accurate surgical staging can give information that will help to safely reduce the time and extent of postoperative radiotherapy it will benefit both patients (less acute and long-term toxicity) and an already overburdened service. Full surgical staging should therefore be offered to patients with high-risk factors. (See Table III) Sometimes pre-operative information may be inadequate to plan for the extent of the surgery and intra-operative frozen section can be useful. (See Table IV)

Table III: Pelvic lymphadenectomy – Indications

- Grade 3, with or without myometrial invasion
- Type of histology (UPSC-Clear cell carcinoma)
- Stage II disease
- High risk factors on intra-operative frozen section

Table IV: Indications for frozen section

Pre-operative complex atypical hyperplasia
 Grades 1 and 2 adenocarcinoma
 *Pathologist to assess (frozen section) histological type, grade, depth of myometrial invasion, and cervical involvement. If the frozen section indicates more than 50% myometrial invasion, grade 3 or cervical stromal involvement, proceed to pelvic lymphadenectomy.

Locally advanced disease

In the presence of locally advanced stage disease, cytoreductive surgery including total hysterectomy and salpingo oophorectomy should be attempted.

Adjuvant treatment after surgery

Radiotherapy

Many controversies exist about the exact postoperative management of a patient with intermediate and high-risk endometrial carcinoma and also cases with non-endometrioid type histologies. High-risk stage I and II endometrioid carcinoma without lymph node involvement should receive vaginal vault brachytherapy within eight weeks of the surgical removal of the primary tumour. Where information about lymph node involvement is not available, postoperative radical whole pelvic irradiation combined with vaginal vault brachytherapy is indicated. It is clear that determining lymph node status in early stage *high-risk* carcinomas may obviate the need for whole pelvic irradiation if the nodes are found to be negative. In high risk disease there is a protective effect of radiotherapy against pelvic recurrence.^{32,33,34} The recent publication of data about adjuvant external beam radiotherapy in the treatment of *early stage* endometrial carcinoma (ASTEC and NCIC CTG EN.5) questions adjuvant whole pelvis radiotherapy for improving survival. The benefit of external beam radiotherapy in preventing isolated local recurrence in early stage disease was small and not without toxicity.³⁵ That leaves us with the question of what to do currently. A practical solution in a resource restricted environment would be to offer only vault brachytherapy to those patients with intermediate and high-risk disease. The side-effects are considerably less and there would be no use made of external beam radiation thus significantly reducing the burden on machine time. In more advanced stages with extra-uterine disease or positive nodes, whole pelvic- or extended field radiotherapy becomes necessary.

Chemotherapy

Recently adjuvant chemotherapy has become an accepted option for treatment of high-risk, advanced endometrial carcinoma.³⁶ A study where whole abdominal irradiation was compared to doxorubicin combined with cisplatin chemotherapy in women with stage III or IV endometrial carcinoma, found that at 60 months 50% of patients receiving chemotherapy were still alive and disease free compared to 38% of patients receiving whole abdominal irradiation. However, this improvement in survival was at the cost of greater acute toxicity.³⁷ In an editorial in the same issue of the Journal of Clinical Oncology the following questions were raised:³⁸

- Should chemotherapy and radiotherapy be combined?
- Should earlier stage disease also be treated with chemotherapy?
- Is cisplatin plus doxorubicin the only appropriate adjuvant regimen?

At this stage chemotherapy in advanced disease should be individualised. Over the next few years more evidence could emerge to guide our decisions.

Hormonal therapy

Management of patients with stage IV disease with extensive systemic spread should be individualised with the focus on symptom control. This may include systemic chemotherapy, palliative radiotherapy and symptomatic treatment. Hormonal therapy with high doses of progesterone has been part of the palliative treatment for endometrial carcinoma for many years.³⁹ There is evidence to support the use of MPA 200 mg/d orally instead of the higher dose of 1 000 mg/d orally.⁴⁰ Twenty percent of those patients who do not respond to progesterone will have a response on tamoxifen.⁴¹

In the *adjuvant setting* however, it has been shown that progesterone not only has no effect on survival but may even have a detrimental effect. In a Cochrane review overall survival was not improved by adjuvant progestogen therapy. Endometrial carcinoma deaths and relapse of disease appeared to be reduced but non-endometrial carcinoma related deaths were more common in treated women.⁴²

Patients not suitable for surgery

In patients with poor performance status and very high risk for surgical morbidity, primary radiotherapy may be considered for treatment of endometrial carcinoma.^{43,44} In these cases the clinical staging by FIGO published in 1972 should be used. In suitable cases whole pelvic irradiation combined with intracavitary brachytherapy can often lead to complete tumour response. In patients with severe obesity, mental incapacity and in the very elderly, where long courses of radiotherapy may be difficult to manage, brachytherapy only may be the best option.⁴³

Conclusion

Endometrial carcinoma usually presents early. Proper pre-operative work-up will make surgery safer because many of the patients presenting with endometrial carcinoma in addition have co-morbid diseases including diabetes and hypertension. With careful postoperative management (including postoperative intensive or high-care admission where necessary) most patients can successfully undergo surgery even in the presence of poor performance status. Furthermore it is important to have good contact with the pathologist regarding the preoperative histological diagnosis. If tumour grading is available it makes planning of surgery significantly easier and planning for lymphadenectomy can be done easily.

Additional radiotherapy treatment after surgery should be decided upon by a multi-disciplinary team. The potential benefits should outweigh the risks of adjuvant therapy and careful follow-up should continue for many years after the initial diagnosis. Chemotherapy is an option in advanced disease and should be considered in patients that have systemic or recurrent disease. In cases with advanced metastatic or recurrent disease, medroxyprogesterone acetate in a dose of 200 mg/day should provide tumour response in some cases. In tumours that are resistant to the effects of MPA, tamoxifen can still offer some hope.

The management of endometrial carcinoma should be planned by a thinking clinical team and a well informed patient.

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