Radiotherapy for endometrial cancer: improved patient selection, techniques and outcomes

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1

CHAPTER 1

GENERAL INTRODUCTION AND THESIS OUTLINE

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Selecting adjuvant treatment for endometrial carcinoma using molecular risk factors

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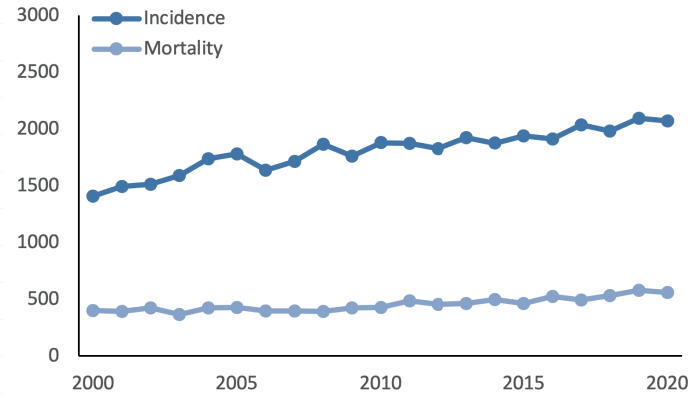
1. INTRODUCTION

1.1 Epidemiology

Endometrial cancer is the most common gynaecological cancer in developed countries, with the highest incidence in postmenopausal women between 65 and 85 years of age. The incidence is rising due to increased prevalence of diabetes and obesity, and ageing of the population.[1, 2] In The Netherlands in 2020, the estimated number of new endometrial cancer cases was 2069 with 559 cancer-related deaths (*Figure 1*).[3] Most women with endometrial cancer are diagnosed at early stage of disease, due to early symptoms such as vaginal bleeding. This generally results in a favourable prognosis and a relatively low number of cancer-related deaths.[4]

Figure 1. Incidence and mortality of endometrial cancer in the Netherlands.[3]



1.2 Histology and risk factors

Endometrial cancer is diagnosed by physical and pelvic examination, including transvaginal ultrasound, and pathology assessment of a biopsy, curettage or hysterectomy. The most common histological type is endometrioid adenocarcinoma, accounting for approximately 70-80% of endometrial cancers. Non-endometrioid cancers mainly comprise serous and clear cell cancers, accounting for approximately 5-10% and 1-5% of endometrial cancers, respectively, and the other aggressive subtypes are undifferentiated endometrial cancer and uterine carcinosarcomas. Well-established clinicopathological risk factors, used in the current treatment guidelines, are age, histological type, tumour grade, International Federation of Gynaecology and Obstetrics (FIGO)-stage (*Table 1*), depth of myometrial invasion and presence and extent of lymph-vascular space invasion (LVSI).[5, 6] Endometrioid endometrial cancer is usually graded using the FIGO grading system: low grade (grade 1), intermediate grade (grade 2) or high grade (grade 3) based on the

proportion of solid growth and nuclear atypia, while non-endometrioid endometrial cancers are high grade by definition. More recently, a binary grading system has been suggested, separating low-grade (FIGO grade 1 and 2) and high-grade (FIGO grade 3) endometrial cancer which seems more in line with their outcome.[7, 8]

1.3 Pathology

To determine the pathological risk factors of endometrial cancer, multiple features of pathology assessment are needed, and reproducibility is essential to ensure completeness and accuracy of the diagnosis. However, the female reproductive tract has been described as one of the organ systems with the highest inter-observer variation between pathologists.[9] Previous studies reported that a limited proportion of the reviewed pathology specimen resulted in major discrepancies, ranging from 8% to 12%.[10] Pathology review within the PORTEC-1 and 2 trials has shown that 24% and 14% of included patients were, in retrospect, not eligible for the trial.[11-13] Most frequent discrepancies were observed in histological grade, suggesting that a two-tiered grading system (low- versus high grade) could be beneficial.[14] In another inter-observer pathology study on high-grade endometrial cancer, histological subtyping was also a common discrepancy.[15] Pathology review in daily clinical practice could result in a reduction of over- and undertreatment. In the PORTEC-3 trial, upfront pathology review was performed to verify whether patients were truly eligible and would not receive unnecessary toxic treatment. Challenges of standard pathology review are that it can be time-consuming, costly, and comes with logistical difficulties.

