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Chapter 11

Adenocarcinoma of the Endometrium — The Art of Its Diagnosis

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/61578

Abstract

The diagnostic process begins at the first meeting with the patient, where we must relate the symptoms and signs associated with endometrial disease. Communication skills are fundamental for excellence in medical care. Even with the development and improvement of new technologies in recent decades, be it endoscopy, ultrasound, computed tomography or magnetic resonance imaging, the communication is also essential. We must have skills to recognize and elucidate a wide variety of signs and symptoms when we take a history and do a physical examination of the patient, where abnormal uterine bleeding is the first main sign that can lead to an early diagnosis of endometrial cancer. The endometrium, as every target organ of steroid hormones, shows involutional changes during ovarian failure. In peri-menopause, however, tissue hyperactivity stages occur with some frequency, showing a marked endometrial sensitivity to hormonal fluctuations, whether on an absolute or relative level. Irregular blood loss occurs in many women during this period, and although being most times of functional origin, it requires investigation. It is noteworthy that the most frequent cause of abnormal bleeding of organic origin in menopause is endometrial. Endometrial pathologies appear with advancing age. Therefore an appropriate workup should diagnose or rule out disease at this site. Thus, preventive measures should be adopted, such as screening and early diagnosis, and the best treatment for the patient should be established.

Keywords: Endometrial cancer, diagnosis, new technologies, staging, prognosis, treatment

1. Introduction

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Communication skills are fundamental for excellence in medical care. Even with the development and improvement of new technologies in recent decades, be it endoscopy, ultrasound, computed tomography, or magnetic resonance imaging, the communication is also essential.

We must have skills to recognize and elucidate a wide variety of signs and symptoms when we take a history and do a physical examination of the patient, where abnormal uterine bleeding is the first main sign that can lead to an early diagnosis of endometrial cancer.[1]

The endometrium, as every target organ of steroid hormones, shows involutional changes during ovarian failure. In perimenopause, however, tissue hyperactivity stages occur with some frequency, showing a marked endometrial sensitivity to hormonal fluctuations, whether on an absolute or relative level. Irregular blood loss occurs in many women during this period, and although being most times of functional origin, it requires investigation. It is noteworthy that the most frequent cause of abnormal bleeding of organic origin in menopause is endometrial. Endometrial pathologies appear with advancing age. Therefore an appropriate workup should diagnose or rule out disease at this site. Thus, preventive measures should be adopted, such as screening and early diagnosis, and the best treatment for the patient should be established.[2]

The annual incidence of endometrial carcinoma is 2 in 100,000 women under 40 years and 40 to 50 per 100,000 women between the sixth and eighth decades, and it is expected to gradually increase due to obesity and increased longevity, especially in North America and Western Europe. In Brazil, the highest incidences are in the South and Southeast regions.[3, 4] In the United States, endometrial cancer is the most common gynecologic malignancy, and it accounted for about 39,080 new cases and 7,400 deaths from cancer in 2007.[5] The signs are early and the most common is vaginal bleeding after menopause. When diagnosed early, about 80% are confined to the uterus, in the early stages, with good outcome and low mortality. In Brazil, it is the second most frequent pelvic malignancy, with an incidence of 5.7 per 100,000 women and mortality estimated at 1.6 per 100,000 women.[6] Staging of the International Federation of Gynecology and Obstetrics (FIGO), introduced in 1988 and updated in 2009, is defined by total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic lymphadenectomy, and periaortic and peritoneal cytology, where prognostic factors include age, grade and histological type of tumor, depth of invasion into the myometrium, cervical involvement, and the presence of lymph node metastases.

2. Diagnosis

The diagnosis is histological but should be considered based on the symptoms and physical examination. The main symptom is abnormal uterine bleeding. Other findings associated with the disease are: heaviness in the lower abdomen, pelvic pain, presence of pyometra, hematometra, presence of atypical glandular cells in cervical Pap smear, menorrhagia, and intermenstrual bleeding. Later symptoms are pain in the lower abdomen, foul-smelling secretion, urinary or intestinal disorders, and weight loss.

http://dx.doi.org/10.5772/61578

In postmenopausal women with uterine bleeding, premenopausal women with abnormal uterine bleeding and before hematometra and pyometra especially in older women, it is imperative to evaluate the endometrial cavity. This evaluation can be performed by blind endometrial biopsy or through hysteroscopy or curettage after gynecological examination. Endometrial biopsy is simple to perform and should be considered of value only when positive for malignancy, because it could give false-negative results. Hysteroscopy has better performance, which surpasses curettage in the diagnosis, where possible visualization of the uterine cavity leads to fewer false-negative results as curettage. If the diagnostic biopsy is atypical hyperplasia, it is necessary to evaluate the whole endometrial cavity to rule out carcinoma.

Transvaginal ultrasound in postmenopausal women, taking into account a cutoff of 5 mm endometrial thickness, has a 96% sensitivity for endometrial cancer detection. However, there is no evidence showing that the use of ultrasound in screening asymptomatic women decreases mortality.[7]

A cervical Pap smear should not be considered a screening method or diagnosis of endometrial cancer.[8] There is no indication for screening for endometrial carcinoma by any method in asymptomatic women with or without medium or high risk factors for endometrial carcinoma, such as hormone therapy with estrogen, tamoxifen users, late menopause, nulliparity, infertility or chronic anovulation, obesity, diabetes, hypertension, or metabolic syndrome. It is recommended to inform these women about the risk factors and symptoms of endometrial carcinoma, such as abnormal uterine bleeding in premenopause and any bleeding after menopause, and to advise them to seek immediate medical attention.[4, 6]

Annual screening tests by endometrial biopsy should be indicated only in women ≥35 years old, with Lynch syndrome (hereditary nonpolyposis colorectal cancer, HNPCC-II) and/or a family history of carrying the mutation in the absence of confirmation of the mutation genetics, or family history with suspicion of autosomal dominant genetic predisposition.[3, 4]

