# INTRODUCTION

Endometrial cancer is the most frequent malignancy of the female genital tract, and the fourth most common site after breast, lung, and colorectal cancers. The incidence is rising as life expectancy increases. [1]Developing countries and Japan have incidence rates four to five times lower than Western industrialized nations, with the lowest rates being in India and south Asia.[2]The death rate has increased during the most recent decades, probably due to an increase in life span and coexisting medical comorbidities.[3] Approximately 43.470 new cases of uterine cancer are estimated for 2010 worldwide, with 7950 estimated deaths from this disease.[4]

## Epidemiology and Risk Factors

Two different clinicopathological subtypes of endometrial cancer are recognized: the estrogen-related (type I, endometrioid), and the non-estrogen-related (type II, nonendometrioid). Each subtype has specific genetic alterations, with endometrioid tumors showing microsatellite instability and mutations in Phosphatase and tensin homolog (PTEN) tumor suppressive gene, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (PIK3CA),and Kirsten rat sarcoma viral oncogene (K-ras), although nonendometrioid (predominantly serous and clear cell) tumors exhibit phosphor protein (p53) mutations and chromosomal instability.[5]

Approximately 80% of newly diagnosed endometrial carcinomas in the Western world are endometrioid in type.[5] Any factor that increases exposure to unopposed estrogen, either endogenous or exogenous, (e.g., estrogen-replacement therapy, obesity, anovulatory cycles, estrogen-secreting tumors) increases the risk of these tumors, whereas factors that decrease exposure to estrogens or increase progesterone levels (e.g., oral contraceptives) tend to be protective. [6]

The average age of patients with endometrioid cancer is approximately 63 years, and around 70% of cases are confined to the corpus at the time of diagnosis. In these women, tumors begin as hyperplastic endometrium and then progress to carcinoma. These "estrogen-dependent" tumors tend to be better differentiated and have a more favorable prognosis than"non-estrogen-dependent" tumors. Their 5-year survival is approximately 83%. [5,7]

By contrast, the average age of patients with nonendometrioid cancer is 67 years, and at least half have already spread beyond the corpus at the time of diagnosis. This nonendometroid type occurs in women with no source of estrogen stimulation of the endometrium. They are not associated pathologically with endometrial hyperplasia, but may arise in a background of atrophic endometrium. They are less differentiated and associated with a poorer prognosis than estrogen-dependent tumors. Their 5-year survival is approximately 62% for clear cell carcinomas and 53% for papillary serous cancers. [5,7]

Women with hereditary nonpolyposis colorectal cancer syndrome (HNPCC),a cancer susceptibility syndrome with germline mutations in mismatch repair genes; MutL homolog 1(MLH1), MutS protein homolog 2 (MSH2), and mutS homolog 6 (MSH6), have a 40% to 60% lifetime risk for endometrial as well as colon cancer.[8]

Black women have a 40% lower risk of developing the disease but a 54% greater risk of dying from it, mainly because of late diagnosis. [2]

## Screening of Asymptomatic Women:

The ideal method for outpatient sampling of the endometrium has not yet been established, and no screening blood test of sufficient sensitivity and specificity has been developed. Therefore, mass screening of the population is not practical. However, screening for endometrial carcinoma or its precursors is justified for certain high-risk people, including Postmenopausal women on exogenous estrogens without progestins, Women from families with hereditary nonpolyposis colorectal cancer syndrome and Premenopausal women with an ovulatory cycles, such as those with polycystic ovarian disease.[9]

Only approximately 50% of women with endometrial cancer have malignant cells on a Papanicolaou (Pap) smear [9]. However, compared with patients who have normal cervical cytologic findings, patients with suspicious or malignant cells are more likely to havea more advanced stage of disease with deeper myometrial invasion, higher tumor grade and positive peritoneal cytologic findings.[10]

The unsatisfactory results obtained with cervical cytology are the result of the indirect sampling of the endometrium, and several commercially available devices have been developed to allow direct endometrial sampling (e.g., Pipelle, Gyno Sampler, Vabra aspirator). A satisfactory endometrial biopsy specimen also may be obtained in the office with a small curette such as a Novak or Kevorkian. All of these outpatient techniques for endometrial sampling cause the patient some discomfort, and in approximately 8% of patients it is not possible to obtain an endometrial biopsy specimen because of a stenotic cervix. This failure rate increases to approximately 18% for women older than 70 years of age.[11]

Patients taking tamoxifen should be informed of the increased risk of endometrial cancer. A retrospective review of tamoxifen treated women who underwent dilatation and curettage found that uterine cancer was found only in those with vaginal bleeding, so these patients should be told to report any abnormal bleeding or spotting immediately that must be investigated by biopsy. [12]

In the 1990s, transvaginal ultrasonography, with or without color-flow imaging, was studied as a screening technique. Mean thickness of the endometrial strip was measured as 3.4 ± 1.2 mm in women with atrophic endometrium, 9.7 ± 2.5 mm in women with hyperplasia, and 18.2 ± 6.2 mm in women with endometrial cancer.[13] In a large, multiinstutional study of 1,168 women, all 114 women with endometrial cancer and 95% of the 112 women with endometrial hyperplasia had an endometrial thickness of 5 mm or more. [14]A metaanalysis reported that 4% of endometrial cancers would be missed using transvaginal ultrasonography for the investigation of postmenopausal bleeding, with a false positive rate as high as 50%.[15]

# Clinical Features

## Symptoms

Ninety percent of women with endometrial cancer will have alarming symptom : abnormal vaginal bleeding, most commonly postmenopausal bleeding, and the bleeding usually occurs early in the course of the disease. Intermenstrual bleeding or heavy prolonged bleeding in perimenopausal or anovulatory premenopausal women should arouse suspicion.(16)

The diagnosis may be delayed unnecessarily in these women because the bleeding is usually ascribed to "hormonal imbalance." A high index of suspicion also is needed to make an early diagnosis in women younger than 40 years of age.(16)

Occasionally, vaginal bleeding does not occur because of cervical stenosis, particularly in thin, elderly, estrogen-deficient patients. In some of these patients, a hematometra develops, and a small percentage have a purulent vaginal discharge resulting from a pyometra.(16)

## Signs

Physical examination commonly reveals an obese, hypertensive, postmenopausal woman. Abdominal examination is usually unremarkable except in advanced cases when ascites, hepatic or omental metastases may be present. Occasionally, a hematometra appears as a large, smooth midline mass arising from the pelvis.