Table 1. FIGO 2009 staging of endometrial cancer.[5]

Stage	Description
I	Tumour confined to the corpus uteri
IA	No or less than half myometrial invasion
IB	Invasion equal to or more than half of the myometrium
II	Tumour invades cervical stroma, but does not extend beyond the uterus
III	Local and/or regional spread of the tumour
IIIA	Invasion of 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/without positive pelvic lymph nodes
IV	Tumour invades bladder and/or bowel mucosa, and/or distant metastases
IVA	Invasion of bladder and/or bowel mucosa
IVB	Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes

1.4 Treatment

Standard treatment for women with endometrial cancer is surgery, consisting of laparoscopic or abdominal hysterectomy and bilateral salpingo-oophorectomy, with or without lymph node evaluation. With lymphadenectomy the nodal status can be assessed, and FIGO stage can be assigned adequately. However, routinely performed lymphadenectomy in early stage endometrial cancer remains controversial, as two large randomised trials have shown no improvement in overall survival or disease free survival in early stage endometrial cancer, while there is an increased risk of treatment related morbidity, mostly lymphoedema.[16-18] More recently sentinel node biopsy has emerged as a reliable method for lymph node evaluation, which has been investigated in several studies and has shown to have high sensitivity with lower risk of toxicity.[19-22]

1.5 Adjuvant Treatment

The current guidelines for adjuvant treatment of endometrial cancer are based on the clinicopathologic factors age, FIGO stage, histologic type and grade, myometrial invasion and the presence of LVSI. Based on the clinicopathological risk factors, four risk groups (low, intermediate, high-intermediate and high risk) have been defined, with each risk group having a different prognosis (*Table 2*).[6]

Table 2. Risk groups in endometrial cancer according to PORTEC and the ESMO-ESGO-ESTRO guideline.

Risk Group	PORTEC (2002-2013)[11]	ESMO-ESGO-ESTRO guideline 2021[64]
Low	FIGO stage IA EEC: grade 1-2	FIGO stage IA EEC: grade 1-2, LVSI neg.
Intermediate	FIGO stage IB EEC: grade 1-2, age <60	FIGO stage IB EEC: grade 1-2, LVSI neg.
		FIGO stage IA EEC: grade 3, LVSI neg.
		FIGO stage IA NEEC: no myometrial invasion
High-intermediate	FIGO stage IA EEC: grade 3, age ≥60	FIGO stage IA/B EEC: grade 1-3, LVSI pos.
	FIGO stage IB EEC: grade 1-2, age ≥60	FIGO stage IB EEC: grade 3, LVSI neg.
		FIGO stage II EEC
High	FIGO stage IB EEC: grade 3	FIGO stage III-IVA EEC without residual disease
	FIGO stage II-III EEC	FIGO stage I-IVA NEEC: without residual disease
	FIGO stage I-III NEEC	

EEC endometrioid endometrial cancer; LVSI lymph-vascular space invasion (neg.: negative, pos.: substantial LVSI); NEEC non-endometrioid endometrial cancer (serous or clear cell carcinoma)

Low risk

Previous studies have shown that women with low-risk endometrial cancer have a very low risk of locoregional or distant recurrences. Even without adjuvant radiotherapy, a 5-year disease-free survival of 95% has been reported.[13, 23-25] For this risk group, no adjuvant treatment is recommended.

Intermediate and high-intermediate risk

In the PORTEC-1 and GOG-99 trials women with intermediate risk endometrial cancer were randomised to pelvic external beam radiotherapy (EBRT) versus no adjuvant treatment. Results showed that EBRT significantly reduced locoregional recurrences, without a survival benefit.[13, 24, 26] In the observation group, 75% of the locoregional recurrences were located at the vaginal vault, and with salvage radiotherapy with vaginal brachytherapy survival rates of up to 65% at 5 years could still be reached.[13, 24, 27] These trials led to a reduction of the indication for adjuvant treatment, limiting this to women with high-intermediate risk factors (*Table 2*). As most locoregional recurrences were located at the vaginal vault and there was no survival benefit after pelvic EBRT, vaginal brachytherapy was investigated for women with high-intermediate risk endometrial cancer in the PORTEC-2 trial. Results showed that both vaginal brachytherapy and EBRT were equally effective and had a vaginal control rate of 98% at 5 years without differences in overall and disease-free survival. Women who received vaginal brachytherapy however, had less toxicity and improved quality of life.[28-30] Based on these findings, adjuvant vaginal brachytherapy became the standard adjuvant treatment for women with high-intermediate risk endometrial cancer. However, for women at lower risk of recurrence (age below 60) no adjuvant treatment can also be considered as effective salvage treatment is available.