Any postmenopausal bleeding should be investigated because it is the main symptom of endometrial carcinoma, and the assessment should start with ultrasound and/or endometrial biopsy, depending on the choice and ease in carrying out the procedure. The accuracy of ultrasound as to the measurement of normal endometrial thickness of ≤4–5 mm in postmenopausal women to exclude endometrial disease is very high. If the thickness is ≤4 mm, the negative predictive value (NPV) is 99.79%, and if ≤5 mm, it is 99.47%. It is rare that a woman with endometrial thickness of <4 cm has carcinoma of the endometrium, but in the presence of endometrial thickening, there are difficulties in differentiating between benign and malignant disease. Prospective studies have shown that the risk of cancer in women with bleeding and endometrial thickness of ≤4 mm is about 1 in 1,000 women.[11, 12, 13]

Endometrial aspiration biopsy (Pipelle being the most common) has been widely used because it is done on an outpatient basis and causes little discomfort to the patient. However, there are important limitations, such as small endometrial area evaluated and very variable diagnostic sensitivity. Studies have shown a rate of false-negative results of 2.5–32.4% in Pipelle biopsies

for endometrial carcinoma, especially in tumors occupying <50% of the endometrial cavity, such as polyps.[13, 14]

Women with abnormal uterine bleeding should be investigated with ultrasound (US) and/or biopsy. In menopausal women, ultrasonographic endometrial thickness of ≤4–5 mm, and/or result in a negative aspiration biopsy for endometrial cancer or hyperplasia can be followed up, but should be targeted for further tests in the persistence of any bleeding.

The endoscopic hysteroscopy examination was introduced in 1864 by the English physician Pantaleoni, and with improvements mainly in optics, proved to be since the 1980s an excellent procedure for the diagnosis of diseases of the cervical canal and the uterine cavity.

Hysteroscopy is a procedure that every day reaches a greater importance in medical examination and therapeutic arsenals of gynecologists. This is because the necessary equipment has evolved systematically and quickly toward making the procedure more and more delicate and less traumatic. Among the many changes, we can highlight the wide use of hysteroscopic instrumental with 2.0- and 2.9-mm optics.[15]

Hysteroscopy allows the complete examination of the uterine cavity: its distention, morphology, and size; anterior and posterior wall, cones, and tubal ostia; and color, appearance, surface, vascularization, and thickness of the endometrial mucosa. Endometrial sampling is targeted, where the biopsy can be performed via hysteroscopy or immediately after the procedure.

In symptomatic patients, hysteroscopy combined with histological sampling is considered first-line in the diagnostic process; it is also for asymptomatic patients with abnormal endometrial cytology or ultrasound, or even with normal endometrial cells in cervicovaginal cytology.

A randomized study showed that women with abnormal uterine bleeding can start the investigation with ultrasound and endometrial Pipelle biopsy and only use hysteroscopy and/or curettage in a second option. A systematic review showed high diagnostic accuracy of hysteroscopy for cancer, with a sensitivity of 86.4% (95% CI, 84.0–88.6%) and specificity of 99.2% (95% CI, 99.1–99.3%). The sensitivity for diagnosis of benign endometrial pathology was 78.0% (95% CI, 76.3–79.6%), while specificity was 95.8% (95% CI, 95.6–96.1%), which would correspond to moderate accuracy. It is a safe procedure, with few complications and good diagnostic performance for endometrial carcinoma in women with abnormal uterine bleeding.[16] Another systematic review compared endometrial biopsy or hysteroscopy and dilatation and curettage (D&C) combined with endometrial cytology and demonstrated high diagnostic sensitivity of hysteroscopy with cytology, but cytology was more associated with sub-staging of the disease, compared with the biopsy or D&C. If the diagnostic biopsy revealed a precursor lesion, that is, atypical hyperplasia, it is necessary to evaluate the whole endometrial cavity to rule out carcinoma. The endometrial cavity should be examined in elderly women in the presence of hematometra and pyometra and in premenopausal women with abnormal uterine bleeding. Later symptoms are pain in the lower abdomen, foul-smelling secretion, urinary or intestinal disorders, and weight loss.[17]

http://dx.doi.org/10.5772/61578

Curettage and hysteroscopy have high diagnostic accuracy, but hysteroscopy is the method of choice for small and focal lesions such as polyps and can be performed on an outpatient basis. The diagnostic procedure chosen should be in accordance with its accessibility and the surgeon's experience. Hysteroscopy is considered by many authors as the gold standard for evaluation of the uterine cavity. This examination provides enormous benefits with hits in macroscopic visual information, especially when it identifies organic changes in polyps, submucosal fibroids, complete inactivity states, or atrophic endometrium (figure 1); it also shows a high success in states of high endometrial activity: complex hyperplasia with atypia or endometrial cancer (figure 2).

