Endometrial Cancer

GYNE/ONC Practice Guideline

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This guideline is a statement of consensus of the Gynecologic Oncology Disease Site Team regarding their views of currently accepted approaches to treatment. It is not intended to replace the independent medical judgment of the physician in the context of individual clinical circumstances to determine any patient's care or treatment.

Background & Incidence

Endometrial cancer is the most common gynaecologic malignancy. One in 42 Canadian women is affected by endometrial cancer; one in 175 is expected to die from it. It is the fourth most common cancer and the eighth leading cancer causing death among Canadian women. The peak age range at diagnosis is between 60 and 79 years, the average age at diagnosis is 63 years.

Canadian Cancer Statistics for 2010, estimate that there will be 4,500 new cases of endometrial cancer with 790 deaths. Survival is dependent on stage of cancer at initial presentation; early stage disease has a 5-year survival rate of 83% and advanced stage disease, a survival rate of 26%. Unfortunately, the incidence of endometrial cancer is increasing over time in Canada, currently to 19 cases per 100,000 women per year.

The risk of endometrial cancer increases when the balance of female hormones shifts toward relatively more estrogens. Because fat tissue can change some hormones into estrogens, being overweight increases a women's risk by two to threefold. Associated with obesity, high dietary fat, diabetes and hypertension convey an increased risk of endometrial cancer as well.

Clinical Assessment of a Patient with Suspected Endometrial Cancer

Most patients with endometrial carcinoma present with abnormal vaginal bleeding, commonly in the post-menopausal period.

At a primary care level testing and procedures that a patient should undergo prior to referral are:

- History & physical
- Blood work (CBC, Chemistry, INR/PTT)
- Endometrial biopsy or referral to gynaecologist for biopsy

Diagnosis can often be made by an outpatient endometrial biopsy although there is a false negative rate of approximately 10%. A negative endometrial biopsy in a symptomatic patient warrants curettage under anaesthesia. An alternative approach, in patients considered high risk for anaesthesia, would be an ultrasound to measure endometrial thickness. When cervix involvement is suspected, cervical biopsy and/or MRI should be considered. Cervical cytology should be assessed.

When clinical symptoms, physical findings or laboratory findings warrant, additional investigations that may be carried out at the discretion of the specialist to rule out extra uterine involvement are:

- Abdominal/pelvic ultrasound and/or CT/MRI
- Cystoscopy and/or sigmoidoscopy
- CA125 assay.

Referral to a Gynecologic Oncologist:

- If preoperative histology such as Grade 3, papillary serous, clear cell or carcinosarcoma is found, suggestive of a greater risk of extra uterine spread
- If final pathology reveals an unexpected endometrial cancer following a hysterectomy for other reasons
- If there is evidence of cervical or extra uterine disease
- If pelvic washings contain malignant cells
- For diagnosis or suspicion of recurrent disease
- For consideration of non-surgical treatment

Surgical Treatment and Surgical Staging

The standard treatment for the majority of patients with endometrial cancer is hysterectomy, bilateral salpingo-oophorectomy with or without surgical staging.

At the preoperative consultation, the gynecologic oncologist should consider referring back to the general obstetrician gynecologist patients with clinical stage I, grade 1 endometrial cancer, where the risk of pelvic lymph node involvement is low, and the risks of lymphadenectomy may outweigh the benefits. However if the gynecologic oncologist elects to perform the surgery for patients with low grade endometrial cancer, s/he should consider surgical staging if deep myometrial invasion is suspected in the surgical specimen, to justify using gynecologic oncology surgical time for cases that could otherwise be treated in the community. Patients with grade 2 or grade 3 endometrioid adenocarcinoma or high risk histology, that is clear cell or papillary serous adenocarcinoma, on endometrial biopsy or curettage, should have their pathology reviewed in the tertiary care center whenever possible. If the grade or histological type is confirmed, the rationale for and against, and the risks and benefits of surgical staging and lymphadenectomy should be discussed by the gynecologic oncologist during the preoperative consultation and documented.

The following points should be discussed with the patient. The risk of pelvic lymph node metastases will be in the range of 5% to 34%, and half of that for para-aortic lymph nodes. If lymph nodes are positive for metastatic cancer then systemic chemotherapy with paclitaxel and carboplatin chemotherapy may result in a modest improvement in survival. If the lymph nodes are negative for metastases, then the prognosis is much better so that chemotherapy and external beam radiation therapy may be withheld, unless the patient is a candidate for, and elects to participate in a clinical trial of adjuvant therapy based on uterine risk factors. Negative lymph nodes do not guarantee a cure, however the likelihood of recurrence is much lower. Conversely patients with low risk features in the uterus, who would otherwise not be considered for adjuvant treatment, may benefit from adjuvant treatment, including chemotherapy, if a lymphadenectomy showed evidence of metastatic disease. Pelvic lymphadenectomy is associated with a 2% to 3% risk of chronic unremitting lymph edema in the lower extremities. With this information as part of the informed consent, patients should be

given the opportunity to participate in the decision as to whether or not they would like to proceed with staging lymphadenectomy.