In the recent years, more knowledge has been gained on risk factors for disease recurrence in endometrial cancer, such as LVSI. In a study of the combined data of the PORTEC-1 and 2 trials, LVSI scored as substantial in a three-tiered scoring system (no, focal or substantial LVSI) showed to be the strongest independent prognostic factor for pelvic and distant metastasis and overall survival.[31, 32] A Swedish nationwide study reported similar findings, even for women that were adequately staged and node negative, the presence of substantial ('obvious') LVSI was associated with decreased overall survival.[33] To lower the risk of distant metastasis, the addition of 3 cycles of chemotherapy to vaginal brachytherapy was investigated and compared to EBRT in the GOG-249 trial. Results showed that there were no significant differences in recurrence-free and overall survival. However, more pelvic and para-aortal nodal recurrences were observed in the arm with vaginal brachytherapy and chemotherapy, even though these women were surgically staged and node negative. In the combined PORTEC-1 and 2 analysis the risk of pelvic metastases was also reduced by pelvic EBRT as compared to vaginal brachytherapy. This could imply that pelvic EBRT should be considered for women with risk factors such as substantial LVSI.[31-33]

High risk

Women with high-risk endometrial cancer are at higher risk of pelvic and distant metastases and endometrial cancer related death.[34-36] In the current treatment guidelines these women receive

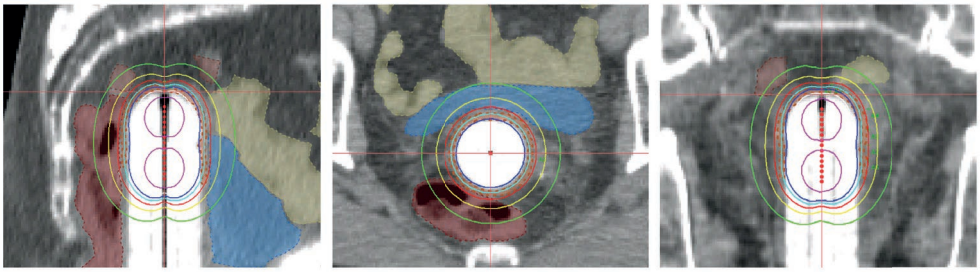
pelvic external beam radiotherapy with or without adjuvant chemotherapy. The role of adjuvant chemotherapy, in combination with EBRT, has been the subject of several randomised trials. The PORTEC-3 trial investigated radiotherapy alone versus radiotherapy combined with chemotherapy (two cycles of cisplatin during radiotherapy followed by four cycles of carboplatin-paclitaxel) for women with high-risk endometrial cancer. Results showed improved recurrence-free and overall survival after combined radiotherapy and chemotherapy compared to radiotherapy alone, at the cost of increased toxicity. Radiotherapy combined with chemotherapy was mainly recommended for stage III disease and serous type cancers.[37-40] Chemotherapy alone could be considered, based on the findings of the GOG-258 trial that investigated radiotherapy combined with chemotherapy versus chemotherapy (six cycles of carboplatin-paclitaxel) alone for women with stage III-IV endometrial cancer. Results showed similar relapse-free survival rates, but increased rates of pelvic and peri-aortic relapses with chemotherapy alone.[41]