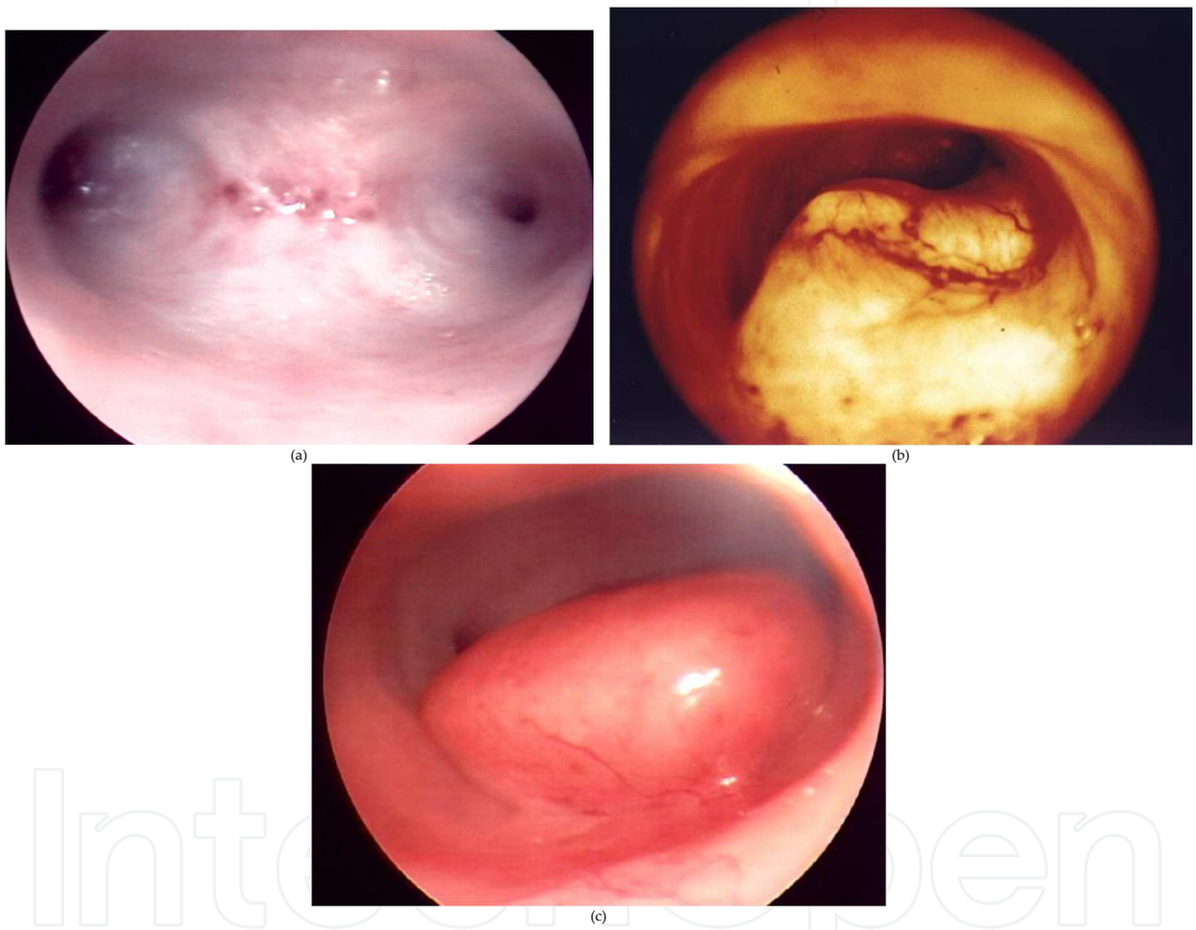
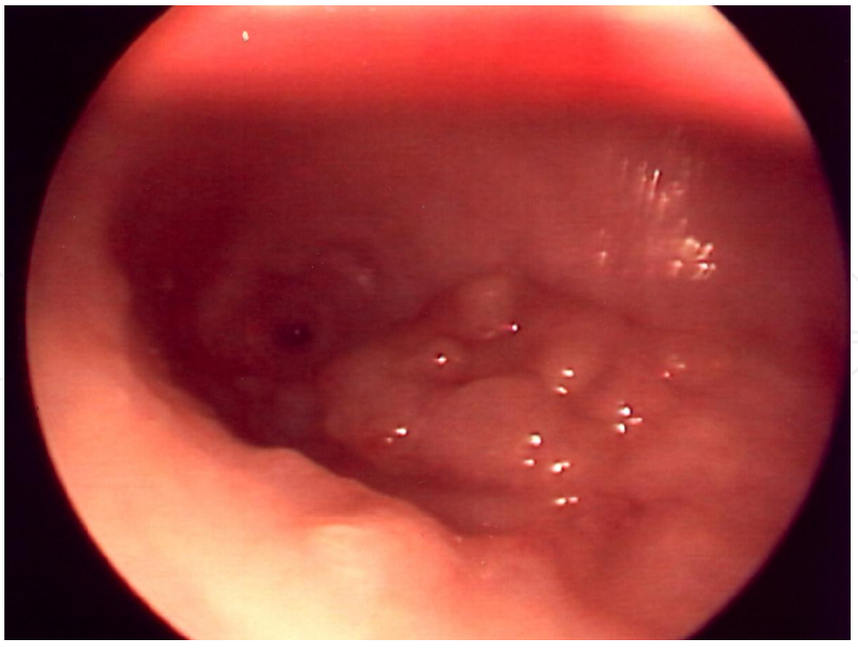
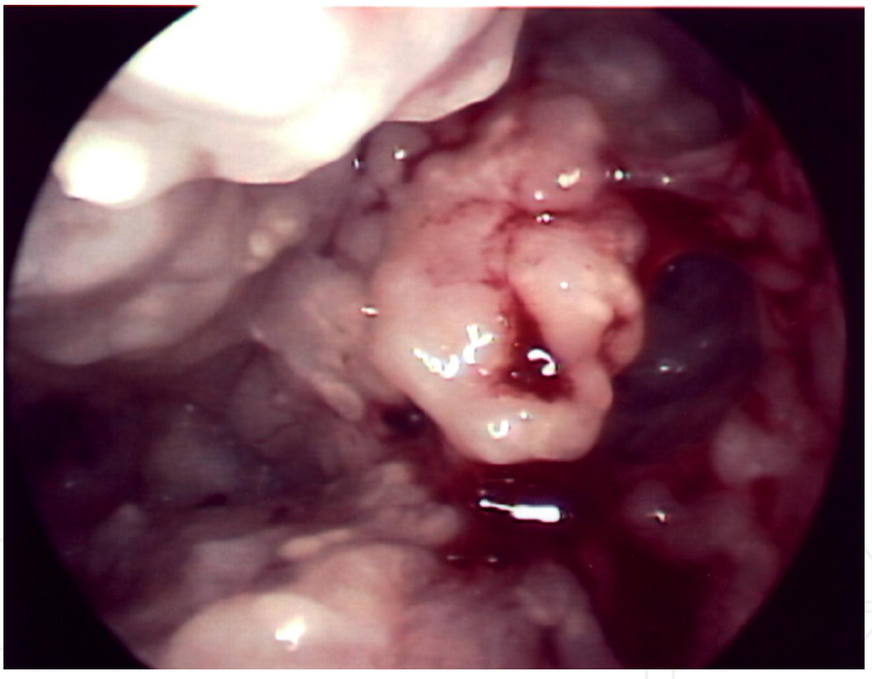


