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Uitgangsvraag 2

Voor welke patiënten met endometriumcarcinoom geeft adjuvante therapie een betere (ziektevrije) overleving en/of betere kwaliteit van leven dan chirurgie zonder adjuvante therapie?

Study (trial) ID	Study type	Source of funding/Conflicts of interest	Setting	Country	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up
1. Writing committee on behalf of ASTEC study group, 2009 (Blake et al.) (1)	Updated meta-analysis and intergroup RCT	*Funding* Medical Research Council, National Cancer Research Network, National Cancer Institute of Canada, with funds from the Canadian Cancer Society *Conflict of interest* None declared	112 centres in 7 countries	UK, USA, Canada, Poland, Norway, New Zealand, Australia,	- Is there a benefit for external beam radiotherapy for early endometrial cancer at intermediate or high risk of recurrence, in terms of overall, disease-specific, and disease-specific recurrence-free survival? - The main aim of updating the review of Kong et al. 2007 (2) was to assess the effect of radiotherapy in intermediate-risk and high-risk early-stage disease	*Inclusion* - Women with histologically confirmed endometrial cancer, macroscopically confined to the uterine corpus (FIGO stage I) or endocervical glands (IIA), with pathological features suggestive of an intermediate or high risk of recurrence including: FIGO stage IA/IB grade 3; IC all grades; papillary serous; or clear cell histology all stages and grades - Lymphadenectomy as part of surgical staging was not required for randomisation - Pelvic lymph nodes could be negative or not examined; women with positive pelvic lymph nodes were eligible for ASTEC - Peritoneal cytology could be negative, positive, or not done - Women had to be fit to receive external beam radiotherapy and all women gave written informed consent *Exclusion* - Positive para-aortic nodes were viewed as indicative of unrecognised macroscopic disease and were excluded of randomisation - Women with positive pelvic lymph nodes excluded for EN.5	*ASTEC/EN.5* - 905 women with intermediate-risk or high-risk early-stage disease (789 ASTEC; 116 EN.5) - Randomly assigned after surgery to: • Observation n=453 • External beam radiotherapy n=452 *Updated meta-analysis* - 2 included RCTs (3, 4) - 2 excluded RCTs (5, 6)
2. Gien et al., 2008 (7, 8)	Systematic review with meta-analyses and practice CCO guideline	*Funding* The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source *Conflict of interest* None declared	NA	Canada	What is the role of hormonal therapy as adjuvant therapy in patients with stage I endometrial cancer?	- Medline (1966-January 2007) - Embase (1988-January 2007) - Cochrane Library database (Issue 1, 2007) - Physician Data Query database - Canadian Medical Association InfoBase - National Guideline Clearinghouse - Abstracts published in the proceedings of the meetings of the American Society of Clinical Oncology (1997-2006) and European Society for Medical Oncology (2002-2006) *Search terms* - Combination disease-specific terms (endometrial neoplasms/or endomet:.ti. and cancer.ti. or neoplasms/ or carcinoma:.ti. or	- 9 RCTs (9-17) - The Urbanski et al. trial (11) was excluded from meta-analysis - 1 meta-analysis (18)

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						adenocarcinoma:.ti.) with treatment specific terms (antineoplastic agents, hormonal/) for the following study designs: RCTs, practice guidelines, systematic reviews, metaanalyses *Inclusion* - Study randomized patients with stage I endometrial cancer either to adjuvant hormonal therapy or to no adjuvant treatment or other forms of hormonal therapy - At least 60% of the patients reported had stage I disease or results were reported separately for patients with stage I disease - Report had to include at least one of the following outcomes: overall survival, disease-free survival, recurrence (local, or distant, or both), adverse effects, quality of life *Exclusion* - Case reports, letters, editorials, or papers published in a language other than English	
3. Johnson et al., 2007 (19)	Systematic review and meta-analysis	*Conflict of interest* None declared	NA	UK	To clarify the effect of postoperative (adjuvant) external-beam pelvic radiotherapy (EBRT) for different grades of early endometrial cancer	- The search strategy followed the Cochrane Gynaecological Cancer Collaborative Review Group search strategy - Medline (1951-16 March 2005) - Embase (1974-16 March 2005) - CENTRAL on the Cochrane Library - Cochrane Database of Systematic Reviews - Gynaecological Cancer Group Specialised Register, PubMed, TRIP, Trials Central, Current Controlled Trials, and Centerwatch Clinical Trials Listing Service - Other results from the PORTEC study were obtained directly from the authors *Inclusion* - All RCTs studying prophylactic radiotherapy for excised endometrial cancer - Only RCTs considering FIGO stage I and II treated by primary hysterectomy and bilateral salpingo-oophorectomy were considered *Exclusion* - RCTs comparing radio- with chemotherapy, cancer beyond the uterus, and serous papillary pathology	- 7 RCTs were identified; 5 were eligible for meta-analysis (3-6, 20-22) - Homogeneity was confirmed (I^2 < 25%)
4. Kong et	Meta-	*Internal sources of support*	NA	UK	To assess the efficacy of adjuvant	- Used Cochrane Collaboration guidelines to	- 29 studies were chosen for