1.6 Radiotherapy techniques

Vaginal brachytherapy

Vaginal brachytherapy is a highly effective adjuvant radiotherapy treatment for women with intermediate to high-intermediate risk endometrial cancer, with 5-year vaginal control rates of over 95%.[12, 42-44] Radiation dose is generally administered with high-dose rate (HDR) in three to four fractions of 6 to 7 Gray (Gy), usually by a single channel vaginal cylinder, starting within 6 (-8) weeks from surgery. For specific indications, multichannel cylinders are available with enable MRI-based optimization of the dose distribution and/or local boosts. Brachytherapy planning is based on delineation of the target volume and organs-at-risk on CT or MR-images with the cylinder in situ during at least one fraction to provide data on dose distribution to the clinical target volume and organs-at-risk (*Figure 2*). These data are used to avoid added toxicity to the bladder, rectum and small bowel, even though toxicity of vaginal brachytherapy is mild. Within the PORTEC-2 trial, patients who received vaginal brachytherapy had significantly lower rates of grade 1-2 gastro-intestinal toxicity during treatment compared to those receiving EBRT (12.0% versus 53.8%, $p<0.05$). At 1 and 2 years still significant differences were observed (9.3% and 8.0% versus 22.2% and 17.4%, $p <0.05$). Analysis of patient-reported symptoms showed similar differences between vaginal brachytherapy and EBRT, with 5.6% versus 22.7% of patients reporting moderate to severe diarrhoea.[12, 30] Long-term analysis of the PORTEC-2 showed that only 1.8% and 0.9% of patients treated with vaginal brachytherapy had persistent moderate to severe symptoms of faecal leakage and diarrhoea, respectively, versus 10.6% and 8.4% after EBRT. Genito- urinary symptoms as vaginal dryness, narrowing, or pain did not differ significantly between vaginal brachytherapy and EBRT.[29]

Figure 2. Vaginal brachytherapy dose distribution and organs-at risk.



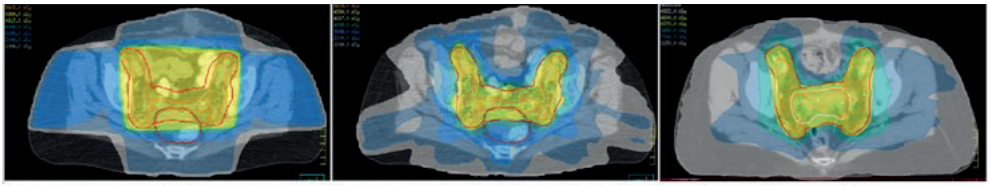
Single channel cylinder for vaginal brachytherapy with the 100% isodose line being 7Gy (red) covering the proximal 4 cm of the vaginal mucosa. Organs-at-risk are contoured: bladder (blue), rectum (red), sigmoid (brown) and small bowel (yellow).

External beam radiotherapy

Over the past 10 to 20 years, radiotherapy techniques have developed from 2-dimensionally planned radiotherapy to three and four field techniques, and three-dimensional (3D) conformal radiotherapy. Most recent developments are 3D image-guided intensity-modulated radiotherapy (IMRT) and volumetric-modulated arc radiotherapy (VMAT) (*Figure 3*). With IMRT and VMAT, the radiation dose is delivered more conformally to the target volume and the dose to the adjacent organs at risk is reduced, compared to 3D conformal radiotherapy, without compromising clinical outcome.[45-50] With the introduction of more advanced radiotherapy techniques, it is expected that treatment related toxicity for pelvic radiotherapy can be reduced. Multiple retrospective studies and two prospective randomised trials have shown that intensity modulated techniques significantly reduce treatment related acute and late adverse events and patient-reported symptoms in women with endometrial or cervical cancer.[49-57]

Analyses of acute toxicity showed that pelvic radiotherapy was associated with mostly gastro-intestinal acute toxicity of mild to moderate severity, and that the addition of chemotherapy resulted in added hematological and neurological toxicity.[39, 40] Within the PORTEC-3 trial, 68.5% (94.2% chemoradiation vs 43.2% radiotherapy alone) had any grade $\geq$ 2 toxicity during treatment, and 44.3% and 43.8% of all patients experienced grade $\geq$ 2 gastro-intestinal and hematological toxicity, respectively. Persistent grade $\geq$ 2 toxicity, up to 5 years after treatment, were observed for 31.0%, with 7.3% gastro-intestinal and 2.5% hematological toxicity. Long-term grade 3 to 4 toxicity was observed in 3-6.8% of patients in the PORTEC-1 and 3 trials.[58, 59]

Figure 3. External beam radiotherapy techniques over time.



Improved dose distribution and sparing of organs at risk with different techniques over the past decades (from left to right): 3D-conformal radiotherapy (left), intensity-modulated radiotherapy (IMRT)(middle) and volumetric-arc radiotherapy (VMAT)(right), showing increased conformality of the radiotherapy plans.