Figure 1. (a) Atrophic endometrium, (b) Submucosal fibroids, (c) Polyp

With regard to histological types, the most common is endometrioid adenocarcinoma (75–80%), where it is the most common variant of squamous differentiation. It is related to hyperestrogenism and the precursor lesion is atypical hyperplasia. Serous papilliferous (10%) and clear-cell (4%) adenocarcinomas are similar to those of the ovary and tube and may show peritoneal spread. These tumors are associated with p53 gene mutation will occur in older women, are often diagnosed at more advanced stages and have a worse prognosis. The other histological types are rarer: mucinous, squamous, and undifferentiated.[18, 19]



(a)



(b)

Figure 2. (a) Complex hyperplasia with atypia, (b) Endometrial cancer

Histological types

i. Endometrioid (70–80%)

- **a.** Ciliated adenocarcinoma
- **b.** Secretory adenocarcinoma

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c. Papillary or villoglandular adenocarcinoma

d. Adenocarcinoma with squamous differentiation:

1. Adenoacanthoma

2. Adenosquamous

ii. Serous papilliferous (<10%)

iii. Mucinous (1%)

iv. Clear cells (4%)

v. Squamous cells (<1%)

vi. Mixed (10%)

vii. Undifferentiated

Adenocarcinomas should be grouped according to histopathological differentiation grade:

G1 (well differentiated); 5% or less with nonsquamous growth pattern

G2 (moderately differentiated); 6–50% with nonsquamous growth pattern

G3 (undifferentiated); more than with nonsquamous growth pattern

When nuclear atypia is inappropriate for architectural grade, increase G1 to G2 and G2 to G3.

Adenocarcinoma with squamous component is graded by the glandular component.

3. Staging

Staging begins with a general physical examination, palpation of supraclavicular and inguinal lymph nodes, vaginal examination, and digital rectal examination, eventually done under analgesia. Sampling for cervical cancer cytology, blood tests, and chest X-ray are routine. In suspected cases of bladder or rectal invasion, cystoscopy and rectosigmoidoscopy with biopsy are indicated. If the parametrium and vagina do not show neoplastic changes, surgical staging is indicated, according to the International Federation of Gynecology and Obstetrics (FIGO) (established in 1988, revised in 2009; Table 1).[8, 9] For women undergoing radiation therapy as initial treatment, FIGO clinical staging (1971) can be used, correlating with the current. The diagnostic biopsy defines the type and histological grade (Table 2); total hysterectomy with adnexectomy defines myometrial, cervical, and adnexal invasion; and peritoneal lavage defines the presence of neoplastic cells. Endometrial ablation can be performed intraoperatively, along with a biopsy of the omentum. It is only possible to prove lymph node metastasis by conducting a pelvic and para-aortic retroperitoneal lymphadenectomy in patients with poor prognostic factors. A lymph node biopsy is indicated in the presence of enlarged lymph nodes. Retroperitoneal lymphadenectomy can increase perioperative morbidity, depending on the clinical conditions of the patient and the training of the surgical team.[10, 11]

Stage	Postoperative pathological findings
I*	Tumor confined to uterine corpus
IA*	No invasion or myometrial invasion less than 50%
IB*	Myometrial invasion less than or equal to 50%
II*	Tumor invading cervical stroma, but without extending beyond uterus**
III*	Tumor local and/or regionally spreading
IIIA*	Tumor invading serosa and/or adnexa#
IIIB*	Tumor invading vagina and/or parametrium#
IIIC*	Metastasis to pelvic and/or para-aortic lymph nodes #
IIIC1*	Positive pelvic lymph nodes
IIIC2*	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
IV*	Tumor invading bladder and/or rectal mucosa and/or distant metastases
IVA*	Tumor invading bladder and/or rectal mucosa
IVB*	Distant metastases, including intra-abdominal and/or inguinal lymph node metastases

FIGO Staging – 1988, revised in 2009 [9, 10]

* G1, G2 or G3.

** Only endocervical gland involvement should be considered as stage I and no longer as stage II.

Positive cytology should be reported separately without changing the stage.

Table 1. Surgical staging of endometrial carcinoma

Clinical examination	General physical examination
	Examination of lymphatic drainage with palpation of supraclavicular and inguinal lymph nodes
	Gynecological examination
	Rectovaginal examination with or without analgesia
Radiological examinations	Chest X-ray
Specific examinations	Endometrial biopsy
	Hysteroscopy with biopsy or curettage
	Cystoscopy*
	Rectosigmoidoscopy*
Other examinations that are not considered for staging but can be done for treatment planning	Ultrasound
	Computed tomography
	Magnetic resonance
	Positron emission tomography
	Bone scintigraphy
	Laparoscopy
	Serum CA-125