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al., 2007 (2, 23)	analysis	- NHS R & D programme, UK - Medical Research Council, UK *External sources* - No sources of support supplied *Conflict of interest* None declared			radiotherapy (both external beam radiotherapy and vaginal intracavity brachytherapy) when used following surgery for stage I endometrial cancer	carry out the systematic review after written a predefined protocol - CENTRAL on the Cochrane Library (2005) - Medline (1966-2005) - Embase (1980-2005) - CancerLit (1966-2005) - Physician Data Query (PDQ) of National Cancer Institute (open and closed trials) - Specialised Register of the Cochrane Gynaecological Cancer Review Group (CGCRG) - Reference lists of relevant papers found - Meta-register and its links searched for ongoing trials - Proceedings of the Annual Meetings of the American Society of Clinical Oncology *Search terms* Cancer*, carcinoma*, tum?r*, adenocarcinom* ,"neoplas*, endometrium-tumour, uter*, endometr*, corp* near uter*, radiotherap*, radiation*, brachytherap*, teletherap*,irradiat*, external beam therapy, cobalt, radium,iridium, radiotherapy, controlled-study, clinical-trials, phase-3-clinical-trial, random*, randomized-controlled-trial, trial*, compar*, control*,study*, follow* and up, clinic*, blind, double-blind-procedure, singleblind-procedure , placebo*, cross?over*, comparative-study, allocat* *Inclusion* - Closed randomised and quasi RCTs comparing surgery and radiotherapy with surgery alone for stage I endometrial cancer *Exclusion* - Non-randomised trials, trials of preoperative radiotherapy, trials of sarcoma, or in trials of mixed histology, those where the data on sarcoma cannot separated out, trials where one /more of the groups contains >10 patients	further assessment - Meta-analysis performed on 4 trials (3 published, 1 unpublished) (3-6) - In total 1770 patients • Treatment group n=870 • Control group n=900
5. Deeks, 2007 (24)	Systematic review	*Conflict of interest* None declared	NA	New Zealand	To examine the evidence for the efficacy and tolerability of local therapies in the treatment of patients with endometrial cancer	- Medline (1966-April 2007) - Embase (1980-April 2007) - Cochrane Library - Odyssey (proprietary database of WK Health)	- 5 RCTs (3, 4, 6, 25-28) - 1 Cochrane review (23) - 2 systematic reviews (29, 30)

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						Search terms (brachytherapy OR intracavitary radiation OR external beam radiation OR pelvic radiation therapy OR irradiation OR surgery) AND (endometrial cancer OR endometrial carcinoma OR endometrial adenocarcinoma) *Inclusion* RCTs and systematic reviews or meta-analyses of RCTs *Exclusion* Individual RCTs with <3-year follow-up and trials published >10 years previously	
6. Lukka et al., 2006 (29)	Systematic review	*Funding* - Cancer Care Ontario's Program in Evidence-based Care - Ontario Ministry of Health and Long-term Care *Conflict of interest* None declared	NA	Canada	- What is the role of postoperative radiotherapy in women with stage I endometrial cancer, whether completely or incompletely surgically staged? - Are there any subgroups of patients with stage I endometrial cancer who would benefit from postoperative radiotherapy? If so, which radiotherapy treatment is recommended?	- Medline (1966-October 2005) - Embase (1980-October 2005) - Cochrane Library (2005, Issue 2) - Abstracts published in proceedings of the annual meetings of the American Society of Clinical Oncology (1997-2005) and American Society of Therapeutic Radiology and Oncology (1996-2004) *Search terms* Endometrial neoplasms (MeSH) and uterine neoplasms (MeSH) combined with radiation (MeSH) and postoperative (MeSH), which were combined with search terms for study designs: practice guidelines, meta-analyses, RCTs, controlled clinical trials *Inclusion* - Systematic reviews, practice guidelines, meta-analyses or RCTs comparing adjuvant radiotherapy to either no adjuvant radiotherapy or another form of adjuvant radiotherapy in women with early stage endometrial cancer - Reported at least 1 of the following outcome measures: survival, rate of recurrence (or metastases) or toxicity	- 5 RCTs were identified that evaluated adjuvant external beam radiotherapy (EBRT) and/or intracavitary radiotherapy (ICRT) including one in which women had undergone complete surgical staging (3-5, 31, 32) - 1 RCT was a small study and beyond the scope of the review as it did not shed light on the role of radiotherapy since the comparison was made to endocrine treatment (32)
7. Martin-Hirsch et al., 2000 (18)	Meta-analysis	*Internal sources of support* - University of Manchester, UK *External sources* - Royal College of	NA	UK	To ascertain if adjuvant progestagen therapy effects outcome after surgical treatment of endometrial cancer with regards to overall death, death due to endometrial cancer, or death due to intercurrent disease and relapse rate of	- Search strategy was similar to the one that is advocated by the Cochrane Collaboration - MEDLINE (< May 1999) - Cochrane Gynaecological Cancer Group trials register (< May 1999) - Hand search 16 journals thought to be most	- 6 RCTs involving 4.351 women (12-14, 16, 17, 33) - The trial by Urbanski et al. is eliminated from the meta-analysis, justified by the unequal distribution of risk factors and the

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		Obstetricians and Gynaecologists, UK - WellBeing Charity, UK *Conflict of interest* None declared			disease	likely to contain relevant publications *Search terms* Terms for RCTs/clinical trials in combination with 'genital neoplasms, female' *Inclusion* - RCTs of progestagen therapy in women who have had surgery for endometrial cancer - Trial quality was assessed and 2 reviewers abstracted data independently	extreme heterogeneity induced by its inclusion (11)
8. Kuoppala et al., 2008 (34)	Randomized trial	*Conflict of interest* None declared	4 Finnish university hospitals	Finland	To establish whether platinum-based chemotherapy combined with standard surgery and radiotherapy will improve overall and disease-free survival and lower the recurrence rate in patients with high-risk endometrial cancer	*Inclusion* - Patients with locoregional high-risk endometrial carcinoma, FIGO Stage IA-B Grade 3 or Stage IC-IIIA Grade 1-3, based on surgical staging(total abdominal hysterectomy bilateral salpingo-ophorectomy and peritoneal cytological sampling, along with at least a pelvic lymphadenectomy in 80% of the patients)	- Postoperative treatment in 156 patients: • Radiotherapy n=72 • Radio- & chemotherapy n=84 - All analyses were based on the intention-to-treat principle - All randomized patients were included in the analysis
9. Susumu et al., 2008 (35)	Randomized phase III trial	*Conflict of interest* None declared	103 member institutions of the JGOG	Japan	To establish an optimal adjuvant therapy for intermediate- and high-risk endometrial cancer patients a RCT was conducted of adjuvant pelvic radiation therapy (PRT) versus cyclophosphamide-doxorubicin-cisplatin (CAP) chemotherapy in women with endometrioid adeno-carcinoma with deeper than 50% myometrial invasion	*Inclusion* - FIGO stage IC-IIIC endometrial carcinoma with deeper than 50% myometrial invasion and absence of any prior chemotherapy, irradiation, or surgery for the treatment of any other cancer - <75 years old, WHO performance status of 0 to 3, initial surgery (including total abdominal hysterectomy and bilateral salpingo-oophorectomy, with no residual tumor) - Treatment was initiated within 4 weeks of surgery *Exclusion* - Patients with stage II or III without deeper than 50% myometrial invasion - Patients with other active cancers or without adequate liver, renal, bone marrow functions	- 385 eligible patients: • PRT n=193 • CAP n=192 - Initial enrolment was 475 patients, 41 of whom were ineligible due to myometrial invasion of less than 50%, histological diagnosis of sarcoma, or rapid progression of disease after enrollment. An additional 49 patients with non-endometrioid histology were excluded - All analyses were based on the intention-to-treat principle
10. Randall et al., 2006 (36)	Randomized phase III trial (GOG 122)	*Funding* - National Cancer Institute grants to the Gynecologic Oncology Group Administrative Office (CA 27469) and the Gynecologic Oncology Group Statistical and Data Center	Multicenter	USA	To compare whole-abdominal irradiation (WAI) and doxorubicin-cisplatin (AP) chemotherapy in women with stage III or IV endometrial carcinoma having a maximum of 2 cm of postoperative residual disease	*Inclusion* - Patients with FIGO stage III or IV endometrial carcinoma of any histology - Total abdominal hysterectomy and bilateral salpingo-oophorectomy, surgical staging, tumor resection, and no single site of residual tumor >2 cm. Nodal sampling was optional for patients with stage III or IV disease by clinical	- 422 women entered the study; 396 were initially eligible: • WAI n=202 • AP n=194 - Reasons for the exclusion of 34 patients (15 on the WAI arm and 19 on the AP arm) included