On pelvic examination, it is important to inspect and palpate the vulva, vagina, and cervix to exclude metastatic spread or other causes of abnormal vaginal bleeding. The uterus may be bulky, but often it is not significantly enlarged. Rectovaginal examination should be performed to evaluate the ovaries, fallopian tubesand cul-de-sac. Peripheral lymph nodes and breasts examination should be assessed carefully not to be ignored. (16)

# Diagnosis

All patients suspected of having endometrial carcinoma should have endocervical curettage and office endometrial biopsy. A histologically positive endometrial biopsy allows the planning of definitive treatment.

Because there is a false negative rate of approximately 10%, a negative endometrial biopsy in a symptomatic patient must be followed by a fractional curettage under anesthesia. (11, 17)

Hysteroscopy is often performed in conjunction with curettage and may identify some small bleeding polyps that would otherwise have been missed. (18, 19)

Transvaginal ultrasonography may be a useful adjunct to endometrial biopsy for evaluating abnormal uterine bleeding and selecting patients for additional testing.(13,20,21) Transvaginal ultrasonography, with or without endometrial fluid instillation (sonohysterography), may be helpful in distinguishing between patients with minimal endometrial tissue whose bleeding is related to perimenopausal an ovulation or

postmenopausal atrophy and patients with significant amounts of endometrial tissue or polyps who are in need of further evaluation. The finding of an endometrial thickness greater than 5 mm, a polypoid endometrial mass, or a collection of fluid within the uterus requires further evaluation. Although most studies agree that an endometrial thickness of 5 mm or less in a postmenopausal woman is consistent with atrophy, more data are needed before ultrasonography findings can be considered to eliminate the need for endometrial biopsy in a patient who has symptoms. [14, 15]

# Preoperative Investigations

Routine preoperative investigations for early stage endometrial carcinoma are complete blood count, Renal and liver function tests, Blood sugar level, lipid profile, coagulation profile, Urinalysis and CT scan of chest, pelvis, and abdomen, particularly for high-risk histologies. If a fractional curettage has not been performed, then endocervical curettage should be performed to evaluate the endocervix. [3]

Nonroutine tests are sometimes indicated, particularly for more advanced cases or high-risk histologies on curettage. A colonoscopy should be performed if there is occult blood in the stool or a recent change in bowel habits because concomitant colon cancer occasionally occurs, particularly if there is a family history of bowel cancer. [16]

A pelvic and abdominal computed tomographic (CT) scan may be helpful to determine the extent of metastatic disease in the following circumstances: abnormal liver function test results, clinical hepatomegaly, palpable upper abdominal mass, palpable extrauterine pelvic disease, clinical ascites and grade 3 endometrioid or nonendometrioid carcinomas. However, it has limited usefulness in determining the depth of myometrial invasion or the presence of nodal disease. [22,23] Magnetic resonance imaging (MRI) was evaluated as a tool for preoperative staging in a National Cancer Institute cooperative study and other subsequent studies that have shown that MRI may have a role for evaluating the depth of myometrial invasion and may be of help to differentiate between low- and high-risk patients.[24-26]

Elevated CA125 levels have been demonstrated to correlate with advanced stage of disease and positive lymph node status.[27]

# Staging

In 1988, the Cancer Committee of the International Federation of Gynecology and Obstetrics (FIGO) replaced the old clinical staging system (Table I) with a surgical staging system for endometrial cancer (Table II) that was updated in 2009 (Table III).[28]

Previously, the disease was staged clinically, based on examination under anesthesia, sounding the uterus, and a limited number of preoperative investigations. The change was mainly in response to the Gynecologic Oncology Group (GOG) studies, which demonstrated the high incidence of lymph node metastases in high-risk cases. [29, 30]

As increasing experience with the surgical staging of endometrial cancer has been reported, it seems apparent that there is no need to perform systematic lymphadenectomy in low-risk cases (grade 1 or 2 endometrioid tumors confined to the inner half of the myometrium).[31]These patients require only removal of palpably suspicious nodes.

For high-risk cases (grade 3, serous or clear cell histologies, stages IC or II disease), a systematic pelvic lymphadenectomy should be performed, with at least removal of any clinically suspicious paraaortic lymph nodes.[31]

Because endometrial cancer is now staged surgically, procedures previously used for determination of stages are no longer applicable, such as the findings from fractional dilatation and curettage to differentiate between stage I and stage II. [28]

**Table (I): 1971 FIGO Clinical Staging for Endometrial Carcinoma [28]**

| | |
|---|---|
| Stage 0 | Carcinoma in situ |
| Stage I | The carcinoma is confined to the corpus. |
| Stage IA | The length of the uterine cavity is 8 cm or less. |
| Stage IB | The length of the uterine cavity is more than 8 cm. |
| Stage I cases should be subgrouped with regard to the histologic grade of the adenocarcinoma as follows: | |
| Grade 1 | Highly differentiated adenomatous carcinoma |
| Grade 2 | Moderately differentiated adenomatous carcinoma with partly solid areas |
| Grade 3 | Predominantly solid or entirely undifferentiated carcinoma |
| Stage II | The carcinoma has involved the corpus and the cervix but has not extended outside the uterus. |
| Stage III | The carcinoma has extended outside the uterus but not outside the true pelvis. |
| Stage IV | The carcinoma has extended outside the true pelvis or has obviously involved the mucosa of the bladder or rectum. A bullous edema as such does not permit a case to be allocated to stage IV. |
| Stage IVA | Spread of the growth to adjacent organs. |
| Stage IVB | Spread to distant organs. |
| FIGO, International Federation of Gynecology and Obstetrics. | |

**Table (II): 1988 FIGO Surgical Staging for Endometrial Carcinoma [28]**

| | |
|---|---|
| Stage IA G123 | Tumor limited to endometrium |
| Stage IB G123 | Invasion to less than one-half the myometrium |
| Stage IC G123 | Invasion to more than one-half the myometrium |
| Stage IIA G123 | Endocervical glandular involvement only |
| Stage IIB G123 | Cervical stromal invasion |
| Stage IIIA G123 | Tumor invades serosa and/or adnexa, and/or positive peritoneal cytology |
| Stage IIIB G123 | Vaginal metastases |
| Stage IIIC G123 | Metastases to pelvic and/or paraaortic lymph nodes |
| Stage IVA G123 | Tumor invasion of bladder and/or bowel mucosa |
| Stage IVB G123 | Distant metastases including intraabdominal and/or inguinal lymph nodes |