Intraoperatively the gynecologic surgeon should consider opening the uterus to assess depth of invasion into the myometrium, with the understanding that gross examination may underestimate or overestimate depth of invasion. For patients with disease confined to the uterine fundus, or clinical stage I, who are not morbidly obese or compromised by severe medical co-morbidities, and based on preoperative grade and estimated depth of invasion, the following algorithm is appropriate for consideration of surgical staging:

Grade 1 and 2, no myometrial invasion: no surgical staging
Grade 1 and 2, with superficial myometrial invasion: surgical staging optional
Grade 1 and 2 with deep (>50%) myometrial invasion: consider surgical staging
Grade 3, papillary serous and clear cell carcinoma: surgical staging is indicated.

Surgical staging should include resection of pelvic nodes along the external iliac artery from the common iliac artery bifurcation to the circumflex iliac vein, along the internal iliac artery and obturator fossa. The dissection should aim to sample a minimum of 11 pelvic lymph nodes. If there is grade 3 disease, clear cell or papillary serous histology, gross adnexal involvement or grossly positive pelvic nodes, the para-aortic or pre-caval nodes should be sampled. Staging should include biopsy of any suspicious peritoneal lesion and omentectomy or omental biopsy for high risk histological types.

Surgery for advanced endometrial cancer:

In patients with clinical stage II disease where the cervix is clinically involved by non bulky tumour, the options include a radical hysterectomy, bilateral salpingo-oophorectomy, with pelvic and para-aortic lymphadenectomy if the patient is a suitable surgical candidate. Alternatively the patient may be treated with a simple hysterectomy, bilateral salpingo-oophorectomy and staging, with decision for adjuvant treatment based on final pathology. If the patient has bulky cervical disease, preoperative radiation therapy followed by a simple hysterectomy and bilateral salpingo-oophorectomy is an alternative option. If there is stage III disease based on vaginal metastases, treatment should be individualized based on the size and location of vaginal metastases between primary surgery and preoperative irradiation followed by surgery. If there is advanced intra-abdominal tumour at surgery, with extension to the ovaries, omentum, peritoneal surfaces, or gastrointestinal tract, an effort at surgical cytoreduction or debulking should be attempted and individualized to the extent that in can be safely performed.

Surgical approach to hysterectomy in endometrial carcinoma:

The standard approach to total hysterectomy and bilateral salpingo-oophorectomy for endometrial cancer has been by laparotomy through a midline incision. The alternative approach by minimally invasive surgery has the potential to reduce hospital stay and patient morbidity, and shorten the recovery time. When feasible, laparoscopically

assisted bilateral salpingo-oophorectomy and vaginal hysterectomy, and if appropriate staging lymphadenectomy should be considered and discussed with the patient. There is ample evidence that the oncologic outcome of patients treated with minimally invasive surgery is equivalent to those managed with laparotomy. In selected cases of morbid obesity or severely compromised cardiorespiratory impairment, where the risks of a laparotomy are substantial, and with specific patient counseling, a vaginal approach to hysterectomy and bilateral salpingo-oophorectomy, with the possibility that the ovaries and fallopian tubes may not be removed, can be considered. The risk of metastases to the ovaries/fallopian tubes in endometrial carcinoma is in the realm of 3%. If the patient accepts this risk and a vaginal hysterectomy is feasible, then this approach may be undertaken.

Radiation Therapy

The use of adjuvant radiotherapy for women with endometrial cancer is based on the estimated risk of recurrent disease and is one of the most controversial areas in gynecologic oncology. The risk of local failure is determined from pathologic assessment of the hysterectomy specimen. This takes into account the depth of invasion in the uterus (endometrium alone, inner half or outer half of myometrium), involvement of the cervical stroma and margins (vaginal, parametrial). The primary information in decision-making for radiotherapy obtained by surgical staging over hysterectomy alone is the status of lymph nodes. Without this information, an estimate is made of there being occult disease in pelvic lymph nodes and the benefits of adding external beam radiation. Individual FIGO staging can contain patients whose diseases are associated with vastly different patterns of failure and prognosis. Recent changes in the FIGO system have also changed the staging classification significantly. Characteristics such as age, histologic grade, lymphovascular space invasion, tumour volume, and extent of surgical staging are also used in part to determine subgroup risk classifications to tailor our management for these individuals.