1.7 Molecular risk factors

In 2013 the Cancer Genome Atlas Group (TCGA) analysed the molecular genetic basis of endometrial cancer development, which has been pivotal in understanding the molecular pathways involved in endometrial cancer development and their prognostic implications. By comprehensive genomic analysis of 373 endometrial cancer cases, 4 different molecular subclasses were identified based on mutation rates and somatic copy number alterations (SCNA). The ultra-mutated subclass, characterised by mutations in the exonuclease domain of DNA polymerase-epsilon (*POLE)*, is associated with a very favourable prognosis. The hypermutated subclass based on microsatellite instability (MSI) has been shown to have an intermediate prognosis. The copy number low subclass with low mutation frequency (also called subclass with no specific molecular profile or NSMP), has also been associated with an (stage dependent) intermediate prognosis. The copy number high subclass, characterised by *TP53* mutations, with mainly serous type endometrial cancer has a very high degree of SCNAs and a low mutation rate, and is associated with the most unfavourable prognosis.[60] Several research groups have reproduced and validated the four TCGA subclasses in formalin-fixed, paraffin-embedded tissues in different endometrial cancer cohorts by using their surrogate markers. These findings have led to a clinically available molecular classification tool for diagnosis and decision making and is implemented more and more into the risk classification and treatment guidelines, such as the recent ESGO-ESTRO-ESP endometrial cancer guidelines.[61-66] The value of incorporating molecular classification in clinical decision making for adjuvant treatment is currently being investigated in the randomised PORTEC-4a trial for women with high-intermediate risk endometrial cancer. In this trial, women are randomised 1:2 to either the standard brachytherapy arm versus an experimental arm in which women are stratified in a favourable, intermediate or unfavourable profile based on molecular and clinicopathologic risk factors and consequently treated with no adjuvant treatment, vaginal brachytherapy or EBRT, respectively.[67]

1.8 Aims and outline of this thesis

The aims of this thesis are to evaluate the role of radiotherapy for women with endometrial cancer, and the impact molecular factors have on assignment of adjuvant treatment. In the Netherlands, the current standard adjuvant treatment for high-intermediate risk endometrial cancer is vaginal brachytherapy, which is based on the outcomes of the PORTEC-2 trial. The PORTEC-2 trial investigated the efficacy of external beam radiotherapy versus vaginal brachytherapy for women with high-intermediate risk endometrial cancer.

The long-term outcomes of the PORTEC-2 trial, including the evaluation of clinicopathologic and molecular risk factors are described in **chapter 2**. Whether these molecular risk factors could be implemented into the current treatment guidelines is currently investigated in the PORTEC-4a trial. Evaluation of the pilot phase of the trial is described in **chapter 3**. As approximately 60% of women in the PORTEC-4a trial are treated with vaginal brachytherapy, a quality assurance programme, to verify protocol adherence, was implemented in the trial. The results are evaluated in **chapter 4**.

For women with high-risk endometrial cancer the current standard adjuvant treatment is pelvic EBRT with or without chemotherapy. The PORTEC-3 trial investigated radiotherapy versus radiotherapy combined with chemotherapy for women with high-risk endometrial cancer. Before participating in the PORTEC-3 trial, upfront pathology review was performed to ensure a truly high-risk trial population. Results of the upfront pathology review are described in **chapter 5**. Within the PORTEC-3 trial women were treated with pelvic external beam radiotherapy, which has developed from 3D-conformal towards more conformal intensity-modulated radiotherapy techniques as IMRT and VMAT over the past 10-20 years. In **chapter 6** the effect of both techniques on toxicity and quality of life is evaluated. **Chapter 7** provides a general discussion.