**Table (III) A Carcinoma of the Endometrium (2009) [28]**

| | | | |
|---|---|---|---|
| **Stage I*** | | | Tumor confined to the corpus uteri |
| | **IA*** | | No or less than half myometrial invasion |
| | **IB*** | | Invasion equal to or more than half of the myometrium |
| **Stage II*** | | | Tumor invades cervical stroma, but does not extend beyond the uterus** |
| **Stage III*** | | | Local and/or regional spread of the tumor |
| | **IIIA*** | | Tumor invades the serosa of the corpus uteri and/or adnexae# |
| | **IIIB*** | | Vaginal and/or parametrial involvement# |
| | **IIIC*** | | Metastases to pelvic and/or para-aortic lymph nodes# |
| | | **IIIC1*** | Positive pelvic nodes |
| | | **IIIC2*** | Positive para-aortic lymph nodes with or without positive pelvic lymph nodes |
| **Stage IV*** | | | Tumor invades bladder and/or bowel mucosa, and/or distant metastases |
| | **IVA*** | | Tumor invasion of bladder and/or bowel mucosa |
| | **IVB*** | | Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes |

*Either G1, G2, or G3.

** Endocervical glandular involvement only should be considered as Stage I and no longer as Stage II.

# Positive cytology has to be reported separately without changing the stage.

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## Histopathology—degree of differentiation:

Cases of carcinoma of the corpus should be classified (or graded) according to the degree of histologic differentiation, as follows:

$G_1$ = 5% or less of a nonsquamous or nonmorular solid growth pattern

$G_2$ = 6% to 50% of a nonsquamous or nonmorular solid growth pattern

$G_3$ = more than 50% of a nonsquamous or nonmorular solid growth pattern. [28]

## Notes on pathological grading:

Nuclear atypia, inappropriate for the architectural grade, raises the grade of a grade 1 or a grade 2 tumor by 1.

In serous adenocarcinomas, clear cell adenocarcinomas, and squamous cell carcinomas, nuclear grading takes precedence.

Adenocarcinomas with squamous differentiation are graded according to the nuclear grade of the glandular component. [28]

## Spread Patterns

Endometrial carcinoma spreads by the following routes:

A) Direct extension to adjacent structures.
B) Trans-tubal passage of exfoliated cells.
C) Lymphatic dissemination.
D) Hematogenous dissemination

Direct Extension is the most common route of spread, and it results in penetration of the myometrium and eventually the serosa of the uterus. The cervix and fallopian tubes and ultimately the vagina and parametrium may be invaded. Tumors arising in the upper corpus may involve the tube or serosa before involving the cervix, whereas tumors arising from the lower segment of the uterus involve the cervix early. The exact anatomic route by which endometrial cancer involves the cervix has not been clearly defined, but it probably involves a combination of contiguous surface spread, invasion of deep tissue planes, and lymphatic dissemination. [16]

Trans-tubal Dissemination: The presence of malignant cells in peritoneal washings and the development of widespread intraabdominal metastases in some patients with early stage endometrial cancer strongly suggest that cells may be exfoliated from the primary tumor and transported to the peritoneal cavity by retrograde flow along the fallopian tubes.[16]

Lymphatic Dissemination is clearly responsible for spread to pelvic and paraaortic lymph nodes. Although lymphatic channels pass directly from the fundus to the paraaortic nodes through the infundibulopelvic ligament, it is rare to find positive paraaortic nodes in the absence of positive pelvic nodes. However, it is quite common to find microscopic metastases in both pelvic and paraaortic nodes, suggesting simultaneous spread to pelvic

and paraaortic nodes in some patients. This is in contrast to cervical cancer, where paraaortic nodal metastases are always secondary to pelvic nodal metastases. [16, 32] It seems that vaginal metastases also result from lymph-vascular spread. They commonly occur in the absence of cervical involvement, excluding direct spread as the mechanism, and may occur despite preoperative sterilization of the uterus with intracavitary radiation, excluding implantation of cells at the time of surgery as the mechanism. [16, 32]

Hematogenous spread most commonly results in lung metastases, but liver, brain, bone, and other sites can be involved but less commonly. [16, 32]

# Prognostic Variables:

Although stage of disease is the most significant prognostic variable, a number of factors have been shown to correlate with outcome in patients with the same stage of disease.

## Age

Age appears to be an independent prognostic variable. In general, younger women with endometrial cancer have a better prognosis than older women. [2] Japanese workers have reported menopausal status to be an independent prognostic variable for early endometrial cancer but not for patients with advanced disease. [33]

## Histologic Type

Nonendometrioid histologic subtypes account for about 10% of endometrial cancers and carry an increased risk for recurrence and distant spread. [5, 34]

Papillary serous carcinomas have a poor prognosis even in the absence of deep myometrial invasion or lymph node metastasis. [5, 35, 36] These tumors disseminate widely, with a preferential recurrence in the upper abdomen. The mechanisms that have been proposed to explain the characteristic intraabdominal dissemination of these tumors include trans-tubal spread, vascular-lymphatic invasion, and multifocal disease. [36, 37] Clear cell carcinomas represent fewer than 5% of endometrial carcinomas. Vascular space invasion is more common in these lesions. [37] Squamous cell carcinomas of the endometrium are rare. The survival rate for patients with clinical stage I disease was 36 %. [38]

## Histologic Grade and Myometrial Invasion

There is a strong correlation between histologic grade, myometrial invasion, and prognosis. [30] The risk of positive pelvic and paraaortic nodal metastases is associated with increasing the histologic grade and depth of myometrial invasion. When grade 1 carcinomas were confined to the inner third of the myometrium, the incidence of positive pelvic nodes was less than 3%, whereas when grade 3 lesions involved the outer third, the incidence of positive pelvic nodes was 34%. For aortic nodes, the corresponding figures were less than 1% and 23%, respectively. [39]

Local recurrence at the vaginal vault can usually be prevented by prophylactic vault brachytherapy, so it is difficult to be correlated accurately with the histological grade and

myometrial invasion. But the risk of distant metastases increases in relation to histologic grade and myometrial invasion. [16]

## Lymphovascular Space Invasion

Vascular Space Invasion appears to be an independent risk factor for recurrence and for death from endometrial carcinoma of all histologic types. [40, 41] The overall incidence of lymph-vascular invasion in stage I endometrial carcinoma is approximately 15%, although it increases with increasing myometrial invasion and decreasing tumor differentiation. [42,43]