*Examinations to be requested according to symptoms and clinical signs

Table 2. Examinations to be done for staging of endometrial carcinoma

http://dx.doi.org/10.5772/61578

A meta-analysis did not find significant differences in comparing the diagnostic accuracy of ultrasound, CT, and MRI in the staging of endometrial carcinoma, noting that the use of contrast during MRI significantly improves the performance of the method. The advantage of MRI is that it can demonstrate myometrial invasion and later stages of the disease, such as extra-uterine disease. MRI and PET/CT in patients with endometrial carcinoma were similar in the diagnosis of the primary lesion (sensitivity of 91.5 vs. 89.4%, specificity of 33.3% vs. 50.5%, accuracy of 84.9 vs. 84.9%, PPV of 91.5 vs. 93.3%, and VPN of 33.3 vs. 37.5%) and also for the detection of lymph node metastasis. The main benefit of F18-FDG PET/CT is the detection, localization, and characterization of distant metastases, including extraperitoneal metastases, and in the follow-up of recurrence. Due to the high negative predictive value in detecting lymph node metastases, it may be useful in patients with surgical contraindication. Its low positive predictive value can be related to the difficulty in differentiating reactive lymph nodes after endometrial biopsy, so PET/CT cannot replace surgical staging. While PET only demonstrates the existence of the lesion, PET/CT adds anatomic location to study. Endometrial carcinoma, similar to other tumors, has a high rate of glycolysis and uptake of FDG, a radioactive glucose analogue. There is a need for prospective studies comparing the methods, including cost-benefit assessment, so as to define the true benefits of these procedures.[7, 12, 13]

It should not be routinely used in the staging and follow-up considering the need for additional studies of the method and its high cost. Consider the use in cases of surgical and high contraindication risk of distant metastases, evaluating value for money.

4. Factors associated with prognosis

Poor prognostic factors include: serous papilliferous and clear-cell histological types; GH III tumors (poorly differentiated), which have deep myometrial invasion; cervical invasion; invasion of the vascular space; positive peritoneal cytology; and adnexal invasion. The IA G1 stage shows <5% lymph node metastases and IB G2/3 shows 5–9% positive pelvic lymph nodes and 4% para-aortic lymph nodes. However, G3 tumors, deep myometrial invasion, and/or extra-uterine disease show 20–60% pelvic lymph node metastases and 10–30% of para-aortic lymph nodes. Non-endometrioid tumors account for >50% of deaths and recurrences among endometrial carcinomas.[10, 11]

The value of lymphadenectomy is to determine the patient's prognosis and to guide adjuvant therapy, but since FIGO introduced the lymphadenectomy in 1988, there have been questions about the extent of lymphadenectomy, indications, and its risk-benefit ratio. Lymphadenectomy is performed extensively in Australia and North America. A randomized study (ASTEC) by the UK Medical Research Council found no significant differences in disease-free survival and overall survival, comparing stage I – FIGO patients who underwent pelvic lymphadenectomy or just total hysterectomy with bilateral salpingo-oophorectomy without lymphadenectomy. Those subjected to lymphadenectomy had a higher rate of postoperative complications, higher incidence of advanced disease, and IIIc stage disease. It is known that

the invasion of the vascular space and positive pelvic lymph nodes are independent risk factors for metastasis in para-aortic lymph nodes (30–50% of para-aortic lymph nodes are positive in these conditions). The US National Cancer Institute's database (Surveillance, Epidemiology, and End Results program) evaluated 39,306 patients in a retrospective study comparing 12,333 with lymphadenectomy and 27,063 without lymphadenectomy and found no increase in survival in women with endometrial carcinomas of medium and high risk subjected to the procedure.[14, 17, 18]

Since FIGO staging was established in 1988 (updated in 2009), in which lymph node metastasis was categorized as IIIC, which was subdivided into IIIC1 for pelvic and lymph nodes and IIIC2 for para-aortic lymph nodes, it was suggested that pelvic lymphadenectomy be performed in patients in the early stages and the para-aortic lymphadenectomy in women with tumors with high risk of lymph node metastases, especially in the presence of positive pelvic lymph nodes, since they had clinical conditions of operability for proper staging and indication of adjuvant therapy.

Randomized studies comparing laparoscopy with laparotomy in patients with different stages of disease and variable follow-up demonstrated that the safety and efficacy of the procedures were similar and showed no significant differences in disease-free survival. However, despite not observing differences in pelvic recurrences in both groups, some reported more vaginal recurrences and laparoscopic port sites, perhaps because of increased uterine manipulation. Laparoscopy had advantages: smaller incision, better visibility of the operative field, less blood loss, less postoperative pain, faster postoperative recovery with shorter hospital stay, and faster return to normal activities without surgical limitations for obese and elderly patients. The Gynecologic Oncology Group is evaluating quality of life, disease-free survival, and overall survival in a long-term monitoring of 2616 patients, but the results of this randomized study are not yet available.[15, 16]

Laparoscopic hysterectomy is not the standard surgery for endometrial cancer. It is suggested to wait for results on survival in studies comparing laparoscopic with open surgery. It is recommended to perform laparoscopic surgeries linked to research protocols and by professionals trained in high complexity surgeries.

5. Treatment of endometrial cancer

The conventional surgical treatment of endometrial cancer is the extrafascial hysterectomy with bilateral lymphadenectomy combined or not with pelvic adnexectomy (Table 3 and Appendix). However, in the early stages, with disease limited to the uterine corpus, the role of lymphadenectomy is controversial. The results of two randomized clinical studies with patients with endometrial carcinoma in early stages showed no difference in overall survival and disease-free survival between the groups who did or did not undergo pelvic lymphadenectomy. In view of the increased morbidity that pelvic lymphadenectomy can provide and

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the lack of improvement in survival, this is not indicated in patients with endometrial carcinoma in early stages.[17, 30]

1. Stages I and II (occult)

IA G1: Only surgery. No indication of adjuvant radiotherapy.

IA G2: Surgery and high-dose brachytherapy in vaginal vault.

IA G3, IB G1/2/3, occult II, and serous papilliferous and clear-cell types: surgery and radiotherapy – pelvic teletherapy and vaginal vault brachytherapy.