REFERENCES

1. Onstad, M.A., R.E. Schmandt, and K.H. Lu, *Addressing the Role of Obesity in Endometrial Cancer Risk, Prevention, and Treatment.* J Clin Oncol, 2016. **34**(35): p. 4225-4230.
2. Smrz, S.A., et al., *An ecological evaluation of the increasing incidence of endometrial cancer and the obesity epidemic.* Am J Obstet Gynecol, 2021. **224**(5): p. 506 e1-506 e8.
3. IKNL, *Dutch Cancer Registry.* Available at: http://www.cijfersoverkanker.nl. **Accessed May 3, 2022**.
4. Siegel, R.L., K.D. Miller, and A. Jemal, *Cancer statistics, 2020.* CA Cancer J Clin, 2020. **70**(1): p. 7-30.
5. Pecorelli, S., *Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium.* Int J Gynaecol Obstet, 2009. **105**(2): p. 103-4.
6. Colombo, N., et al., *ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up.* Ann Oncol, 2016. **27**(1): p. 16-41.
7. Barline J.N., et al., *Redefining stage I endometrial cancer: incorporating histology, a binary grading system, myometrial invasion, and lymph node assessment.* Int J Gynecol Cancer, 2013. **23**(9): p. 1620-8.
8. Soslow R.A., et al., *Endometrial Carcinoma Diagnosis: Use of FIGO Grading and Genomic Subcategories in Clinical Practice: Recommendations of the International Society of Gynecological Pathologists.* Int J Gynecol Pathol, 2019. **38**(1): p. S64-S74.
9. Manion, E., M.B. Cohen, and J. Weydert, *Mandatory Second Opinion in Surgical Pathology Referral Material: Clinical Consequences of Major Disagreements* Am. J. Surg. Pathol., 2008. **32**: p. 732–737.
10. Chafe, S., et al., *An analysis of the impact of pathology review in gynecologic cancer.* Int. J. Radiation Oncology Biol. Phys., 2000. **48**(5): p. 1433-1438.
11. Scholten, A.N., 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): p. 834-8.
12. Nout, R.A., et al., *Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open- label, non-inferiority, randomised trial.* Lancet, 2010. **375**(9717): p. 816-23.
13. Creutzberg, C.L., et al., *Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma.* Lancet, 2000. **355**(9213): p. 1404-11.
14. Scholten, A.N., et al., *Prognostic significance and interobserver variability of histologic grading systems for endometrial carcinoma.* Cancer, 2004. **100**(4): p. 764- 72.
15. Boennelycke, M., et al., *Prognostic impact of histological review of high-grade endometrial carcinomas in a large Danish cohort.* Virchows Arch, 2021. **479**(3): p. 507-514.
16. Kitchener, H., *Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study.* The Lancet, 2009. **373**(9658): p. 125-136.
17. Benedetti Panici, P., et al., *Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial.* J Natl Cancer Inst, 2008. **100**(23): p. 1707-16.
18. Frost, J.A., et al., *Lymphadenectomy for the management of endometrial cancer.* Cochrane Database Syst Rev, 2017. **10**: p. CD007585.
19. Rossi, E.C., et al., *A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study.* The Lancet Oncology, 2017. **18**(3): p. 384-392.
20. Bogani, G., et al., *Sentinel node mapping vs. lymphadenectomy in endometrial cancer: A systematic review and meta-analysis.* Gynecol Oncol, 2019. **153**(3): p. 676- 683.

21. Persson, J., et al., *Pelvic Sentinel lymph node detection in High-Risk Endometrial Cancer (SHREC-trial)-the final step towards a paradigm shift in surgical staging.* Eur J Cancer, 2019. **116**: p. 77-85.
22. Accorsi, G.S., et al., *Sentinel Lymph Node Mapping vs Systematic Lymphadenectomy for Endometrial Cancer: Surgical Morbidity and Lymphatic Complications.* J Minim Invasive Gynecol, 2020. **27**(4): p. 938-945 e2.
23. Aalders, J., 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): p. 419-27.
24. Keys, H.M., 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**(3): p. 744-51.
25. Blake, P., 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): p. 137-46.
26. Creutzberg, C.L., et al., *Fifteen-year radiotherapy outcomes of the randomized PORTEC-1 trial for endometrial carcinoma.* Int J Radiat Oncol Biol Phys, 2011. **81**(4): p. e631-8.
27. Creutzberg, C.L., et al., *Survival after relapse in patients with endometrial cancer: results from a randomized trial.* Gynecol Oncol, 2003. **89**(2): p. 201-9.
28. Nout, R.A., et al., *Five-year quality of life of endometrial cancer patients treated in the randomised Post Operative Radiation Therapy in Endometrial Cancer (PORTEC-2) trial and comparison with norm data.* Eur J Cancer, 2012. **48**(11): p. 1638-48.
29. de Boer, S.M., et al., *Long-Term Impact of Endometrial Cancer Diagnosis and Treatment on Health-Related Quality of Life and Cancer Survivorship: Results From the Randomized PORTEC-2 Trial.* Int J Radiat Oncol Biol Phys, 2015. **93**(4): p. 797-809.
30. Nout, R.A., 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): p. 3547-56.
31. Guntupalli, S.R., et al., *Lymphovascular space invasion is an independent risk factor for nodal disease and poor outcomes in endometrioid endometrial cancer.* Gynecol Oncol, 2012. **124**(1): p. 31-5.
32. Bosse, T., et al., *Substantial lymph-vascular space invasion (LVSI) is a significant risk factor for recurrence in endometrial cancer--A pooled analysis of PORTEC 1 and 2 trials.* Eur J Cancer, 2015. **51**(13): p. 1742-50.
33. Stalberg, K., et al., *Lymphovascular space invasion as a predictive factor for lymph node metastases and survival in endometrioid endometrial cancer - a Swedish Gynecologic Cancer Group (SweGCG) study.* Acta Oncol, 2019. **58**(11): p. 1628-1633.
34. Creutzberg, C.L., et al., *Outcome of high-risk stage IC, grade 3, compared with stage I endometrial carcinoma patients: the Postoperative Radiation Therapy in Endometrial Carcinoma Trial.* J Clin Oncol, 2004. **22**(7): p. 1234-41.
35. Greven KM, Randall M, and Fanning J, *Patterns of failure in patients with stage I, grade 3 carcinoma of the endometrium.* Int J Radiat Oncol Biol Phys, 1990. **19**(3): p. 529-534.
36. Straughn, J.M., et al., *Stage IC adenocarcinoma of the endometrium: survival comparisons of surgically staged patients with and without adjuvant radiation therapy☆☆Presented at the 33rd Annual Meeting of Gynecologic Oncologists, Miami, FL, March 2002.* Gynecologic Oncology, 2003. **89**(2): p. 295-300.
37. Hogberg, T., et al., *Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer--results from two randomised studies.* Eur J Cancer, 2010. **46**(13): p. 2422-31.
38. de Boer, S.M., et al., *Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial.* The Lancet Oncology, 2019. **20**(9): p. 1273-1285.