## Peritoneal Cytologic Results

The significance of a positive peritoneal cytologic result is controversial. [41]Positive washings are most common in patients with grade 3 histologic type, metastases to the adnexae, deep myometrial invasion, or positive pelvic or paraaortic nodes.[30, 44-47] if the disease was confined to the uterus, then positive peritoneal cytologic results did not influence survival. If the disease had spread to the adnexa, lymph nodes, or peritoneum, then positive peritoneal cytologic findings decreased the 5 years survival rate from 73% to 13%, but all recurrences were at distant sites. [47]

## Hormone Receptor Status

In general, mean estrogen receptor (ER) and progesterone receptor (PR) levels are inversely proportional to histologic grade. [48, 49]However, ER and PR content have been shown to be independent prognostic indicators for endometrial cancer; that is, patients whose tumors are positive for one or both receptors have longer survival than patients whose carcinoma lacks the corresponding receptors. [48-50] It was reported that, even for patients with lymph node metastases, the prognosis was significantly improved if the tumor was receptor positive.[49] PR appears to be a stronger predictor of survival than ER and, at least for the ER, the absolute level of the receptors may be important: The higher the level, the better the prognosis.[50]

## Nuclear Grade

Nuclear grade is a significant prognostic indicator.[51]The FIGO grading system takes into account the nuclear grade of the tumor, and "nuclear atypia" inappropriate for the architectural grade raises the grade by one. [28]

## Tumor Size

Tumor size is a significant prognostic factor for lymph node metastasis and survival in patients with endometrial cancer. [52, 53]

Lymph node metastases occurred in 4% of the patients with tumors no more than 2 cm in diameter, 15% with tumors greater than 2 cm in diameter, and 35% with tumors involving the entire uterine cavity. [53]

## DNA Ploidy and Other Biologic Markers

Approximately one-fourth of patients with endometrial carcinomas have aneuploid tumors, which is a low incidence compared with many other solid tumors, including ovarian and cervical carcinomas. However, patients with aneuploid tumors are at significantly increased risk of early recurrence and death from disease. [54, 55] The GOG estimated the relative risk to be 4.1 for disease-related death for patients with aneuploid tumors. [56]

A number of genetic mutations have also been shown to have prognostic significance in endometrial cancer. It was reported that loss of beta-catenin expression was a strong, independent predictor of a poor prognosis, whereas loss of PTEN was associated with a worse prognosis for patients with early stage disease. [57] The p53 mutation correlated with increased stage, lymph node metastases, and nonendometrioid histology in univariate analysis but was not an independent prognostic factor in multivariate analysis. [57] Increasing expression of matrix metalloproteinases (MMPs) [58], nuclear bcl-2 expression [59], and Ki-67 expression [60] also have prognostic significance. The clinical implications of these biologic markers are not yet clear.

# Treatment of Endometrial Cancer

The cornerstone of treatment for endometrial cancer is total abdominal hysterectomy and bilateral salpingo-oophorectomy, and this operation should be performed in all cases whenever feasible. Radiation therapy alone cannot effectively eliminate disease in the myometrium. [61, 62] In addition, many patients require some type of adjuvant radiation therapy to help prevent vaginal vault recurrence and to sterilize disease in lymph nodes. [61,62]

It is difficult to document that radiation actually improves survival rates, but with the increasing emphasis on surgicopathologic staging, a more individualized approach to adjuvant radiation is now possible. [63, 64]

Microscopic cervical involvement (positive endocervical curettage) is often designated (unofficially) as stage II occult disease. For practical purposes, if the cervix is not hard or expanded, such patients can be managed in the same way as patients with stage I disease. [64, 65]

## Stage I and Stage II Occult

### Operative Technique

A recommended treatment plan is shown in Fig. 1.

The initial approach for all medically fit patients should be total abdominal hysterectomy and bilateral salpingo-oophorectomy. Removal of a vaginal cuff is not necessary. The adnexa should be removed because they may be the site of microscopic metastases. In addition, patients with endometrial carcinoma are at increased risk for ovarian cancer. Such tumors sometimes occur concurrently. [66] Surgical staging, including lymphadenectomy, should be performed in those patients: Patients with grade 3 lesions, Patients with grade 2 tumors >2 cm in diameter, Patients with clear cell or papillary serous

carcinomas, Patients with greater than 50% of myometrial invasion and Patients with cervical extension. [67, 68]