No Radiation Therapy

The risk of pelvic recurrence in patients with grade 1 or 2 endometrial cancer, without myometrial invasion is very low (2-10%), with <5% risk of lymph node involvement. Adjuvant RT (either external beam or brachytherapy) is therefore not warranted in patients having these pathologic features. Low intermediate risk disease can be defined as endometrioid histology, with no LVSI and confined to the endometrium or less than 50% myometrial invasion AND grade 1 or 2 histology. These patients have a low risk of relapse, and a high chance of cure without any further therapy. Balancing the risk/benefit ratio of treatment, adjuvant therapy is not warranted in this patient group.

Brachytherapy

A group of patients with high intermediate risk (HIR) disease has been identified by different investigators based on criteria that differ slightly from one group to another. A commonly used classification uses three high risk factors: grade 3, outer one third

myometrial invasion, and lymphovascular space invasion. HIR includes patients age 70 and above with one risk factor, age 50 and above with two risk factors, and any age with three risk factors. Patients with HIR disease should be considered candidates for vaginal brachytherapy rather than external beam radiation therapy based on risk of recurrence and toxicity. Vaginal brachytherapy (VB) alone is a reasonable choice for most patients with uterine confined endometrial cancer who are deemed candidates for adjuvant radiotherapy. These would include those in the low and high intermediate risk groups for which observation is not sufficient.

External Beam Radiation without or without Brachytherapy (no Chemotherapy)

Several randomized control trials have shown that in a selected group of patients with early endometrial cancer, the addition of pelvic EBRT after surgery reduces the rate of loco regional recurrence without an overall survival benefit. This approach has been associated with an increase in gastro-intestinal toxicity and a decreased quality of life. In patients who have negative surgical staging, adjuvant external beam radiation therapy may still be considered if there are high risk prognostic factors (e.g. deep invasion, high grade, LVSI and/or suboptimal lymph node sampling). Surgically staged women aged 70 or more with one above risk factor, aged 50 or more with two risk factors and any age with three risk factors may benefit from EBRT. Published studies do not address the treatment of all Stage I and II patients. This includes unstaged patients; stage IIB, stage IC (grade 1 or 2) with LVSI and surgically staged patients IC or II who are less than 50 years of age. We favour the use of adjuvant RT for such patients, which may consist of EBRT and/or VB. There is also a judgment required whether an adequate staging procedure has been done or what to do in cases where the presence of multifocal LVSI raises the risk of recurrence despite negative nodes sampled.

Using Brachytherapy with External Beam Radiation

There is not much data available in the literature to support the use of combined VB with pelvic EBRT. Yet there is a rationale to use this approach. In most of clinical trials assessing the value of adjuvant pelvic radiation (EBRT only) for patients with endometrial cancer, the dose was in the range of 50 Gy. An alternative strategy is to limit the dose of external beam radiation to 45 Gy to minimize gastro-intestinal toxicity and to combine to the external beam radiation with VB for those patients deemed at risk for vaginal recurrence (e.g. deep myometrial invasion, cervical stromal involvement).

Radiation Integrated with Chemotherapy

A multidisciplinary team discussion is helpful in deciding on the post-operative management of patients with endometrial cancer in cases where evidence is inconclusive. Enrolment in clinical trials when available is recommended.
We define “locally advanced” as meaning Stage III and IVa disease (FIGO 2009 Uterine Cancer Staging) irrespective of histology. The following section refers to adjuvant therapy for women who have undergone a hysterectomy, bilateral salpingo-

oophorectomy, and a surgical staging procedure (which generally includes pelvic and para-aortic nodal sampling, omental biopsy and selected biopsies of suspicious areas and peritoneal washings) and are diagnosed with stage III or IVA disease. Adjuvant radiotherapy has been used alone historically (pelvic, extended field or whole abdomen) and is associated with high rates of distant failure and death in this patient group. However, there are select patients treated with limited nodal disease who have been cured with radiotherapy alone. With obvious room for improvement, chemotherapy has been increasingly used in the adjuvant setting. Given the favourable side effect profile and response rates with carboplatin and paclitaxel chemotherapy from use in ovarian cancer, this combination has become the most common choice for locally advanced endometrial cancer. With adjuvant pelvic radiation alone, pelvic control rates are reasonable, but the problem is upper abdominal and distant failures. Chemotherapy is thought to better address the issue of disease in these sites. However, pelvic failure rates remain significant with chemotherapy alone. Therefore, multimodality treatment with chemotherapy and radiation may offer an advantage with better pelvic disease control if toxicity is acceptable.