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		(CA 37517) *Conflict of interest* - Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest: H. Muss, J. Fowler, J. Thigpen				or surgical criteria - Patients with positive para-aortic lymph nodes were required to have negative scalene node biopsies and chest CT scans - Adequate hematologic (WBC ≥3,000/µL, platelets ≥100,000/µL; granulocytes ≥1,500/ µL), renal (creatinine ≤2 mg%), and hepatic (bilirubin ≤1.5X the institutional normal value and AST ≤3X the institutional normal value) function, normal cardiac ejection fraction, and Zubrod (GOG) performance status of 0 to 3 *Exclusion* - Patients with recurrent disease; parenchymal liver, lung, or other hematogenous metastasis; inguinal lymphnode involvement; or a history of pelvic or abdominal radiation or chemotherapy	wrong stage (n=3), double primary (n=8), wrong cell type (n=4), prior malignancy (n=1), residual disease more than 2 cm (n=1), incomplete lymph node sampling or laparoscopic surgery (n=8), registration error (n=1), and inadequate documentation of pathology (n=8). The 8 patients (4 on each arm) deemed ineligible because of unilateral lymph node sampling or use of laparoscopic surgery are included in the analyses - Analyses were based on the intention-to-treat principle after excluding ineligible patients
11. Bruner et al., 2007 (37)	Randomized phase III trial (GOG 122) on quality of life	*Funding* For details see Randall et al., row above *Conflict of interest* None declared	Multicenter	USA	Objectives of the QOL component in GOG 122 trial were to: 1. Compare between-arm differences in serial changes in QOL-specific parameters including fatigue, changes in elimination, neurologic impairment, and overall QOL 2. Assess changes in QOL from pre-treatment to end of treatment and through 6 months post-treatment, for each arm	*Inclusion* For details see Randall et al., row above *Exclusion* For details see Randall et al., row above	- 317 of 396 (80%) eligible patients enrolled on the clinical study provided a baseline QOL assessment: • WAI n=163 • AP n=154 - Analyses were based on the intention-to-treat principle after excluding ineligible patients
12. Homesly et al., 2009 (38)	Randomized phase III trial	*Funding* - National Cancer Institute grants to the Gynecologic Oncology Group (GOG) Administrative Office (CA 27469) and the GOG Statistical and Data Center (CA 37517) *Conflict of interest* The authors declare that there are no conflicts of interest with the exception of Dr. Susan Gibbons who reports EntreMed Millennium Stock purchase 2003 <$1500 and Dr. Harry Long III who reports stock ownership of	Multicenter	USA	To test the hypothesis of no increase in recurrence-free survival associated with the addition of paclitaxel to cisplatin and doxorubicin in patients with Stage III or IV endometrial carcinoma (≤2 cm residual disease) following initial surgery and tumor volume directed irradiation	*Inclusion* - Patients diagnosed with Stage III or IV endometrial carcinoma of any histology, including clear cell and serous papillary carcinomas, with disease limited to the pelvis and abdomen, were initially eligible - As of June 2003, eligible patients had to have positive adnexa, tumor invading the uterine serosa, positive pelvic and/or para-aortic nodes, positive pelvic washings or vaginal involvement within the radiation port - Surgery must have included hysterectomy and bilateral salpingoophorectomy. Pelvic or para-aortic lymph node sampling was not required. Tumor debulking must have resulted in a maximal residual diameter of 2 cm - Radiotherapy was to be initiated within 8 weeks after surgery, and chemotherapy was	- Of 659 patients enrolled following surgery, 552 eligible patients were randomized to chemotherapy after irradiation: • Cisplatin/doxorubicin (CD) n=270 (18 of 288 not eligible) • Cisplatin/doxorubicin/paclitaxel (CDP) n=282 (16 of 298 not eligible)

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		<$10,000 per company: AstraZeneca, Amgen, Bristol Myers Squibb, Genentech, GlaxoSmithKline, Novartis, Sanofi-Aventis, Pfizer				to be initiated within 8 weeks after radiation - Pre-entry chemistry requirements: absolute neutrophil count (ANC) ≥1500/mcl, platelet count ≥100,000/mcl, SGOT, SGPT, and alkaline phosphatase ≤3× normal, bilirubin ≤1.5× normal, creatinine ≤1.6 mg/dl, and LVEF ≥50% measured within 6 months of entry. Patients must have had a GOG performance status of no more than 2. IRB approval and informed consent were required *Exclusion* - Patients with recurrent disease, history of pelvic/abdominal radiation therapy, history of malignancy evident within the last 5 years or who had received prior chemo- or radiation therapy for that malignancy or history of a serious comorbid illness that would preclude protocol therapy were ineligible and those with an expected survival < 3 months - If scalene node biopsy and/or chest CT scan was positive for metastasis	
13. Fujimura et al., 2000 (39)	Randomized trial	*Conflict of interest* None declared	Tokai Endometrial Cancer Study Group (Nagoya University and related institutions)	Japan	To determine the outcome of patients with endometrial endometrioid adenocarcinoma following adjuvant chemotherapy, CAP (cyclophosphamide, pirarubicin and cisplatin) and EP (etoposide and cisplatin) were assigned at random to patients with IC or more advanced stage carcinoma, and their efficacy was compared	*Inclusion* - Patients with endometrioid adenocarcinoma *Exclusion* - Patients with metastatic ovarian carcinoma or double carcinoma - Patients undergoing preoperative chemotherapy, patients undergoing combined radiotherapy and patients who were lost to follow-up before study completion were excluded from the study	- 134 patients were registered and treated, 98 were included in the trial: • CAP n=55 • EP n=43 - Patients who were lost to follow-up before study completion were excluded from the study