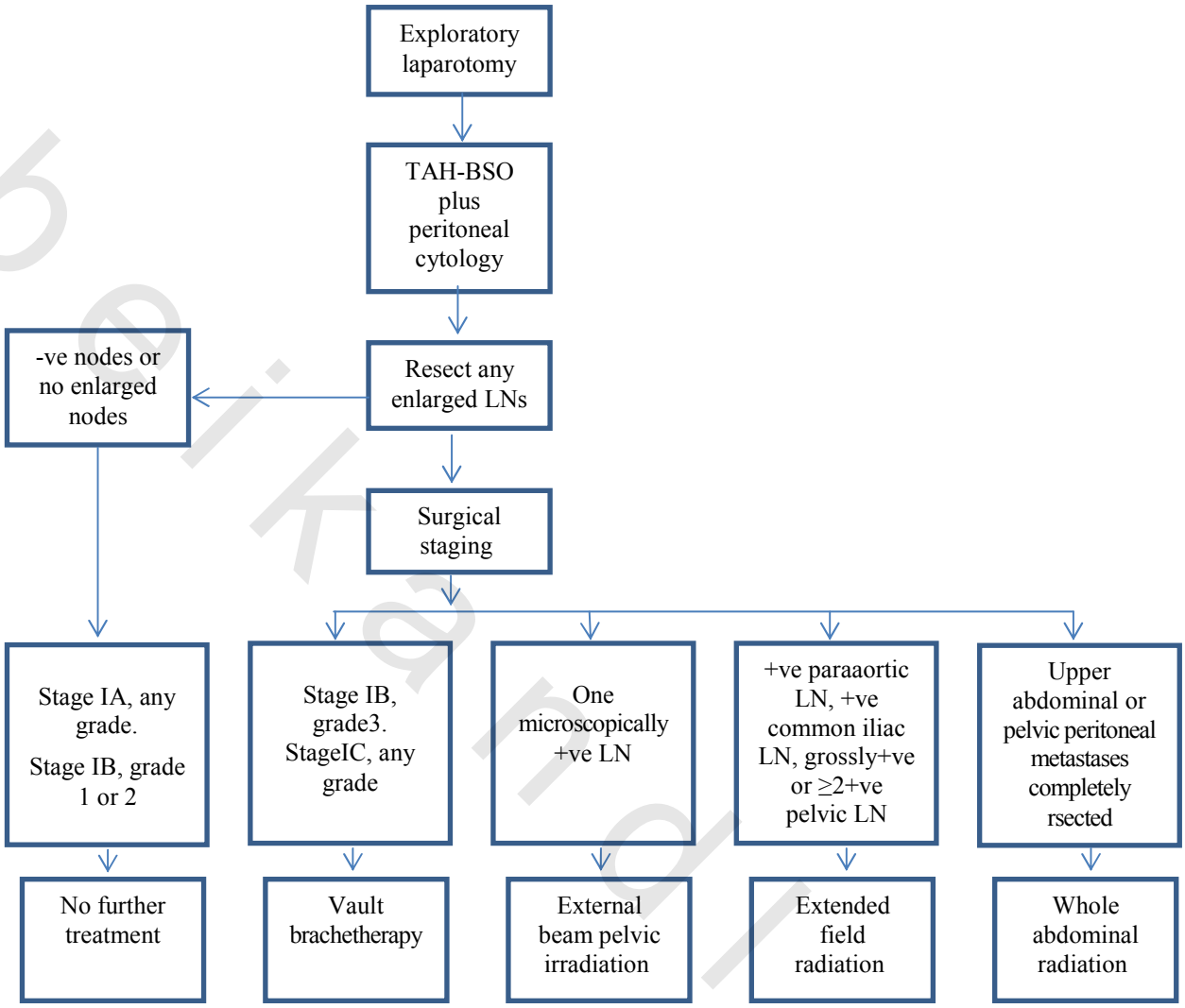


**Figure (1):** Management of patients with stage I and occult stage II endometrial carcinoma. [67, 68]

The use of laparoscopically assisted vaginal hysterectomy could be done. The laparotomy is best performed through a lower midline abdominal incision, particularly in the obese patient. This incision allows easy access to the upper abdomen, including the omentum and paraaortic lymph nodes. A Pfannenstiel incision is commonly used for patients with grade 1 or 2 tumors and a normally sized uterus. An alternative approach is to use a transverse, muscle-dividing incision (e.g., the Maylard or Cherney). This incision also gives reasonable access to the upper abdomen. [67, 68]

After the abdomen is opened, peritoneal washings are taken with 50 mL normal saline solution. Thorough exploration of the abdomen and pelvis is performed, with particular attention to the liver, diaphragm, omentum, and paraaortic nodes. Any suspicious lesions are excised or biopsied. [67, 68]

The uterus is grasped with clamps that encompass the round and ovarian ligaments and the fallopian tube. After the round ligaments are divided, the incision is carried anteriorly around the vesicouterine fold of peritoneum and posteriorly parallel and lateral to the infundibulopelvic ligaments. With a narrow Deaver retractor in the retroperitoneum providing gentle traction cephalad in the direction of the common iliac vessels, the iliac vessels and ureter are displayed. With the retroperitoneum displayed, the pelvic lymph nodes can be visualized and palpated, and any enlarged nodes can be removed. [67, 68]

With each ureter under direct vision, the infundibulopelvic ligaments are divided and tied. The bladder is dissected off the front of the cervix, and then the uterine vessels are skeletonized and divided at the level of the isthmus. Straight Kocher clamps are used to secure the cardinal and uterosacral ligaments. The uterus, tubes, and ovaries are removed, and the vaginal vault is closed. The uterus is opened in the operating room, and tumor size, depth of myometrial invasion, and cervical extension are assessed. This information, along with the surgical findings and knowledge of the preoperative histology, influences whether pelvic and aortic lymph node dissection is indicated. The pelvic peritoneum is not closed, and it usually is not necessary to place drains in the pelvis. The sigmoid colon is placed in the pelvis to help exclude loops of small bowel. A vertical abdominal wound is best closed with a continuous Smead-Jones type of internal retention suture, using a long-acting, absorbable suture such as Maxon or polydioxanone (PDS). [67, 68]

## Surgical Staging

The decision to undertake surgical staging is usually based on the histopathology from the uterine curettings, the gross findings on opening the uterus on the operating table, and possibly a frozen section of the resected uterus. [67, 68, 69]

A relatively poor correlation has been reported between the grade of cancer on curettings or biopsy and the final grade in the resected uterus, presumably because of a sampling error in the diagnostic procedure. The poorest correlation is for grade 1 tumors, where 20% to 40% may be upgraded after evaluation of the hysterectomy specimen. [69, 70]

## Pelvic Lymphadenectomy

Micrometastases in lymph nodes cannot be detected by preoperative imaging techniques, so if accurate surgical staging is to be obtained, then full pelvic lymphadenectomy should be performed on all patients who meet the criteria for this procedure. Sampling will only lead to inaccurate information. [71, 72]

Pelvic lymph node count was an important prognostic variable for patients with FIGO stages I and II endometrial carcinoma and high-risk histology. [72, 73]

The dissection should include removal of common iliac nodes and of the fat pad overlying the distal inferior vena cava. If full pelvic lymphadenectomy is considered inadvisable because of the patient's general medical condition, which is uncommon, then resection of any enlarged pelvic nodes should be performed. [72]

## Management of Paraaortic Lymph Nodes

Systematic paraaortic lymphadenectomy is considered a major surgery for patients who are elderly and obese. As it significantly increases operating time and blood loss and also increases postoperative morbidity, particularly lower limb lymphedema. [74]

In spite of that some authors recommend asystematic paraaortic lymphadenectomy on all high-risk patients [75] or in patients with two or more positive pelvic lymph nodes [76]It was suggested that patients with positive paraaortic nodes were likely to have grossly positive pelvic nodes, grossly positive adnexae, or grade 2 or 3 lesions with outer-third myometrial invasion. [77]

## Role of Lymphadenectomy

Pelvic lymphadenectomy, with or without paraaortic lymphadenectomy, plays an important role in the surgical staging of endometrial cancer and thus provides more accurate prognostic information. The therapeutic role of lymphadenectomy is less well understood, but its ability to modify adjuvant therapy is being increasingly accepted. [78, 79]

## Omental Biopsy

In addition to the lymphadenectomy, an omental biopsy is also performed as part of the surgical staging because occult omental metastases may occur, particularly in patients with grade 3 tumors or deeply invasive lesions. [80]The omentum should be carefully inspected, along with all peritoneal surfaces, and any suspicious lesions excised. If the omentum appears normal, then a generous biopsy (e.g., 5 × 5 cm) should be taken. [80]