Whole abdomen radiation has generally fallen out of favor. “Involved field” radiotherapy, where radiation is given to areas of known disease can provide good disease control rates in select patients. However when used routinely alone in all Stage III/IV patients, upper abdominal and distant failure become an issue. Radiotherapy should be delivered to sites of suspected microscopic or gross disease often described as the Clinical Target Volume (CTV) or Gross Tumour Volume (GTV). Vaginal cuff brachytherapy treats a very small volume of tissue (generally the upper vagina and extending less than 1cm beyond the mucosal surface). In order to adequately treat a proper CTV, external beam radiation is usually required. The defined treatment volume will depend on several factors, including the extent of the surgical procedure, distribution of disease and patient factors. Treatment volumes may range from “limited” pelvic field, whole pelvis or extended fields that include a portion of the para-aortic nodes. External beam doses are in the range of 4500-5040 cGy using 180-200 cGy daily fractions. Vaginal cuff brachytherapy is often used in combination with external beam.

Systemic Therapy as Adjuvant Therapy for Resected Endometrial Cancer

The use of combination therapy has theoretical advantages in cases of resected advanced endometrial cancer. Published and ongoing studies have used and are evaluating a sequencing of modalities of radiation and chemotherapy in the combination arm. In resected stage III and IV disease, cisplatin / doxorubicin chemotherapy was associated with a survival advantage over whole abdominal radiation, but with a high pelvic recurrence rate in the chemotherapy arm. This has led many to advocate for combined chemotherapy and radiotherapy in high-risk endometrial cancer. Several studies compared radiation alone to radiation and chemotherapy. In addition to a negative study, one study did show a progression-free survival benefit of approximately 7% in favor of chemotherapy and radiation over radiation alone for high-risk patients with stage I-III endometrial cancer.

Given the uncertainties on what is the optimal treatment for these groups of patients, enrollment of patients is encouraged to help answer these important study questions, currently PORTEC 3 or EN7 at this institution. PORTEC-3 is seeking to answer the question of whether the addition of carboplatin and paclitaxel sequentially, as well as the addition of concurrent cisplatin with radiotherapy, improves survival in high-risk resected endometrial cancer.

Our current off study protocol involves giving sequential therapy in a so-called "sandwich" approach to treat patients with high-risk endometrial cancer (high-risk histology, stage III). This includes: four cycles of carboplatin (AUC6)/ paclitaxel (175 mg / m^2), followed by 45 Gy EBRT +/- brachytherapy (5Gy x 3), followed by two further cycles of carboplatin / paclitaxel (if tolerated). The advantage to this approach is even if a patient declines treatment after radiation, she has received a reasonable amount of chemotherapy. Adjuvant chemotherapy with carboplatin and paclitaxel is recommended for papillary serous and clear cell histologies, with the exception of stage IA disease.

We generally consider carcinosarcomas a high-risk histology and consider resected patients with this disease for adjuvant chemotherapy and radiotherapy. Randomized evidence exists to suggest a survival advantage to adjuvant chemotherapy for patients with resected stage IC to IV, treated with three cycles of cisplatin / ifosfamide. Again, carboplatin / paclitaxel appear active in this disease, and have replaced ifosfamide-containing regimens by most practitioners.

Systemic Therapy for Metastatic, Unresectable or Recurrent Endometrial Cancer

Disseminated metastatic disease, or isolated but unresectable disease, can be treated with palliative intent using various systemic agents.

Hormonal Therapy

- Megestrol acetate
- Medroxyprogesterone acetate
- Tamoxifen
- Aromatase inhibitors (e.g. Letrozole)

No dose or type of hormonal therapy has been proven superior to any other.

Main predictors of benefit from hormonal therapy include: low grade disease, long disease-free interval, location and extent of extra pelvic metastatic disease.

Chemotherapy

Combination chemotherapy is preferred over monotherapy in fit patients with good performance status, as combination therapy has been shown to be more efficacious

than single agents. However, combination chemotherapy is associated with greater side-effects.

The ideal regimen to be used as adjuvant therapy in endometrial cancer is not clear based on available evidence. For advanced disease, the regimen with highest activity is cisplatin, paclitaxel and doxorubicin. This regimen is toxic, requires prophylactic filgrastim, and is impractical for most patients. Carboplatin / paclitaxel is a well-tolerated regimen and those who treat gynecologic cancer have extensive experience with this regimen from use in ovarian cancer. The standard regimen is carboplatin dosed at an AUC of 5/6 plus paclitaxel 175 mg / m^2. Acceptable alternatives include the following:

- Cisplatin / doxorubicin
- Cisplatin / doxorubicin / paclitaxel / G-CSF
- Cisplatin
- Carboplatin
- Doxorubicin
- Liposomal doxorubicin
- Gemcitabine
- Paclitaxel
- Ifosfamide

Response rates to 2nd line (salvage) chemotherapy after failure of first-line chemotherapy for metastatic disease is poor. Any of the above agents, or hormonal therapy, would be reasonable in this situation, although best supportive care or enrolment in a clinical trial exploring an investigational agent are preferred.