The most important treatment is surgery: extensive longitudinal or wide transverse Maylard type incision, lavage sample for peritoneal cytology, inventory of the abdominal cavity with extrafascicular palpation of the pelvic and para-aortic lymph nodes, total hysterectomy (TH), bilateral salpingo-oophorectomy (BSO), and in some cases (Table 4) retroperitoneal lymph node biopsy and assessment of the omentum. Selective biopsy of lymph nodes routine is controversial, and a complete lymphadenectomy is indicated in the presence of poor prognostic factors and in women ≤70 years and only if there is no clinical or technical contraindication. The presence of metastases contraindicates extensive surgery, vaginal and/or laparoscopic, avoiding the risk of implants in the portals. The MRC ASTEC randomized study did not demonstrate therapeutic benefits in stage I patients subjected or not to pelvic lymphadenectomy.[17, 18] Biopsy of enlarged lymph nodes and discontinuation of the procedure are indicated if the trans-surgical pathology result is positive.

Adjuvant RT: in tumors with a good prognosis, the more frequent recurrence, that is vaginal, decreases.[19] The PORTEC randomized study of two groups after surgery without lymphadenectomy, pelvic RT compared with follow-up showed that RT decreased vaginal recurrences without survival benefits, and that survival after recurrence was significantly higher in the control group, that is, there was no benefit with external RT in tumors of low and intermediate risk.[19] Another randomized study was started of vaginal vault brachytherapy (brachy) in these cases.[20] RT decreases the incidence of local and regional recurrences but causes undesirable effects in 1–10% of patients, about 4% with intestinal complications, which can be greater than in those subjected to resection of lymph nodes.[21]1

2. Stage II

II G1/2/3: Surgery and radiotherapy – pelvic teletherapy and vaginal vault brachytherapy.

Surgery: TH + BSO or radical hysterectomy with BSO in selected cases, pelvic and para-aortic lymphadenectomy, peritoneal cytology, and biopsy of the omentum. The performance of MRI in the preoperative period may assist in the evaluation of resectability and rule out bladder invasion, especially in cases of indication for radical hysterectomy.

Adjuvant radiotherapy: pelvic teletherapy and high dose rate brachytherapy.

Intracavitary neoadjuvant radiotherapy and external radiotherapy: it may be indicated in cases of extensive cervical invasion and surgery should be performed 4–6 weeks after the end

of radiotherapy to reduce intraoperative and postoperative complications: TH + BSO, peritoneal cytology, and biopsy of para-aortic lymph nodes and omentum.

3. Stage III

III: Surgery and radiotherapy

Only radiotherapy

Chemotherapy or hormone therapy

Surgery: If the entire tumor is resected, para-aortic lymph nodes and omentum should be biopsied.

Adjuvant RT:

IIIA: Extending to serosa or tumor implants – Pelvic teletherapy and vaginal vault brachytherapy.

IIIB: Pelvic teletherapy and brachytherapy in the entire vagina.

IIIC: Pelvic and para-aortic lymph node teletherapy and vaginal vault brachytherapy.

Only RT:

If disease unresectable: pelvic teletherapy and brachytherapy with complementation if parametrium compromised.

Chemotherapy (CT) or hormone therapy (HT):

Hormone therapy:

- Medroxyprogesterone acetate
- Megestrol acetate
- Tamoxifen

Chemotherapy:

- Doxorubicin (60 mg/m2)
- Doxorubicin + cisplatin (50 mg/m2)
- Doxorubicin + cisplatin (50 mg/m2) + paclitaxel (170 mg/m2)

It is the main treatment for extrapelvic metastases.

G1/G2 hormone receptor positive: HT with progestins (medroxyprogesterone acetate at 50–100 mg/day or megestrol acetate at 160 mg/day). Randomized studies have not shown benefits in the use of hormone therapy in overall survival.[21] G3 or serous papillary and clear-cell tumors: GOG randomized studies demonstrated antiblastic activity with doxorubicin. Adding cisplatin to doxorubicin increases the response rate and the disease-free interval but not overall survival.[22]

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A randomized trial comparing doxorubicin + cisplatin with total abdomen RT demonstrated increased overall survival in III/IV patients with ≤2 cm postoperative residual disease and no parenchymal involvement of organs (overall survival of 5 years: 55% x 42%).[1] Doxorubicin, paclitaxel, and cisplatin + bone marrow stimulator produced 57% response compared to 34% responding with cisplatin and doxorubicin. The disease-free interval was 8.3 months vs. 5.3 months and overall survival 15.3 vs. 12.3 months. However, 39% moderate to severe neuropathy occurred.[24]

4. Stage IV and recurrent or refractory disease

IVA: Only radiotherapy

Chemotherapy or hormone therapy

IVB: Palliative radiotherapy

Chemotherapy or hormone therapy

Treatment is individualized depending on the patient's performance, location, and size of metastatic disease in addition to symptoms presented.

Radiation therapy can be used with symptomatic goal, such as for analgesic, decompressive, or hemostatic purposes. In extrapelvic metastases: chemotherapy (see stage III) or hormone therapy. In patients with G1/2 tumors, progestogens show response in 25–30% and a significant increase in survival, especially in those with pulmonary metastases. Tamoxifen (20 mg/day) may be indicated in the absence of response to progestogens.

Palliative RT is indicated in pelvic, lymph node, brain, or bone recurrence, and may be curative in isolated vaginal recurrences.

5. Special conditions

Diagnosis after hysterectomy: It is more frequent after vaginal prolapse surgeries and the greatest problem is usually not the removal of adnexa, where in these cases, the removal of adnexa and surgical staging are indicated. The adjuvant will be given in accordance with the protocol.

Inoperable patients: The most common causes of surgical contraindication are morbid obesity or severe cardiopulmonary disease. Brachytherapy can be successful in local control and can be combined with radiotherapy in the presence of recurrence or poor prognostic factors. Patients with hormone receptor-positive, G1/2 tumors, and contraindications for radiotherapy can be candidates for treatment with progestogens at high doses.