## Vaginal Hysterectomy

Vaginal hysterectomy should be considered the elective approach for the treatment of elderly patients with endometrial cancer. [81, 82] Laparoscopically assisted vaginal hysterectomy is increasingly being used for the management of endometrial cancer, particularly in obese patients. Use of the laparoscope facilitates removal of the adnexae and the pelvic lymph nodes. [83, 84]

# Adjuvant Irradiation

Adequate surgical staging has allowed the adjuvant therapy to be better tailored to the needs of the individual endometrial cancer patient. Thus decrease overall use of adjuvant radiation for endometrial cancer patients. The options for postoperative radiation are as follows: observation, vault brachytherapy, external pelvic irradiation, extended-field irradiation and whole-abdominal irradiation (WAR). [85, 86]

## Observation

Patients with stage IA or IB, grade 1 or 2 tumors have an excellent prognosis, and need no further adjuvant radiation. Carful follow up is necessary for those patients who treated without adjuvant radiotherapy so that vault recurrences can be diagnosed early. The diagnosis of recurrence is sometimes first suspected when adenocarcinoma cells are seen on a routine vault smear. [86-89]

## Vaginal Brachytherapy

The incidence of vault recurrence is significantly decreased after vaginal brachytherapy. Treatment with high dose-rate postoperative vaginal cuff brachytherapy can be accomplished as an outpatient with low morbidity. [90-93]

Several studies have reported low vaginal vault and pelvic sidewall recurrence rates after using vault brachytherapy without external pelvic radiation after pelvic lymphadenectomy with negative nodes. [40]If lymph node sampling only has been performed, then it may be safer to use external pelvic radiation because of the increased risk of pelvic sidewall recurrence. [63]

## External Pelvic Irradiation (Teletherapy)

The indications for external pelvic irradiation are decreasing after increasing the number of endometrial cancer patients having adequate surgical staging and pelvic lymphadenectomy. Patients with negative pelvic nodes generally receive vault brachytherapy alone, whereas patients with bulky positive pelvic nodes or more than one microscopically positive pelvic node are better treated with pelvic and paraaortic radiation. External pelvic radiation is a reasonable option for Patients with 1 microscopically positive pelvic node after surgical staging and Patients with high-risk features who have undergone TAH-BSO without surgical staging, and who have a negative pelvic and abdominal CT scan and a normal serum CA125 level. [63, 64, 94-96]

## Extended-Field Radiation

Approximately 50% of patients with positive pelvic nodes will have positive paraaortic nodes. [97]Paraaortic lymph node metastases are associated with an increasing number of pelvic lymph node metastases and with bilateral pelvic nodal involvement. [75, 97, 98]

Extended-field irradiation is indicated in patients with biopsy-proven paraaortic nodal metastasis, grossly positive pelvic nodes and 2 or more positive pelvic nodes. [99]

## Whole-Abdominal Radiation

Whole-abdominal radiation is indicated in:

1. Patients with endometrioid, serous papillary or clear cell carcinomas and omental, adnexal, or peritoneal metastases that have been completely excised.

2. Patients with serous papillary or clear cell carcinomas with positive peritoneal washings. [100-104]

## Adjuvant Progestins

Progestins have not a role as adjuvant therapy in endometrial cancer, although they do have an established therapeutic role in the management of patients of advanced and recurrent endometrial carcinoma. [105-107]

## Adjuvant Chemotherapy

The use of systemic chemotherapy as adjuvant therapy in patients with high-risk early stage endometrial cancer is still controversial. The data reported from various studies reinforce the need for adequate powered randomized trials studying the role of adjuvant chemotherapy in endometrial cancer treatment. [108-111]

## Clinical Stage II

When both the cervix and the endometrium are clinically involved with adenocarcinoma, it may be difficult to distinguish between a stage IB adenocarcinoma of the cervix and a stage II endometrial carcinoma.Histopathological evaluation is not helpful in the differentiation of these two conditions, and the diagnosis must be based on clinical and epidemiologic features. The old, obese woman with a bulky uterus is more likely to have endometrial cancer not adenocarcinoma of the cervix, while the younger woman with normal size uterus and a bulky cervix is more likely to have cancer cervix. [112]

There is a lack of adequate prospective randomized studies about the optimal therapeutic tool, but the current approach of management favors primary surgery, with adjuvant radiation tailored to the surgical findings. [112-114]

The surgery includes: modified (type II) radical hysterectomy, bilateral salpingo-oophorectomy, peritoneal washings for cytologic study, pelvic lymphadenectomy to the aortic bifurcation, resection of grossly enlarged paraaortic nodes, omental biopsy and biopsy of any suspicious peritoneal nodules. [112-114]

Adjuvant radiotherapy is tailored to the surgical finding; if lymph nodes are negative, then adjuvant radiation is not given. Patients with one microscopically positive pelvic node receive external pelvic radiation, whereas those with multiple positive pelvic nodes or grossly positive pelvic nodes are given extended-field irradiation. Patients with upper abdominal disease should have cytoreductive surgery. [114]

## Treatment following surgery in cases above clinical stage II

### Surgical Stage III

All macroscopic disease can be removed in these patients followed by adjuvant chemotherapy with or without pelvic radiation. [115]

### Surgical Stage IVA

Isolated bladder or rectal mucosal metastases in endometrial cancer is very uncommon. In the 26th FIGO annual report, only (0.6%) of endometrial cancer patients had stage IVA disease. [7] Treatment must be individualized but modified pelvic exenteration would be required, with or without pelvic radiation or chemotherapy. [116]

**Surgical Stage IVB**

Stage IVB endometrial carcinoma is rare with poor therapeutic results in general. Treatment of stage IV disease must be individualized but usually involves a combination of surgery, radiation therapy, chemotherapy or hormonal therapy. [116]In making a decision to undertake primary surgery in a patient with advanced endometrial cancer, both the location and the extent of the disease whether metastasized to the lungs, bone, bladder, pelvic side wall or liver metastases must be taken in account. [116]The main objective of therapy should be to try to achieve local disease control in the pelvis and to palliate bleeding, discharge, pain, and fistula formation. [116]

**Follow-Up**

Patients should be examined every 3 to 4 months during the first 2 years and every 6 months until 5 years. With each visit relevant history should be taken with proper pelvic, abdominal and peripheral lymph nodes examination. [117-120]About one half of patients discovered to have recurrent cancer have symptoms, and 75% to 80% of recurrences are detected initially on physical examination. Approximately 10% of recurrences occur beyond 5 years [119], Very few asymptomatic recurrences are detected by vaginal cytology.[121]Measurement of CA125 should be done in patients with elevated levels at the time of diagnosis or with known extrauterine disease. [122, 123]Chest x-ray every 12 months is an important method of post treatment follow up. Almost one half of all asymptomatic recurrences are detected by chest x-ray. Other radiologic studies, such as intravenous pyelography and CT scans, are not indicated for routine follow-up of patients who do not have symptoms. [119]