Monitoring & Follow-up

The traditional purpose of regular routine follow-up is to help determine the need for and timing of further treatment. In addition it is recognized that important goals of follow-up are to provide continuous education, psycho-emotional support and reassurance. This follow-up should be consistent and created with the patient's quality of life at the forefront of consideration. Wherever possible, opportunity for follow-up should be made available in their own community, with the understanding that expeditious referral back to the specialist center will be made at the first sign of symptomatic recurrence.

For some patients follow-up visits may provoke anxiety, worry and fear. The follow-up strategy needs to be individualized based on each patient's specific needs.

There is a lack of literature regarding optimal frequency of follow-up. We suggest the following for patients:

- Clinic visit with physical exam and patient education regarding symptoms every 3-6 months for 2 years, then at 6 month to 1 year intervals

- Imaging as clinically indicated based on signs and symptoms

Patients with bleeding (vaginal, bladder, or rectal), decreased appetite, weight loss, pain (pelvis, abdomen, hips, or back), cough, shortness of breath, and swelling (abdomen or legs) should seek **prompt** evaluation and not delay until next scheduled appointment.

When follow-up is at the cancer centre and multiple specialists are involved, visits should alternate between physicians to avoid close repeat examinations, if appropriate.

Palliative Care

For patients who have documented evidence of disease progression and who have had a critical point of care conversation, consideration should be given to a referral for Palliative Care. This provides the opportunity to maximize symptom management, explore local resources, and to begin advance care planning for the future, even while active treatment is being implemented.

Genetic Counselling

Hereditary Non-Polyposis Colon Cancer (HNPCC) or Lynch syndrome is caused by a mutation in the mismatch repair (MMR) genes. It is an inherited disorder which increases an individual's chance of developing not only colon cancer, but other types of cancer, including endometrial cancer. Those with HNPCC have an 80% lifetime risk of developing colon cancer, and more specifically, women with HNPCC have a 20-60% lifetime risk of developing endometrial cancer.

Obtaining a detailed family history at the time of initial consultation is extremely important for a genetics referral to be considered. Genetic counseling is an assessment of cancer risk based on personal and family medical history. Individuals with a family history of cancer in multiple family members, cancer diagnosed before 50 years of age in the individual or another family member, or a known cancer syndrome, such as breast and ovarian or colon may be referred to genetics.

Genetic counseling can provide information to help individuals manage their risk for cancer, and their eligibility for genetic testing. Genetic testing is done to determine an individuals predisposition to cancer and helps the genetics team to advise on the proper screening and preventative methods for each individual.

Individuals to Consider for Genetic Counselling

Gene mutations associated with familial colon cancer may also increase the risk for developing endometrial cancer.

A genetic test for cancer predisposition is a blood test that shows whether an individual has inherited a gene mutation that increases the risk for certain cancers. Individuals diagnosed with endometrial cancer and with a personal or family history of breast, ovarian or colon cancer, who meets published criteria, should be referred to a genetic counselor to discuss cancer risks and clarify eligibility for genetic testing. Women with

known HNPCC (Hereditary Non Polyposis Colon Cancer) mutation should be evaluated and counseled for prophylactic hysterectomy after completion of childbearing.

Genetic counseling is an assessment of cancer risk based on personal and family medical history. Genetic counseling can provide information to help individuals manage their risk for cancer, whether or not they have genetic testing. It also determines a person’s eligibility for a blood test for genetic testing to determine cancer predisposition, and helps the genetic team advise on the proper screening and preventive methods for each individual.

Appendix 1

STAGE INFORMATION

A hysterectomy is required to determine the degree of myometrial invasion. The following surgical staging has been adopted by the International Federation of Gynecology and Obstetrics (FIGO) and by the American Joint Committee on Cancer (AJCC): [16-19]

Stage I

Stage I* endometrial cancer is carcinoma confined to the corpus uteri.

Stage IA: no or less than half myometrial invasion
Stage IB: invasion equal to or more than half of the myometrium

Stage II b

Stage II* endometrial cancer involves the corpus and the cervix, but has not extended outside the uterus.

Stage II: Tumor invades cervical stroma, but does not extend beyond the uterus**

Stage III

Stage IIIA: tumor invades serosa of the corpus uteri and/or adnexa#
Stage IIIB: vaginal and/or parametrial involvement#
Stage IIIC: Metastases to pelvic and/or para-aortic lymph nodes#
IIIC1: positive pelvic nodes
IIIC2: positive para-arotic lymph nodes +/- positive pelvic lymph nodes

Stage IV

Stage IV* endometrial cancer involves the bladder or bowel mucosa or has metastasized to distant sites.