Young women: Endometrial carcinoma is unusual and is associated with hyperestrogenism, obesity, polycystic ovary syndrome, estrogen-producing tumors, or genetic mutations. A careful histological diagnosis is needed due to difficulty in differential diagnosis between atypical hyperplasia and well-differentiated endometrioid carcinomas. In the case of nulliparous patients ≤35 years and wishing to preserve fertility, there must be interdisciplinary discussion with psychological evaluation and signed informed consent is essential, when

conventional treatment is not done (HT + SOB). Non-surgical treatment using high doses of progestogens and subsequent pregnancy has been described in the literature.

Stage	Clinical picture	Treatment
IA G1	Tumor limited to endometrium and/or <50% myometrial invasion Well differentiated	TH + BSO + PERITONEAL CYTOLOGY, biopsy of enlarged lymph nodes
IA G2 IA G1/2	≤50% myometrial invasion Well and moderately differentiated	TH+ BSO + PERITONEAL CYTOLOGY, biopsy of enlarged lymph nodes, vaginal vault Brachy
IA G3 IB G1/2/3	Tumors poorly differentiated and limited to uterine corpus Invasion "/>50% myometrium, without invading serosa	TH + BSO + PERITONEAL CYTOLOGY, pelvic, and para-aortic lymphadenectomy or biopsy of enlarged lymph nodes and omentum RT (Tele + Brachy, only Brachy)
I A/B Non-endometrioid tumors	Serous-papilliferous and clear-cell tumors limited to uterine corpus, without invading serosa	TH + BSO + PERITONEAL CYTOLOGY, pelvic, and para-aortic lymphadenectomy or biopsy of enlarged lymph nodes and omentum RT (Tele + Brachy) CT
II	Tumor invades cervix without extra-uterine disease: involves endocervical glands	TH + BSO + PERITONEAL CYTOLOGY, pelvic and para-aortic lymphadenectomy or biopsy of enlarged lymph nodes and omentum RT (Tele + Brachy)
II	Tumor invades cervix without extra-uterine disease: involves cervical stroma	TH or radical hysterectomy + BSO + PERITONEAL CYTOLOGY, pelvic and para-aortic lymphadenectomy or biopsy of enlarged lymph nodes and omentum or TH + BSO + PERITONEAL CYTOLOGY, biopsy de para-aortic and enlarged lymph nodes and omentum RT (Tele + Brachy) If preoperative RT: RT (Tele + Brachy) + TH + BSO + PERITONEAL CYTOLOGY, biopsy of para-aortic and enlarged lymph nodes and omentum
IIIA	Involvement of serosa or adnexa or positive PERITONEAL CYTOLOGY	TH + BSO + PERITONEAL CYTOLOGY, biopsy of para-aortic and enlarged lymph nodes and omentum RT (Tele + Brachy) CT or TH
IIIB	Vaginal involvement	RT (Tele + Brachy of entire vagina) CT or hormone therapy
IIIC (1 and 2)	Metastases to pelvic and/or para-aortic lymph nodes and/or parametria	If tumor resectable: surgery and RT If tumor resectable: RT only

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Stage	Clinical picture	Treatment
		CT or hormone therapy
IVA/B	Rectal/vaginal or distant metastases	RT
		CT or palliative hormone therapy

High-dose vaginal vault brachytherapy (Brachy): 5 fractions of 700 cGy.

Teletherapy (Tele): 4500 cGy and high-dose brachy: 4 X 400 cGy.

Preoperative RT-intracavitary Brachy: 2 X 750 cGy and Tele: 4500 cGy

Brachy: 4 X 500 cGy of entire vagina.

IIIC – Tele: 4500 cGy pelvic, 4500 cGy/180 cGy para-aortic + Brachy: 4 X 400 cGy.

Only RT: Tele 4500 cGy pelvic, Brachy 4 X 700 cGy and complementation if parametria compromised 1440/180 cGy.

IVA – Only Tele: 5040 cGy pelvic and "boost" 1980 cGy/180 cGy.

Table 3. Treatment algorithm for endometrial carcinoma

6. Radiotherapy

The PORTEC1 study showed that patients with early carcinomas undergoing RT had significantly more complications than those without RT (25% vs. 6%) and that 1/3 of complications were severe. The recurrence rate was significantly higher in the control group (14% vs. 4%), with only vaginal in 73%, and overall survival was similar in the two groups. There is no indication of RT in women with low-risk carcinomas undergoing surgery. The results of a systematic review and meta-analysis by ASTEC/EN.5 contraindicate routine adjuvant RT in endometrial carcinomas of medium and high initial risk: (FIGO 2009) IA G3, IB G1/2/3, serous papillary and-clear cell tumors, regardless of stage and histologic grade. The benefit in the prevention of isolated local recurrence was small and the side effects of treatment were not negligible. Due to the high acute toxicity and its long-term use, even compared with brachytherapy, RT must not be the treatment of choice only for preventing local recurrence. In the study, women after surgery were randomized into two groups, with and without RT, and each group was randomized to receive brachytherapy or not, which was applied in 53% of them. Disease-free survival (R 1.05; 95% CI 0.75–1.48; p = 0.77) and overall survival after 5 years (R 1.04; 95% CI 0.84–1.29) was similar and 5-year survival was 84%. The cumulative incidence of vaginal recurrence was 6.1% without RT and 3.2% with RT, with an absolute difference of 2.9% (95% CI <0.1%–5.9%). Local recurrence was 6.1% among those who received brachytherapy alone, which was associated with lower toxicity and could be the treatment of choice to prevent local recurrence. RT with or without brachytherapy should be indicated for patients without clinical conditions for surgery or with incomplete surgical treatment. PORTEC2, a multicenter randomized study compares RT with brachytherapy and can advise on the best choice of adjuvant

treatment in early carcinomas. Since RT does not prevent distant metastasis, women with poor prognosis tumors may be candidates for study protocols for systemic treatment.[25, 26]