39. Post, C.C.B., et al., *Long-Term Toxicity and Health-Related Quality of Life After Adjuvant Chemoradiation Therapy or Radiation Therapy Alone for High-Risk Endometrial Cancer in the Randomized PORTEC-3 Trial.* Int J Radiat Oncol Biol Phys, 2020.
40. de Boer, S.M., et al., *Toxicity and quality of life after adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): an open-label, multicentre, randomised, phase 3 trial.* Lancet Oncol, 2016. **17**(8): p. 1114-26.
41. Matei, D., et al., *Adjuvant Chemotherapy plus Radiation for Locally Advanced Endometrial Cancer.* N Engl J Med, 2019. **380**(24): p. 2317-2326.
42. Sorbe, B., et al., *Intravaginal brachytherapy in FIGO stage I low-risk endometrial cancer: a controlled randomized study.* Int J Gynecol Cancer, 2009. **19**(5): p. 873-8.
43. Sorbe, B., et al., *External pelvic and vaginal irradiation versus vaginal irradiation alone as postoperative therapy in medium-risk endometrial carcinoma--a prospective randomized study.* Int J Radiat Oncol Biol Phys, 2012. **82**(3): p. 1249-55.
44. Pearcey, R.G. and D.G. Petereit, *Post-operative high dose rate brachytherapy in patients with low to intermediate risk endometrial cancer.* Radiotherapy and Oncology, 2000. **56**: p. 17-22.
45. Heron, D.E., et al., *Conventional 3D conformal versus intensity-modulated radiotherapy for the adjuvant treatment of gynecologic malignancies: a comparative dosimetric study of dose–volume histograms☆*. Gynecologic Oncology, 2003. **91**(1): p. 39-45.
46. Ahamad, A., et al., *Intensity-modulated radiation therapy after hysterectomy: comparison with conventional treatment and sensitivity of the normal-tissue-sparing effect to margin size.* Int J Radiat Oncol Biol Phys, 2005. **62**(4): p. 1117-24.
47. Chan, P., et al., *Dosimetric comparison of intensity-modulated, conformal, and four- field pelvic radiotherapy boost plans for gynecologic cancer: a retrospective planning study.* Radiat Oncol, 2006. **1**: p. 13.
48. Ferrigno, R., et al., *Comparison of conformal and intensity modulated radiation therapy techniques for treatment of pelvic tumors. Analysis of acute toxicity.* Radiat Oncol, 2010. **5**: p. 117.
49. Gandhi, A.K., et al., *Early clinical outcomes and toxicity of intensity modulated versus conventional pelvic radiation therapy for locally advanced cervix carcinoma: a prospective randomized study.* Int J Radiat Oncol Biol Phys, 2013. **87**(3): p. 542-8.
50. Chen, L.A., et al., *Toxicity and cost-effectiveness analysis of intensity modulated radiation therapy versus 3-dimensional conformal radiation therapy for postoperative treatment of gynecologic cancers.* Gynecol Oncol, 2015. **136**(3): p. 521- 8.
51. Roeske, J.C., et al., *Intensity-Modulated Whole Pelvic Radiation Therapy in Patients with Gynecologic Malignancies.* Int J Radiat Oncol Biol Phys, 2000. **48**(5): p. 1613- 1621.
52. Brixey, C.J., et al., *Impact of Intensity-Modulated Radiotherapy on Acute Hematologic Toxicity in Women with Gynecologic Malignancies.* Int J Radiat Oncol Biol Phys, 2002. **54**(5): p. 1388-1396.
53. Mundt, A.J., et al., *Intensity-Modulated Whole Pelvic Radiotherapy in Women with Gynecologic Malignancies.* Int J Radiat Oncol Biol Phys, 2002. **52**(5): p. 1330-1337.
54. Mundt, A.J., L.K. Mell, and J.C. Roeske, *Preliminary analysis of chronic gastrointestinal toxicity in gynecology patients treated with intensity-modulated whole pelvic radiation therapy.* International Journal of Radiation Oncology*Biology*Physics, 2003. **56**(5): p. 1354-1360.
55. Klopp, A.H., et al., *Patient-Reported Toxicity During Pelvic Intensity-Modulated Radiation Therapy: NRG Oncology-RTOG 1203.* J Clin Oncol, 2018. **36**(24): p. 2538-2544.
56. Yeung, A.R., et al., *Improvement in Patient-Reported Outcomes With Intensity- Modulated Radiotherapy (RT) Compared With Standard RT: A Report From the NRG Oncology RTOG 1203 Study.* Journal of Clinical Oncology, 2020. **38**(15): p. 1685-1692.