**Recurrent Endometrial Cancer**

Approximately 22% of treated endometrial cancer patients die within 5 years. [7] About one fourth of patients treated for early endometrial cancer develop recurrent disease. More than one half of the recurrences develop within 2 years, and about three fourths occur within 3 years of initial treatment. Vaginal bleeding was the most common symptom associated with local recurrence, and pelvic pain was most often present with pelvic recurrence. [119, 124]

## Isolated Vaginal Recurrence

Isolated vaginal metastases are the most amenable to therapy with curative intent. A CT scan should be done before the treatment to exclude systemic spread. [89]

Treatment of isolated vaginal recurrence includes High-dose-rate brachytherapy usually combined with external-beam therapy. For bulky lesions (>4 cm diameter), surgical resection before radiation may improve local control. Laparotomy has the advantage of allowing a thorough exploration of the pelvis and abdomen to exclude other metastatic foci. Exploratory laparotomy with some type of pelvic exenteration is the only line of management for patients who have had prior pelvic irradiation. [124, 125]

## Systemic Recurrence: Role of Surgery

Surgery usually combined with radiation, chemotherapy, or hormonal therapy may play a role in selected patients with recurrent endometrial cancer, particularly if all residual

disease can be resected.[126, 127]Patients with isolated recurrence at any site (e.g., lymph nodes, liver or lung) and had long disease-free interval (>2 years) should be planned for surgical resection as long as the patient is medically fit and the surgery is technically feasible.[126, 127]

## Role of Hormonal Therapy

Progestational agents have been used successfully as treatment for patients with advanced or recurrent endometrial cancer. Although parenteral administration has been used, oral administration is equally effective. [128, 129]

The GOG concluded that 200 mg per day of medroxy progesterone acetate (MPA) was a reasonable initial approach to the treatment of advanced or recurrent endometrial cancer, particularly for patients whose tumors were well differentiated or PR positive with 25% response rate. Patients with poorly differentiated or PR negative tumors had only an 8% to 9% response rate. Treatment should be continued for as long as there is an objective response. [130]

The first-generation selective estrogen response modulator (SERM) tamoxifen has also been used to treat patients with recurrent endometrial cancer. Responses are usually seen in patients who have previously responded to progestins, but an occasional response may occur in a patient who is unresponsive to them. Tamoxifen may be administered orally in a dose of 10 to 20 mg twice daily and continued for as long as the disease is responding. [128, 131]

The third-generation SERM arzoxifene has been evaluated in patients with advanced or recurrent endometrial cancer. The drug was administered orally in a dose of 20 mg per day, and toxicity was minimal. [132]

## Role of Cytotoxic Chemotherapy

Cytotoxic chemotherapy for endometrial cancer is considered as palliative treatment, and responses are generally disappointing and of short duration. Many women with endometrial cancer are elderly and have other comorbidities such as obesity, diabetes mellitus, cardiovascular disease and they may have had pelvic irradiation with limited hematological reserve. All of these factors have to be taken into consideration when making the plan of treatment, but chemotherapy should be considered in patients with a good performance status. [133-136]

The most active chemotherapeutic agents are doxorubicin, the platinum compounds cisplatin and carboplatin [137], and paclitaxel (Taxol). Alkylating agents such as cyclophosphamide and melphalan, fluorouracil, altretamine (hexamethylmelamine) [138], liposomal doxorubicin [139], and topotecan [140, 141] have shown activity against endometrial cancer. Most responses obtained with use of these agents have been partial, generally averaging only 3 to 6 months, with the median survival time ranging from 4 to 8 months. [141]

Combination chemotherapy regimens employing doxorubicin and cisplatin [100,142-143]; cyclophosphamide, doxorubicin, and cisplatin [144] paclitaxel and cisplatin with or without doxorubicin [145-147]; and carboplatin and paclitaxel [148-150] have resulted in

response rates ranging from 38% to 76%. Despite these fairly impressive response rates, most responses have been partial, with durations of 4 to 8 months, and the median survival time has generally been less than 12 months. [151, 152]

# Prognosis

There is different survival data provided by different individual institutions, the most comprehensive survival data are provided in the Annual Report on the Results of Treatment in Gynecological Cancer (Table IV) [7]Concerning the survival by histological grade, patients with stage II, grade 1 and 2 tumors have a better prognosis than patients with stage I, grade 3 lesions.[7]

Survival in relation to histopathological type indicates that poor prognosis is associated with papillary serous and clear cell carcinomas. [7]

**Table (IV): Carcinoma of the Corpus Uteri: Patients Treated from 1999 to 2001; Survival Rates by FIGO Surgical Stage (n = 7,990)** [7]

| Overall Survival (%) | | | | |
|---|---|---|---|---|
| Stage | Patients | One year | 3-Year | 5-Year |
| IA | 1,054 | 98.2 | 95.3 | 90.8 |
| IB | 2,833 | 98.7 | 94.6 | 91.1 |
| IC | 1,426 | 97.5 | 89.7 | 85.4 |
| IIA | 430 | 95.2 | 89.0 | 83.3 |
| IIB | 543 | 93.5 | 80.3 | 74.2 |
| IIIA | 612 | 89.0 | 73.3 | 66.2 |
| IIIB | 80 | 73.5 | 56.7 | 49.9 |
| IIIC | 356 | 89.9 | 66.3 | 57.3 |
| IVA | 49 | 63.4 | 34.4 | 25.5 |
| IVB | 206 | 59.5 | 29.0 | 20.1 |

## Lymphangiogenesis of endometrial adenocarcinoma

Tumor cell dissemination is mediated by several mechanisms, including local invasion, lymphatic or hematogenous spread, and direct seeding of body cavities or surfaces. Clinical and pathological observations suggest that for many carcinomas, transport of tumor cells via lymphatics to regional lymph nodes is a common pathway of initial dissemination, with patterns of spread via afferent lymphatics following routes of natural drainage. [153, 154]