RT decreases locoregional recurrences but does not affect overall survival. There is no indication for adjuvant RT in early carcinomas in the absence of risk factors for metastasis after staging surgery. In the presence of risk factors and after staging surgery, the indication for RT with or without brachytherapy or brachytherapy only should follow protocols of each service. RT with or without brachytherapy should be indicated for patients unsuitable for surgery or with incomplete surgical treatment.[25, 26]

Patients with high risk endometrial carcinoma, FIGO 2009 IBG3, IIG3 with myometrial invasion >50%, and III receive adjuvant therapy after surgery, but it is not clear which is better: CT or RT. A randomized study compared chemotherapy (cisplatin, doxorubicin, and cyclophosphamide) and RT for high-risk tumors and failed to show any difference between treatments with respect to increase in disease-free survival and overall survival. RT delayed local recurrences and CT distant recurrences, but without significant differences, and both treatments were well tolerated. It is expected that randomized trials combining pelvic RT with CT can demonstrate better results. The systematic review compared chemotherapy with other treatments in patients with advanced disease, recurrent or metastatic, and demonstrated that there was a significant increase in disease-free survival but not overall survival when using high-dose chemotherapy compared with lower doses. Toxicity was proportional to drug dose, with high dose producing grade 3 and 4 myelosuppression and increased gastrointestinal toxicity. The addition of anthracyclines (e.g., doxorubicin) or taxanes (e.g., paclitaxel) to cisplatin increased the response rate and are still the most promising drugs. Stage III/IV patients undergoing cytoreductive surgery, who were treated with cisplatin with doxorubicin, showed a significant increase in disease-free survival and overall survival compared with total abdominal RT with reinforcement in the pelvis. A randomized phase III study with paclitaxel combined with cisplatin and doxorubicin after surgery and RT showed no increase in disease-free survival and increased toxicity. Studies are needed evaluating the effect of chemotherapy on symptoms and its impact on quality of life in these women.[27, 28, 29]

Adjuvant CT in the early stages should be indicated according to research protocols of services, and there is indication in and stages III and IV, considering risk-benefit ratio.

7. Hormone therapy

There is no indication for adjuvant hormone therapy in early endometrial carcinomas. There may be indication for progestational agents for tumors that are advanced stage III/IV, unresectable or recurrent and hormone receptor-positive, usually histological grade 1 and 2. The most commonly used agent is medroxyprogesterone acetate at 200 mg/day. There are few studies and they show difficulties in evaluating the results because they generally involve patients with clinical conditions and contraindication for other types of treatment. The systematic review showed no increase in overall survival with progestins therapy (OR 1.05, 95% CI 0.88-1.24). There was a reduction in endometrial cancer mortality (OR 0.88, 95% CI

http://dx.doi.org/10.5772/61578

0.7-1.1) and recurrence of the disease (OR 0.82 95% CI 1.02-1.01), but death from other causes such as thromboembolism, stroke, and heart failure was more common in women treated with progestogens (OR 1.33 95% CI 01.02-1.73). No indication of palliative hormonal therapy in advanced tumors.[30]

There is no indication of adjuvant hormone therapy, only palliative in advanced tumors, considering risk-benefit ratio.

8. Follow-up after treatment

In the literature, there is no evidence that routine follow-up of asymptomatic patients with imaging is better than requesting it only in symptomatic patients and according to symptoms. Patients should have or do:

- Clinical, gynecological, and rectal examination 4/4 months for 2 years and every 6 months up to 5 years
- Chest X-ray and annual abdominal/vaginal US for 3 years
- Mammography (MG) and annual cancer cytology (CC)

After differentiated follow-up, all should have annual clinical and gynecological examinations, CC sampling, and MG. Other imaging tests would be requested in accordance with symptoms and/or abnormal physical examination.

- The majority of recurrences occur within the first 3 years after treatment, and it is recommended to make doctor visits quarterly or tri-annually for general history directed at symptoms of recurrence, routine physical and pelvic-rectal examinations, mainly for the diagnosis of vaginal or pelvic recurrence, which shows favorable treatment response. After this period, the visits may be semi-annual up to 5 years and then annually. Patients should be informed about the potential adverse effects of RT and the need for diagnosis if experiencing symptoms of recurrence. Further examinations should be requested in accordance with symptoms or abnormal tests, because there is no evidence that the ordering tests (cytology, chest radiography, abdominal US, CT, and Ca 125) reduce mortality. The amended CC was associated with clinical examination or suggestive of vaginal recurrence. Patients with low-risk carcinomas may have biannual routine controls, but many patients find that routine visits provide a beneficial psychological effect. The request for mammography and Pap smear should follow the screening guidelines for breast and cervical cancer. For patients at risk for colon cancer, colonoscopy should be ordered and the need for upper digestive endoscopy assessed.[31, 32]

There is no evidence that follow-up with supplementary tests in asymptomatic women and normal examination reduce mortality. Periodic doctor visits up to 3 years with anamnesis directed according to symptoms and abnormal examination are recommended. Some services suggest chest X-ray and annual abdominal/vaginal US for up to 3 years.

9. Conclusion

The period in which the endometrial mucosa should be under close and careful vigilance is menopause, both in regard to prevention and early diagnosis of its pathologies. At this stage, it is a frequent site of pathologies causing abnormal bleeding, and while myometrial changes decrease in frequency with age after menopause, endometrial changes increase, reaching a plateau or decreasing after 80 years.

The search for early diagnosis starts with a detailed history and physical examination, assessing the differentially symptomatic and asymptomatic patients with risk factors. Transvaginal ultrasound can help in this step, but we preferably use hysteroscopy combined with endometrial sampling when there is indication for evaluation of the uterine cavity.

Most tumors are diagnosed in early stages and have a good outcome because of early symptoms. The standard treatment is surgery including lymph node evaluation, combined with radiotherapy. Considering that radiotherapy decreases local recurrence but does not influence survival, chemotherapy has been used in study protocols for tumors with poorer prognosis.

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