57. Chopra, S., et al., *Late Toxicity After Adjuvant Conventional Radiation Versus Image- Guided Intensity-Modulated Radiotherapy for Cervical Cancer (PARCER): A Randomized Controlled Trial.* J Clin Oncol, 2021. **39**(33): p. 3682-3692.
58. Creutzberg, C.L., et al., *The morbidity of treatment for patients with Stage I endometrial cancer: results from a randomized trial.* Int J Radiat Oncol Biol Phys, 2001. **51**(5): p. 1246-55.
59. Post, C.C.B., et al., *Long-Term Toxicity and Health-Related Quality of Life After Adjuvant Chemoradiation Therapy or Radiation Therapy Alone for High-Risk Endometrial Cancer in the Randomized PORTEC-3 Trial.* Int J Radiat Oncol Biol Phys, 2021. **109**(4): p. 975-986.
60. Kandoth, C., et al., *Integrated genomic characterization of endometrial carcinoma.* Nature, 2013. **497**(7447): p. 67-73.
61. Stelloo, E., et al., *Refining prognosis and identifying targetable pathways for high-risk endometrial cancer; a TransPORTEC initiative.* Mod Pathol, 2015. **28**(6): p. 836-44.
62. Talhouk, A., et al., *A clinically applicable molecular-based classification for endometrial cancers.* Br J Cancer, 2015. **113**(2): p. 299-310.
63. Stelloo, E., et al., *Improved Risk Assessment by Integrating Molecular and Clinicopathological Factors in Early-stage Endometrial Cancer-Combined Analysis of the PORTEC Cohorts.* Clin Cancer Res, 2016. **22**(16): p. 4215-24.
64. Talhouk, A., et al., *Confirmation of ProMisE: A simple, genomics-based clinical classifier for endometrial cancer.* Cancer, 2017. **123**(5): p. 802-813.
65. Kommoss, S., et al., *Final validation of the ProMisE molecular classifier for endometrial carcinoma in a large population-based case series.* Ann Oncol, 2018. **29**(5): p. 1180-1188.
66. Concin, N., et al., *ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma.* Int J Gynecol Cancer, 2021. **31**(1): p. 12-39.
67. Creutzberg, C., *PORTEC-4a: Molecular Profile-based Versus Standard Adjuvant Radiotherapy in Endometrial Cancer (PORTEC-4a).* https://clinicaltrials.gov/ct2/show/NCT03469674, 2016. **Accessed May 3, 2022**.