Stage IVA: tumor invasion of bladder and/or bowel mucosa
Stage IVB: distant metastases, including intra-abdominal 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 stage

References

1. Creasmanb et al, Surgical pathologic spread patterns of endometrial cancer: a Gynecologic Oncology Group study. Cancer 1987; 60:2035-2041

2. Creutzberg et al, Surgery and postoperative radiotherapy versus surgery alone for patients with stage I endometrial carcinoma: multicenter randomized trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet 2000; 355:1404-1411

3. Keys et al, A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2004;92:744-751

4. Chan et al, Role of complete lymphadenectomy in endometrioid uterine cancer, Lancet Oncol 2007;8:831-841

5. Thigpen et al, Phase III trial of doxorubicin with or without cisplatin in advanced endometrial carcinoma, J Clin Oncol 2004;22(19)3902-3908

6. Randall et al, Randomized phase III trial of whole abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group study. J Clin Oncol 2006; 24:36-44

7. Maggi et al, Adjuvant chemotherapy vs radiotherapy in high risk endometrial carcinoma, Br J Cancer2006;95(3):266-271

8. Hogberg et al, A randomized phase III study on adjuvant treatment with radiation (RT) + chemotherapy (CT) in early stage high risk endometrial cancer (NSGO-EC-9501/EORTC 55991) J Clin Oncol 2007;25(18S), Abstract 5503

9. Kilgore et al, Adenocarcinoma of the endometrium: Survival Comparisons of patients with and without pelvic node sampling. Gynecol Oncol. 2005;99:689-695

10. COSA-NZ-UK Endometrial Cancer Study Groups. Pelvic lymphadenectomy in high risk endometrial cancer, Int J Gynecol Cancer 1996;6:102-107

11. Trimle et al, Lymph node sampling and survival in endometrial cancer, Gynecol Oncol 1998;71(3):340-343

12. Chan et al, Therapeutic Role of Lymph Node Resection in Endometrial Corpus Cancer, A Study of 12,333 Patients, Cancer 2006;107:1823-30

13. Benedetti Panici et al, Systematic Pelvic Lymphadenectomy vs No Lymphadenectomy in Early-Stage Endometrial Carcinoma: Randomized Clinical Trial, J Nat Cancer Inst 2008;100:1707-1716

14. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study, The Lancet 2009;373:125-136

15. Cragun et al, Retrospective analysis of selective lymphadenectomy in apparent early-stage endometrial cancer. J Clin Oncol 2005; 23;3668-3675

16. Shepherd JH: Revised FIGO staging for gynaecological cancer. British Journal of Obstetrics and Gynaecology 96(8): 889-892, 1989.

17. FIGO staging for corpus cancer. British Journal of Obstetrics and Gynaecology 99(5): 440, 1992.

18. Corpus uteri. In: American Joint Committee on Cancer: AJCC Cancer Staging Manual. Philadelphia, Pa: Lippincott-Raven Publishers, 5th ed., 1997, pp 195-200.

19. FIGO Committee On Gynecologic Oncology. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. International Journal of Gynecology and Obstetrics. 105 (2009) 103-104.

20. Onda, T. et al. Treatment of node-positive endometrial cancer with complete node dissection, chemotherapy and radiation therapy. Br. J. of Cancer. 1997;75:1836-1841.

21. Mariani, A et al. Predictors of lymphatic failure in Endometrial Cancer. Gynecol Oncol 2002; 84:437-442.

22. McMeekin D et al. Nodal distribution and its significance in FIGO stage IIIc endometrial cancer. Gynecol Oncol. 2001; 82:375-379.

23. McMeekin D et al. Analysis of FIGO stage IIIc endometrial cancer patients. Gynecol Oncol 2001; 81:273-278.

24. Aalders J, et al. Endometrial cancer – revisiting the importance of pelvic and para- aortic lymph nodes. Gynecol Oncol. 2007;104:222-231.

25. Fleming G et al. Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: A gyncologic oncology group study. J Clin Oncol. 2004; 22: 2159-2166.

26. Susumu, N et al. Randomized phase III trial of pelvic radiotherapy versus cisplatin-based combined chemotherapy in patients with intermediate- and high-risk endometrial cancer: a Japanese Gynecolgic Oncology Group study. Gynecol Oncol 2008: 226-233.

27. Lupe K, et al. Adjuvant carboplatin and paclitaxel interposed with involved field radiation for advanced endometrial cancer. Gynecol Oncol. 2009 Jul;114(1):94-8.