Assessment of metastases that proceeds via the lymphatic system to regional LNs plays a crucial role in the management of gynecological malignancy. The pelvic lymphatics are comprised of six nodal systems these include the common, external and internal iliac LNs, as well as the obturator nodes. Pre-sacral and parametrial LNs are also included. (As shown in figure 2) [67, 155]. The incidence of pelvic LN metastasis is more frequent than para-aortic LN

metastasis in endometrial cancer and the incidence increases with the stage of disease, ranging from 0%–30% in early stage disease (stage I–II) to more than 45% in advanced stages (stages III and IV). [67] Surgical evaluation of these LNs is therefore required for precise management and may result in modification of diagnosis, prognosis and management of these patients if metastases are discovered. [155, 156]

However, despite the major role for the lymphatics in the initial spread of cancers, little is known about the mechanisms whereby tumor cells enter the lymphatic system [157, 158] and whether nodal metastasis is dependent on tumor-induced lymphangiogenesis or invasion of preexisting lymphatic vessels. [157]

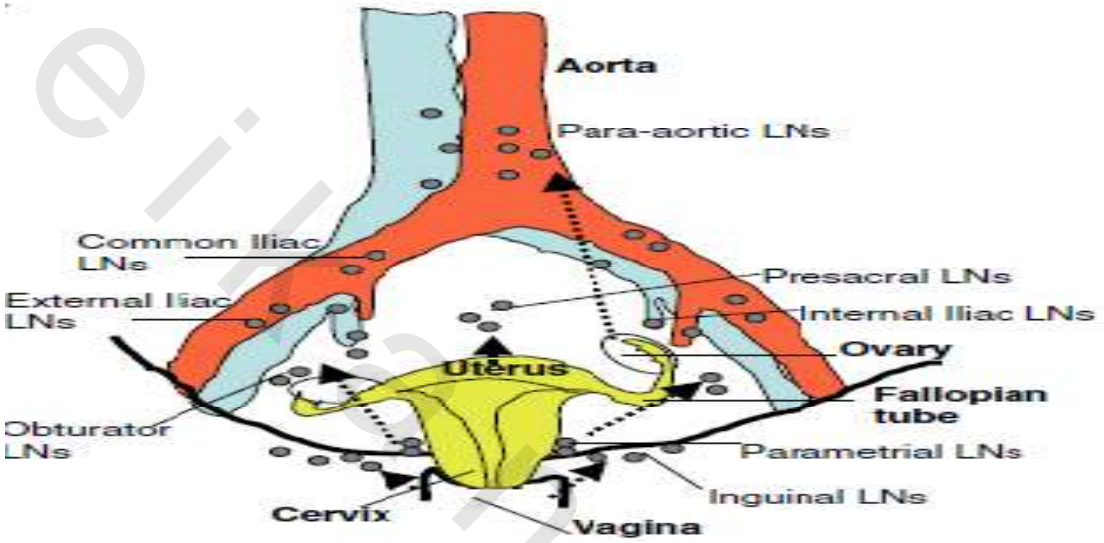


**Figure (2):** Pelvic lymph node (LN) groups include parametrial, obturator, presacral, internal iliac, external iliac and common iliac LNs; para-aortic LNs are found higher up around the aorta; dotted arrows reflect the pattern of lymphatic spread in gynecological cancers. [155]

Tumor angiogenesis, i.e. formation of new blood vessels associated with a neoplasm, is essential for tumor growth and metastases and is regarded as one of the most important events occurring in the neoplastic process. [159-162]The number of microvessels within the tumor has been reported to influence the clinical outcome of patients with a variety of gynecological malignancies. [163]These vessels are structurally and functionally abnormal, with increased permeability, delayed maturation and potential for rapid proliferation. [161]These vascular defects facilitate the lympho-hematogenous spread of tumor cells. [164]

The growth of lymphatic vessels largely depends on many growth factors, such as vascular endothelial growth factor-C and –D (VEGF-C and VEGF-D), platelet derived growth factor-BB (PDGF-BB) and hepatocyte growth factor.[165]However, in cancer, these known lymphangiogenic factors lead to simultaneous stimulation of angiogenesis and lymphangiogenesis.[166] Lymphatic spread of the disease is assumed to occur through cancer cell permeation of tumor lymphatics, thus reaching the regional lymph nodes.[167, 168]However, it is unclear whether lymphatic dissemination occurs as a result of cancer cell infiltration of pre-existing lymphatic vessels or newly formed ones, originating from those of the normal surrounding tissues.[168, 169]

Lymphangiogenesis has been difficult to investigate because there was a lack of specific antibodies distinguish between blood and lymphatic vessels, which might play different roles in the progression of cancer.[170-172]

Most available endothelial markers used to assess intratumoral micro vessel density, a reflection of tumor angiogenesis, stained both lymphatic and vascular vessels without discrimination.[173]

Recently, lymphatic endothelial specific markers have become available, which facilitate analysis of lymph-angiogenesis in cancer and its evaluation through assessment of lymphatic microvascular density (LMVD) [169, 174], including vascular endothelial growth factor(VEGF) receptor 3, the transmembrane proteins LYVE-1 and podoplanin, and the transcription factor Prox-1 [154], have been used to evaluate intratumoral lymphatic vessels in solid tumors and have enabled a more precise study of the lymphatic vasculature and the molecular mechanisms involved in lymphangiogenesis .[167, 169, 175-177] Among these, podoplanin, a 38 kDa mucin-type transmembrane glycoprotein which is recognized by the monoclonal antibody D2–40, is considered the most reliable marker with a high specificity and sensitivity.[165]

Podoplanin was originally found on the surface of rat glomerular epithelial cells (podocytes) and linked to the flattening of foot processes that occurs in glomerular diseases.[178] Podoplanin shows features of a membrane mucoprotein with several conserved O-glycosylation sites and is currently of unknown biological function.[179] As heavily O-glycosylated mucoproteins have been identified as counter-receptors for selectins that mediate adhesion of inflammatory cells [180], it is possible that podoplanin plays a similar role in lymphatic endothelia.[179]

The recently developed monoclonal antibody D2-40 detects a fixation-resistant epitope on podoplanin. [181, 182] It is an IgG2a monoclonal antibody that was generated against an oncofetal membrane antigen M2A and identified in ovarian carcinoma cell lines and germ cell neoplasia.[181] D2-40 was reported to be a specific marker for lymphatic endothelium in normal and neoplastic tissue.[183]D2-40 has shown to stain endothelium of lymphatic vessels and lymphangiomas but negative in hemangiomas.[184]

LMVD has been investigated in many tumors, particularly those characterized by lymphatic dissemination, such as cervical carcinomas, but there are few studies that have evaluated LMVD in endometrial carcinomas, and results have been conflicting. [185, 186]