ID	Duration of the study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/comparator (including duration, dose)
1	- July 1996 (EN.5 1996; ASTEC 1998) - March 2005 - Median follow up 58 months	- Randomisation by telephone to the MRC Clinical Trials Unit (ASTEC centres) or to the NCIC Clinical Trials Group (EN.5 centres) - Computer randomisation in both trials used method of minimisation - Minimisation factors ASTEC: centre, WHO performance status (0-1 vs. 2-4), nodes involved (yes vs. no), depth of invasion (inner half vs. outer half), positive peritoneal cytology (yes vs. no), and tumour grade (G1/G2 vs. G3) - Minimisation factors EN.5: centre, tumour grade (G1 vs. G2 vs. G3), surgical staging defined as at least one pelvic lymph node identified (yes vs. no), and sexual health assessment (yes vs. no) - Randomisation based on local pathology	*Median age* - Observation: 66 years - External beam radiotherapy: 65 years *FIGO stage* Observation (n=453) / External beam radiotherapy (n=452) IA 11 (2%) / 15 (3%) IB 79 (18%) / 76 (17%) IC 336 (75%) / 343 (76%) IIA 21 (5%) / 16 (4%) IIB 3 (1%) / 0 III/IV 0 / 1 (<1%) Unknown 3 (1%) / 1 (<1%) *Differentiation or grade* Observation (n=453) / External beam radiotherapy (n=452) Well (G1) 107 (24%) / 15 (3%) Moderate (G2) 185 (41%) / 76 (17%) Poor (G3) 107 (24%) / 343 (76%) Clear cell/serous papillary/mixed 52 (12%) / 16 (4%) Not applicable 2 (<1%) / 0 - Baseline data generally balanced between the 2 groups, except for a small imbalance in the proportion of high-risk women, with 25% of those in the observation group classified as high risk compared with 20% in the radiotherapy group	*Intervention* - Eligible women randomly allocated after surgery to observation group with no external beam radiotherapy or systemic treatment until recurrence, or to the external beam radiotherapy group - Radiotherapy started as soon as possible after wound healing, 6-8 weeks after surgery. In EN.5, a specified date on which radiotherapy would occur (if allocated) was available at randomisation (no later than 12 weeks after surgery) - Target dose 40-46 Gy (45 Gy in EN.5) in 20-25 daily fractions (25 fractions in EN.5) to the pelvis, treating 5 times a week - Brachytherapy allowed if the centre's policy was to offer it to all stage I or IIA women irrespective of radiotherapy allocation. In ASTEC, 2 fractions of 4 Gy at 0.5 cm over 3-7 days at high dose rate or 15 Gy at low dose rate (50 cGy per h) was recommended to the upper third of the vagina. When using the LDR Selectron at around 170 cGy per h, a dose of 13.5 Gy at 0.5 cm depth. In EN.5, brachytherapy was given in accordance with local practice *Compliance* - 92% of women randomised to external beam radiotherapy received it with or without brachytherapy - Median dose was 45 Gy in 25 fractions over 34 days, giving 82% compliance with the planned dose of 40-46 Gy in 20-25 fractions - Compliance with stated brachytherapy policy was 80% - Similar proportions of women in both groups received brachytherapy, with 235 (52%) in the observation group and 242 (54%) in the external beam radiotherapy group	- Observation with no external beam radiotherapy or systemic treatment until recurrence
2	NA	NA	Women with newly diagnosed stage I endometrial cancer	NA	NA
3	NA	NA	Women with different grades of early endometrial cancer	NA	NA
4	NA	NA	Women with stage I endometrial cancer who had been treated surgically with a hysterectomy and bilateral oophorectomy with or without pelvic and para-aortic lymphadenectomy	Surgery with the addition of either none or one or both of the following, with the intention to start within 3 months of surgery: 1. External beam radiation therapy to the pelvis and/or para-aortic nodes (abdominal radiotherapy) 2. Vaginal intracavitary brachytherapy	NA
5	NA	NA	Patients with endometrial cancer	NA	NA
6	NA	NA	Women with stage I endometrial cancer	NA	NA
7	- Duration of follow-up of patients varied from 12 to 130 months	NA	- Women following hysterectomy for endometrial cancer - 3 trials included women with stage I disease only (12, 16, 17), whereas 3 included women with more	*Intervention* - Adjuvant progestagen therapy - Progestagens used were Medroxy Progesterone Acetate or Hydroxyprogesterone Caproate	No adjuvant therapy