28. Watanabe et al, Evaluation of Parametrial Spread in Endometrial Carcinoma, Obstet & Gynecol;116:5, 1027-1034.

29. Hauspy et al, Laparoscopic Surgery for Endometrial Cancer: A Review, J Obstet Gynaecol Canada 2010;570-579.

1. Creasman WT Morrow CP, Bundy BN et al. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. Cancer 1987, 60(8 Suppl): 2035-41.

2. Straughn JM, Huh WK, Kelly FJ et al. Conservative management of stage I endometrial cancer after surgical staging. Gynecol Oncol 2002, 84(2):194-200.

3. Morrow CP, Bundy BN, Kurman, RJ et al. Relationship between surgical-pathologic risk factors and outcome in clinical stage I and II carcinoma of the endometrium: A Gynecologic Oncology Group study. Gynecol Oncol 1991, 40(1):55-65.

4. Creutzberg CL, van Putten WL, Koper PC et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage I endometrial carcinoma: multicentre randomized trial. Lancet 2000, 355:(9213)1404-11.

5. Keys H, Roberts JA, Brunetto VL et al. A phase III study of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: A Gynecologic Oncology Group study. Gynecol Oncol 2004, 92:(3)744-51.

6. Aalders J, Abeler V, Kolstad P et al. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. Obstet Gynecol 1980, 56(4):419-27.

7. Creutzberg CL, van Putten WL, Koper PC, et al. Survival after relapse in patients with endometrial cancer: results from a randomized trial. Gynecol Oncol 2003, 89(2):201-9.

8. Scholten AN, van Putten WL, Beerman H et al. Postoperative radiotherapy for Stage 1 endometrial carcinoma: long-term outcome of the randomized PORTEC trial with central pathology review. Int J Radiat Oncol Biol Phys 2005, 63(3):834-38.

9. ASTEC/EN.5 Study Group, Blake P, Swart AM et al. Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): pooled trial results, systematic review, and meta-analysis. Lancet 2009, 373(9658):137-46.

10. Nout RA, Putter H, Jürgenliemk-Schulz IM et al. Quality of life after pelvic radiotherapy or vaginal brachytherapy for endometrial cancer: first results of the randomized PORTEC-2 trial. J Clin Oncol 2009, 27(21):3547-56.

11. Johnson N, Cornes P. Survival and recurrent disease after postoperative radiotherapy for early endometrial cancer: systematic review and meta-analysis. BJOG 2007, 114(11):1313-20.

12. Alektiar KM, Venkatraman E, Chi DS et al. Intravaginal brachytherapy alone for intermediate-risk endometrial cancer. Int J Radiat Oncol Biol Phys 2005, 62(1):111-17.

13. Anderson JM, Stea B, Hallum AV et al. : High-dose-rate postoperative vaginal cuff irradiation alone for stage IB and IC endometrial cancer. Int J Radiat Oncol Biol Phys 2000, 46(2):417-25.

14. Cengiz M, Singh AK, Grigsby PW. Postoperative vaginal brachytherapy alone is the treatment of choice for grade 1–2, stage IC endometrial cancer. Int J Gynecol Cancer 2005, 15(5):926-31.

15. Chadha M, Nanavati PJ, Liu P et al. Patterns of failure in endometrial carcinoma stage IB grade 3 and IC patients treated with postoperative vaginal vault brachytherapy. Gynecol Oncol 1999, 75(1):103-7.

16. Eltabbakh GH, Piver MS, Hempling RE et al. Excellent long-term survival and absence of vaginal recurrences in 332 patients with low-risk stage I endometrial adenocarcinoma treated with hysterectomy and vaginal brachytherapy without formal staging lymph node sampling: report of a prospective trial. Int J Radiat Oncol Biol Phys 1997, 38(2):373-80.

17. Fanning J, Hoffman ML, Andrews SJ et al. Cost-effectiveness analysis of the treatment for intermediate risk endometrial cancer: postoperative brachytherapy vs. observation. Gynecol Oncol 2004, 93(3):632-36.

18. Horowitz NS, Peters WA 3rd, Smith MR et al. Adjuvant high dose rate vaginal brachytherapy as treatment of stage I and II endometrial carcinoma. Obstet Gynecol 2002, 99(2):235-40.

19. Jolly S, Vargas C, Kumar T et al. Vaginal brachytherapy alone: an alternative to adjuvant whole pelvis radiation for early stage endometrial cancer. Gynecol Oncol 2005, 97(3):887-92.

20. Kucera H, Vavra N, Weghaupt K. Benefit of external irradiation in pathologic stage I endometrial carcinoma: a prospective clinical trial of 605 patients who received postoperative vaginal irradiation and additional pelvic irradiation in the presence of unfavorable prognostic factors. Gynecol Oncol 1990, 38(1):99-104.

21. Lin LL, Mutch DG, Rader JS et al. External radiotherapy versus vaginal brachytherapy for patients with intermediate risk endometrial cancer. Gynecol Oncol 2007, 106(1):215-20.

22. MacLeod C, Fowler A, Duval P et al. High-dose-rate brachytherapy alone post-hysterectomy for endometrial cancer. Int J Radiat Oncol Biol Phys 1998, 42(5):1033-39.

23. Ng TY, Perrin LC, Nicklin JL et al. Local recurrence in high-risk node-negative stage I endometrial carcinoma treated with postoperative vaginal vault brachytherapy. Gynecol Oncol 2000, 79(3):490-494.

24. Ng TY, Nicklin JL, Perrin LC et al. Postoperative vaginal vault brachytherapy for node-negative Stage II (occult) endometrial carcinoma. Gynecol Oncol 2001, 81(2):193-95.

25. Petereit DG Tannehill SP, Grosen EA et al. Outpatient vaginal cuff brachytherapy for endometrial cancer. Int J Gynecol Cancer 1999, 9(6):456-62.

26. Roper B Astner ST, Heydemann-Obradovic A et al. Ten-year data on 138 patients with endometrial carcinoma and postoperative vaginal brachytherapy alone: no

need for external-beam radiotherapy in low and intermediate risk patients. Gynecol Oncol 2007, 107(3):541-48.

27. Solhjem MC, Petersen I, Haddock MG. Vaginal brachytherapy alone is sufficient adjuvant treatment of surgical stage I endometrial cancer. Int J Radiat Oncol. Biol Phys 2005, 62(5):1379-84.

28. Nout RA, Smit VT, Putter H et al. Vaginal brachytherapy versus pelvic external beam pelvic radiotherapy for patients with endometrial cancer of high-intermediate risk (PORETEC-2): an open-label, non-inferiority randomised trial. Lancet 2010, 375(9717):816-23.

29. NCCN Practice Guidelines in Oncology - Uterine Neoplasms. Version1, 2010.

30. Creasman W: Revised FIGO staging for carcinoma of the endometrium. Int J Gynaecol Obstet 2009, 105(2):109.

31. Kwon J Ackerman I, Franssen E. The role of abdominal-pelvic radiotherapy in the management of uterine papillary serous carcinoma. Int J Radiat Oncol Biol Phys 2004, 59(5):1439-45.

32. Sutton G, Axelrod JH, Bundy BN et al. Whole abdominal radiotherapy in the adjuvant treatment of patients with stage III and IV endometrial cancer: a gynecologic oncology group study. Gynecol Oncol 2005, 97(3):755-63.

33. Potish RA, Twiggs LB, Adcock LL et al. Paraaortic lymph node radiotherapy in cancer of the uterine corpus. Obstet Gynecol 1985, 65(2):251-6.

34. Corn BW, Lanciano R, Greven KM et al. Endometrial cancer with para-aortic adeopathy: Patterns of failure and opportunities for cure. Int J Radiat Oncol Biol Phys 1992, 24(2):223-7.

35. Rose PG, Cha SD, Tak WK,et al. Radiation therapy for surgically proven para-aortic node metastasis in endometrial carcinoma. Int J Radiat Oncol Biol Phys 1992, 24(2):229-33.

36. Mundt AJ, McBride R, Rotmensch J et al. Significant pelvic recurrence in high-risk pathologic stage I--IV endometrial carcinoma patients after adjuvant chemotherapy alone: implications for adjuvant radiation therapy. Int J Radiat Oncol Biol Phys 2001, 50(5):1145-53.

37. Randall ME Filiaci VL, Hyman M et al. Randomized Phase III Trial of Whole-Abdominal Irradiation Versus Doxorubicin and Cisplatin Chemotherapy in Advanced Endometrial Carcinoma : A Gynecologic Oncology Group Study. J Clin Oncol 2006, 24(1):36-44.

38. Lupe K, D'Souza DP, Kwon JS et al. Adjuvant carboplatin and paclitaxel chemotherapy interposed with involved field radiation for advanced endometrial cancer. . Gynecol Oncol 2009 114(1):94-8,

39. Secord AA, Havrilesky LJ, O'Malley DM et al. A multicenter evaluation of sequential multimodality therapy and clinical outcome for the treatment of advanced endometrial cancer. Gynecol Oncol 2009, 114(3):442-7.

40. Greven K Winter K, Underhill K et al. Preliminary analysis of RTOG 9708: Adjuvant postoperative radiotherapy combined with cisplatin/paclitaxel chemotherapy after surgery for patients with high-risk endometrial cancer. Int J Radiat Oncol Biol Phys 2004, 59(1):168-73.