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			advanced disease (13, 14, 33) - In all trials, except that conducted by Lewis (17), patients had surgery (total abdominal hysterectomy and bilateral salpingooophorectomy) and then adjuvant radiotherapy if indicated by standard pathological criteria	*Compliance* - In 2 trials (16, 33) all the patients initially randomised completed the study protocol. Some patients in the studies by MacDonald (14) and De Palo (12) did not complete the study protocol but outcome data for such patients were given. In the studies by Lewis (17) and Vergote (13) there were insufficient data for an intention to treat analysis	
8	- Treatment between April 1992-April 1996 - Follow-up to April 2001 (for 5 years after completion of the treatment)	- Finnish Cancer Registry randomized patients centrally to 2 groups	- Patients with locoregional high-risk endometrial carcinoma, or FIGO Stage IA-B Grade 3 or Stage IC-IIIA Grade 1-3, based on a surgical staging *Median age* - Radiotherapy: 74 years - Radio- and chemotherapy: 73 years *FIGO stage* Radiotherapy (n=72) / Radio- and chemo therapy (n=84) IA+B G3: 14 (20%) / 14 (17%) IC: 36 (50%) / 39 (46%) IIA+B: 13 (18%) / 21 (25%) IIIA: 9 (13%) / 10 (12%) G*rade* Radiotherapy (n=72) / Radio- and chemo therapy (n=84) 1: 21 (29%) / 27 (32%) 2: 27 (38%) / 28 (33%) 3: 24 (33%) / 29 (35%) - The groups were similar in respect of age, body mass index, type of operation, stage, grade, histopathological diagnosis	*Intervention* - 3 chemotherapy cycles consisting of cisplatin 50 mg/m^2, epirubicin 60 mg/m^2 and cyclophosphamide 500 mg/m^2 - 1st cycle was given immediately after final histopathological report was available, or 1 to 2 weeks after surgery - 2nd cycle was carried out during the pause in radiotherapy and the last within 2 weeks after the completion of the 2nd radiation course *Compliance* - Percentage successful radiotherapy treatments equal in both groups (92-94% of the patients) - Chemotherapy was implemented in 3 courses. The treatment according to the protocol was administered during these courses in 79 (94.0%), 70 (83.3%) and 64 (76.2%) patients, respectively	- Pelvic radiotherapy alone without chemotherapy - A total dose of 56 Gy (2 Gy/fraction) was given to the pelvis using a four-field technique. The treatment was carried out in 2 courses 28 Gy each, separated by a pause of 3 weeks. The first course was started 4-5 weeks following surgery
9	- Patient accrual 1994-2000 - The analysis was performed using data finalized on April 14, 2005 - Median follow-up periods in the PRT and CAP groups were 59.5 (2.2-60.8) months and 60.8 (5.0–60.8) months	- An allocation table was prespecified based on a simple randomization - Each participant was assigned by central telephone system	- Patients with endometrioid adenocarcinoma with deeper than 50% myometrial invasion *Average age* - PRT: 59 years - CAP: 59 years *FIGO stage* PRT (n=193) / CAP (n=192) IC: 123 (64%) / 112 (58%) IIA: 10 (5%) / 8 (4%) IIB: 10 (5%) / 25 (13%) IIIA: 28 (15%) / 22 (12%) IIIB: 0 (0%) / 1 (1%)	*Pelvic irradiation* - Given in an open field using the anterio-posterior parallel opposing technique. The scheduled dose of irradiation was 45 to 50 Gy within 4 to 6 weeks, with 9 to 10 Gy of irradiation administered per week (5 working days per week) - Subsequently, additional irradiations were performed in 11 cases (5.7%) with paraaortic lesions and in 6 patients (3.1%) who received brachytherapy *Chemotherapy* - Received cyclophosphamide (333 mg/m^2), doxorubicin (40 mg/m2), and cisplatin (50 mg/m^2) (CAP chemotherapy) every 4 weeks for 3 or more courses - Dose modifications of doxorubicin and cisplatin: a 25%	NA

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			IIIC 22 (11%) 24 (13%) G*rade* PRT (n=193) CAP (n=192) G1 107 (55%) 106 (55%) G2 53 (28%) 64 (33%) G3 33 (17%) 20 (10%) - The study groups were well balanced for patient characteristics including age, postmenopausal status, co-morbidity, type of hysterectomy, postoperative stage, tumor grade, myometrial invasion, lymphovascular space invasion, cervical involvement, parametrial invasion, peritoneal cytology, adnexal metastasis, pelvic lymph node metastasis, and paraaortic lymph node metastasis	reduction of both drugs was allowed for body weight <40 kg or age >70 years old, and a 50% reduction was allowed in patients with G3 or G4 myelosuppression *Compliance* - Treatment was completed in 98.9% (184/186) and 97.3% (183/188) of the patients in the PRT and CAP groups - Pelvic radiation was completed when the total radiation dose reached 40 Gy and chemotherapy when the number of CAP courses reached 3 - Median total doses were 50 Gy of pelvic irradiation and 1309 mg/m^2 cyclophosphamide, 120 mg/m^2 doxorubicin, and 180 mg/m^2 cisplatin. The median number of CAP courses was 3, ranging from 1 to 7. The median duration of treatment was 5.1 weeks and 11.4 weeks in the PRT and CAP groups	
10	- Study entry: May 1992-February 2000 - Median follow-up of 74 months among living patients	- The GOG Statistical and Data Center randomly assigned therapy to each patient with equal probability of assignment to each treatment regimen - A balanced block randomization was used to balance assigned treatment regimens within each institution - The sequence of treatment assignments was concealed from institutions and patients until telephone registration with verification of eligibility	- Patients with stage III or IV endometrial carcinoma having a maximum of 2 cm of postoperative residual disease *FIGO stage* WAI (n=202) AP (n=194) IIIA 57 (28%) 35 (18%) IIIB 4 (2%) 4 (2%) IIIC 90 (45%) 100 (52%) IVA/IVB 51 (25%) 55 (28%) G*rade* WAI (n=202) AP (n=194) 1 30 (15%) 25 (13%) 2 59 (29%) 59 (30%) 3 105 (52%) 102 (53%) - The treatment arms were balanced in terms of patient characteristics. There are slight imbalances with respect to mixed cell type and FIGO stage. More notable imbalances between treatment arms are apparent in nodal involvement and individual sites of disease. Most imbalances are skewed toward poor prognosis in the AP arm	- Protocol treatment was to be started within 8 weeks of surgery *Radiation therapy* - WAI was delivered with an open-field AP/PA technique. Prescribed dose was 30 Gy in 20 daily fractions. Kidney blocks were used posteriorly during WAI; no liver shielding was used - After WAI, patients received a boost to the true pelvis or to an extended field encompassing pelvic lymph nodes (PLNs) and PALNs. A boost to both areas was administered to patients with positive PLN and no PALN sampling or patients with neither PLN nor PALN sampling - Pelvic (±para-aortic) boosts were accomplished using a four-field box technique with custom blocking to minimize the treated small-bowel volume. The boost dose was 15 Gy in 8 fractions. All fields were treated once daily, 5 days per week. If more than a 2-week treatment interruption was required, resumption of treatment was at the physician's discretion, and follow-up continued regardless of treatment *Chemotherapy* - Doxorubicin 60 mg/m^2 plus cisplatin 50 mg/m^2 every 3 weeks for 8 cycles. The maximum allowable cumulative dose of doxorubicin was 420mg/m^2; therefore, only cisplatin was to be infused during the 8th cycle. Hydration was maintained by administering normal saline at 500 mL/h for 2 hours before and after the cisplatin dose - Treatment with chemotherapy required a minimum pretreatment granulocyte count of 1,500/µL and a minimum platelet count of 100,000/µL. Doxorubicin doses were reduced based on pretreatment blood counts, with dose levels reduced from 60 to 15 mg/m^2 in 15-mg/m^2 increments. Doses were	NA

ID	Duration of the study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/comparator (including duration, dose)
				reinstituted with recovery of myelosuppression. Treatment interruption caused by myelosuppression exceeding 6 weeks required discontinuation of protocol therapy - The use of growth factors was not controlled, and data regarding their use were not routinely gathered - A normal cardiac ejection fraction based on institutional values was required. A decline in the ejection fraction of 20% of the baseline value or development of congestive heart failure or other life-threatening cardiac problems required discontinuation of doxorubicin; however, cisplatin treatment continued. Only cisplatin was withheld for serum creatinine >2.0mg. Treatment interruptions as a result of neurotoxicity, including hearing loss, were left to the discretion of the patient and physician *Compliance* - 84% of patients completed radiation therapy - 63% of patients completed 8 cycles of chemotherapy - Patients discontinued therapy early most often as a result of toxicity (17% in the AP arm vs. 3% in the WAI arm) - 5 patients died before completing therapy (4 on the AP arm)	
11	- Study entry: May 1992-February 2000	- The GOG Statistical and Data Center randomly assigned therapy to each patient with equal probability of assignment to each treatment regimen - A balanced block randomization was used to balance assigned treatment regimens within each institution - The sequence of treatment assignments was concealed from institutions and patients until telephone registration with verification of eligibility	- Patients with stage III or IV endometrial carcinoma having a maximum of 2 cm of postoperative residual disease *Median age* - WAI: 64.2 years - AP: 62.9 years *FIGO stage* WAI (n=163) AP (n=154) III 74% 73% IV 26% 27% G*rade* WAI (n=163) AP (n=154) 1 14% 14% 2 28% 29% 3 55% 53% - No significant differences between the treatment groups with regard to patient characteristics except for duration of treatment, which (as designed) was longer on the AP arm	*Radiation therapy* For details see Randall et al., row above *Chemotherapy* For details see Randall et al., row above *Quality of life (QOL) assessments* - QOL was assessed at 4 time points: pretreatment, end of treatment (EOT), and 3 and 6 months after treatment. Only patients who provided a pre-treatment assessment were included in the QOL analysis at subsequent time points - 3 primary Likert-type, self-rating instruments (Fatigue Scale = FS; Assessment for Peripheral Neuropathy Scale = APN; and Functional Alterations due to Changes in Elimination = FACE) and 1 secondary instrument (Functional Assessment of Cancer Therapy-General = FACT-G) were used to measure QOL - A QOL assessment was considered valid only if the patient completed at least 80% of all the items. The total score for each scale was calculated, and for FACT-G the subtotal score for each domain was also reported. The mean imputation method was used to estimate missing values if less than 50% of the items were missing on a given scale/subscale *Compliance* Among the 317 study participants: - 87% of patients completed radiation therapy - 80% of patients completed at least 6 cycles and 65%	NA

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				completed all 8 cycles of chemotherapy - Among 317 patients who provided a pre-treatment QOL assessment, 1 WAI patient died during treatment, 25 patients died (9 in WAI and 16 in AP) during the first 3 months post-treatment, and another 19 died (10 in WAI and 9 in AP) during the period 3–6 months post-treatment - QOL assessments were completed in 91% of patients at the pre-treatment time point, and in approximately 70-80% of (living) patients at EOT and at the 3- and 6-month post-treatment time points. Compliance patterns were similar between treatment groups - The percentage of incomplete QOL assessments was 10% at baseline, which increased to 23% at EOT and remained at this level at the 3- and 6-month post-treatment time points	
12	- July 2000-September 2004 - Median follow-up 47 months	- Following radiation therapy, the GOG Statistical and Data Center (SDC) randomly assigned the treatment regimen to patients agreeing to continue on study and who had no evidence of recurrent disease	- Patients diagnosed with Stage III or IV endometrial carcinoma of any histology, with disease limited to the pelvis and abdomen *Median age* - CD: 58 years - CDP: 58 years *FIGO stage* CD (n=270) CDP (n=282) III 238 (88%) 248 (88%) IV 32 (12%) 34 (12%) G*rade* CD (n=270) CDP (n=282) 1 46 (17%) 45 (16%) 2 98 (36%) 100 (36%) 3 108 (40%) 120 (43%) - Patient characteristics were comparable for the 2 groups	*Radiation therapy* Tumor volume directed pelvic plus or minus para-aortic node irradiation with or without vaginal boost was then to be given to all patients (for details radiation therapy see article) E*xperimental regimen* - The same for doxorubicin and cisplatin on day 1 as control group but on day 2 paclitaxel 160 mg/m^2 IV over 3 h was added - Filgrastim 5 mcg/kg/day on days 3-12 or pegfilgrastim 6 mg on day 3 was to be given - Treatment interval was 21 days for a maximum of 6 cycles - On day 1, antiemetics included dexamethasone 10 mg IV and a 5HT3 antagonist - Paclitaxel premedication consisted of dexamethasone 20 mg 5-12 h prior to paclitaxel - For grade 4 hematologic toxicity, doxorubicin was reduced to 30 mg/m^2, cisplatin to 30 mg/m^2, paclitaxel to 125 and 100mg/m^2 - No cycle of study therapy was to be given until the ANC was ≥1000/mcl and the platelets ≥100,000/mcl. *Compliance* - Approximately 80% of eligible patients completed 6 cycles of chemotherapy - Study treatment was discontinued early for recurrence in 3% of the patients and for toxicity in 10%, while 5% of the patients refused to complete 6 cycles - 1 patient died before completing all 6 cycles of CDP therapy - In each arm, 80% of each drug's cumulative planned total dose was given over a maximum total treatment time of 5 months	- Doxorubicin 45mg/m^2 IV followed immediately by cisplatin 50 mg/m^2 IV with optional filgrastim (G-CSF) 5 mcg/kg/day on days 2-11 - The maximum body surface area used for dose calculations was 2.0 m^2 - Beginning in May 2002, filgrastim or pegfilgrastim was included in this regimen until the absolute neutrophil count (ANC) had reached 10,000/mm^3 following the expected chemotherapy induced neutrophil nadir - Chemotherapy was to be administered every 21 days for a maximum of 6 cycles
13	- Treatment between January 1992-June 1996	- Eligible patients were randomly assigned to CAP (cyclophosphamide,	- patients with stage stage Ic to IV endometrial endometrioid adenocarcinoma	*CAP* - At day 1 cyclophosphamide, pirarubicin, and cisplatin were administered at doses of 250, 30, and 70 mg/m^2	NA

ID	Duration of the study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/comparator (including duration, dose)
	- 5-year follow-up	pirarubicin and cisplatin) and EP (etoposide and cisplatin) treatment	*Median age* - CAP: 55.2 years - EP: 55.4 years *FIGO stage* CAP (n=55) EP (n=43) IC 17 (31%) 11 (26%) IIA 0 (0%) 4 (9%) IIB 6 (11%) 4 (9%) IIIA 14 (25%) 10 (23%) IIIB 0 (0%) 0 (0%) IIIC 15 (27%) 10 (23%) IVA 0 (0%) 1 (2%) IVB 3 (5%) 3 (7%) G*rade* CAP (n=55) EP (n=43) 1 21 (38%) 21 (48%) 2 17 (31%) 10 (23%) 3 17 (31%) 12 (27%) - There were no differences with respect to background factors including age, stage, and degree of differentiation between both groups	*EP* - Etoposide and cisplatin were administered at doses of 30 (days 1, 3, and 5) and 70 mg/m^2 (day 1), respectively - In both groups, chemotherapy began 3 weeks after surgery, and the treatment cycle consisted of 21 days for 5 courses *Compliance* - The mean total doses of cisplatin for adjuvant therapy were 540 ±175 and 540±225 mg in the CAP and the EP groups, showing no significant difference between the 2 groups	

ID	Primary Outcome Measure(s) Secondary outcome(s)	Effect size-Primary Outcome(s) Effect size-Secondary outcome(s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
1	- Overall survival - Disease-specific survival - Disease-specific recurrence-free survival - Isolated loco-regional recurrence - Treatment toxicity	*Overall survival* **ASTEC/EN.5** - 5-year overall survival: 84% - 135 women (15%) had died (68 observation, 67 radiotherapy) - Overall survival curves showed no evidence of a difference between the 2 groups with a hazard ratio of 1.05 (95% CI 0.75-1.48; p=0.77) **Updated meta-analysis** - The updated meta-analysis of the effect of external beam radiotherapy on overall survival, including ASTEC/EN.5 results, gives a hazard ratio of 1.04 (95% CI 0.84-1.29; p=0.38) - The pooled results effectively rule out an absolute benefit of >3% increase in overall survival from adjuvant pelvic radiotherapy *Disease-specific survival* - 5-year disease specific survival: observation 90%; radiotherapy 89% - 87 women (64%) died from disease or treatment (42 observation, 45 radiotherapy) - An analysis which treated the non-disease, non-treatment related deaths as a competing risk showed a hazard ratio of 1.13 (95% CI 0.74-1.72; p=0.57) *Disease-specific recurrence-free survival* - 5-year disease-specific recurrence-free survival: observation 84.7%; radiotherapy 85.3% - 129 women (14%) had disease recurrence or had died from endometrial cancer (67 observation, 62 radiotherapy) - Competing risk analysis gave a hazard ratio of 0.93 (95% CI 0.66-1.31, p=0.68) *Isolated vaginal or pelvic recurrence-free survival* - 5-year cumulative incidence rate: observation 6.1%; radiotherapy 3.2% (absolute difference 2.9%;95% CI <0.1%-5.9%) - 35% (42/120) of total recurrences were isolated local recurrence - Hazard ratio for isolated vaginal or pelvic recurrence-free survival was 0.46 (95% CI 0.24-0.89, p=0.02) *Effect of risk group* - Hazard ratio of 2.71 (95% CI 1.88-3.90; p<0·0001) shows that women at high risk have a significantly increased risk compared to intermediate risk (77 events intermediate risk, 50 events high risk) - 5-year disease-specific recurrence-free survival: intermediate risk	*Acute toxicity* - Any toxicity experienced: observation 27%; radiotherapy 57% - Mild: observation 17%; radiotherapy 32% - Moderate: observation 8%; radiotherapy 22% - Severe/life threatening: observation <1%; radiotherapy 3% → Acute toxicity after completion of all surgery and radiotherapy was greater in the external beam radiotherapy group than with observation *Late toxicity* - Any toxicity experienced: observation 45%; radiotherapy 61% - Mild: observation 24%; radiotherapy 30% - Moderate: observation 16%; radiotherapy 22% - Severe: observation 3%; radiotherapy 7% - Life threatening: observation 0%; radiotherapy 1% → Late toxicity, predominantly gastrointestinal or urogenital, was also more commonly reported after external beam radiotherapy	- EN.5 and ASTEC were set up as individual trials. The EN.5 trial of the National Cancer Institute of Canada (NCIC) Clinical Trials Group started in 1996, but could not recruit sufficient patient numbers to complete the study as it was originally envisaged. In 1998, the UK Medical Research Council (MRC) launched ASTEC, and invited the NCIC Clinical Trials Group to plan a prospective combination of the EN.5 data with those of ASTEC. ASTEC/EN.5 therefore consists of two trials with separate randomisations combined to make one intergroup trial	A1

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		88.8%; high risk 73.7% (absolute difference at 5 years 15.1%; 95% CI 8.1-22.0%) - No evidence that effect of external beam radiotherapy is different in subgroups of women defined as intermediate risk and high risk (test for interaction for overall survival p=0.83, for disease-specific survival p=0.45) - No evidence effect of external beam radiotherapy is different in women who have had lymphadenectomy as part of primary surgery (test for interaction for overall survival=0.79, for disease-specific survival p=0.22) → Adjuvant external beam radiotherapy cannot be recommended as part of routine treatment for women with intermediate- or high-risk early-stage endometrial cancer with the aim of improving survival. The absolute benefit of external beam radiotherapy in preventing isolated local recurrence is small and is not without toxicity			

2	- Overall survival
	- Disease-free survival
	- Recurrence (local, or distant, or both)
	- Adverse effects
	- Rates of non-cancer-related death
		Survival
		- 1 trial detected a statistically significant difference in overall survival between the treatment group (hydroxyprogesterone caproate) and control group (no further treatment) (11)
		Overall survival rate at 5 years: treatment group 97%, control 69%
		Although 70% of the patients had stage I disease, the results were based on all 205 patients with stages I-III endometrial cancer. A clinically important criticism of the trial is that the prognostic variables in the 2 groups were not equally distributed at baseline: treatment group had more patients with less myometrial invasion, and less patients with advanced-stage disease
		- Remaining 8 trials did not find any significant differences between the treatment and control groups (9, 10, 12-17)
		- Meta-analysis demonstrated no statistically significant difference in overall survival between patients who received an adjuvant hormonal therapy and patients in the control groups (OR 1.10; 95% CI 0.91-1.34); Urbanski et al. trial (11) was excluded from meta-analysis (I^2=20.6%; p=0.27)
		
		Recurrence
		- Recurrence rates were reported in 6 of the 9 RCTs (9-13, 15)
		- 2 RCTs reported a statistically significant difference:
		  - Recurrence in Quinn trial: hormonal treatment group 16%, control group 21% (p<0.05) (10)
		  - Recurrence in Urbanski trial: hormonal treatment group 7%, control group 23% (p<0.01) (11)
		- Pooled analysis 5 RCTs (Urbanski et al. trial (11)) was excluded; I^2= 24.5%; p=0.26), difference in recurrence non significant between groups (OR 0.85; 95% CI 0.65-1.10)
			Adverse effects
			- 5 RCTs reported on major harmful side effects or deaths unrelated to the malignancy, and 3 RCTs reported on minor symptomatic side effects or withdrawals because of toxicity
			
			Serious side effects
			- Serious side effects included thromboembolic events (e.g. deep vein thrombosis, pulmonary embolus, stroke) or cardio-vascular disease (e.g. myocardial infarction, deterioration of congestive heart failure)
			- No statistically significant differences reported between the treatment and control groups (9, 10, 12-14)
			- 1 trial indicated a serious side effect rate of 6% in progestogen group vs. 2% in control group (p value not reported) (9)
			- 1 trial reported higher rates of death from cardiovascular disease in the first 2 years in the progestogen group than in the control group (5% vs. 3%, p=0.07) (13)
			
			Deaths unrelated to malignancy
			- Deaths that were not attributable to malignancy were related mainly to cardiovascular or thromboembolic causes
			- 1 trial showed a statistically significant difference in deaths unrelated to malignancy (9% of patients in the hormonal group vs. 6% of patients in the control group, p=0.04) (13)
			- In the Urbanski trial 11 patient deaths unrelated to malignancy occurred in the control arm, and none occurred in the treatment arm (p value not reported) (11)
			- Remaining trials that reported deaths unrelated to malignancy did not detect any statistically significant difference between
				- Reporting conventions have changed over time, and because the identified trials span a 30-year period, some data considered standard by today's conventions are missing in the reporting of the trials (e.g. reporting of HRs, adverse events, compliance)
				- The inconsistent reporting limit the quality assessment of internal validity related to patient and study characteristics and to outcomes
				- No quality-of-life data, little data on adverse events or treatment compliance, and limited data on recurrence and survival outcomes, especially in regard to HRs and time-to-event estimates, were reported
				- Differences in patient populations, unexpected findings that were not consistent with the results of similar randomized trials, and notable discrepancies between patients at baseline despite the randomization process. These limitations affected the external validity of the trials; however, these trials provide the only randomized data that inform the role of adjuvant hormonal therapy in this patient population
					A1

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		Meta-analysis Martin-Hirsch et al. (18) - Meta-analysis of published data comparing adjuvant progestin therapy to no adjuvant therapy in endometrial cancer (10-14, 16, 17) - Results of the 2 meta-analyses were highly comparable - No significant difference in overall survival between patients who received progestin therapy and those who received no adjuvant treatment (OR 1.05; 95% CI 0.88-1.24; p=0.6) - 3 trials reported recurrence rates (10, 12, 13); marginal reduction in recurrence rate detected among women receiving progestin therapy as compared with women receiving no adjuvant therapy (OR 0.81; 95% CI 0.65-1.01; p=0.06) - Rate of non-cancer-related deaths was significantly higher in the progestin group (OR 1.33; 95% CI 1.02-1.73), presumably because of the adverse cardiovascular effects of progestin treatment → *Recommendation* The available evidence does not demonstrate any benefit for adjuvant hormonal therapy. The use of hormonal therapy is not recommended as adjuvant treatment for patients with stage I endometrial cancer	the treatment and control groups (9, 10, 12, 14) *Minor side effects* - Most common minor side effects included weight gain, peripheral edema, and nausea (9, 12) - 1 trial reported an incidence of overall minor side effects of 53% in the progestin group and 16% in the control group, but did not indicate whether the difference was statistically significant (9) - 1 trial reported a minor side effect rate of 12%, but did not calculate side effects for patients in the control group (12) - 4% of patients in the hormonal therapy group developed hypertension, which disappeared after the drug was stopped(14) - Drop-out rate attributable to toxicity ranged from 5-19% (9, 12, 14) *Quality of life* - None of the studies reported data on quality of life	- Interpretation is confounded by the fact that 5 of the 9 RCTs included between 10% and 35% of patients with greater than stage I disease	
3	- Survival - Site of recurrence - Added complications	*Survival* - Women with low- or intermediate-grade cancers were more likely to die if they received prophylactic EBRT (OR for overall survival 0.71; 95% CI 0.52-0.96; statistically and clinically significant) - Crude data suggest that EBRT was associated with 1 extra fatality per 30, at least 95% certain that prophylactic pelvic EBRT is either harmful or ineffective in improving survival in women with low- or intermediate-risk cancers. This conclusion is robust even if data from the preoperative trial are ignored (OR 0.73; 95% CI 0.52-1.01) - Disease-free survival in women with good WHO performance status (2 or less) is similar in women who did not receive adjuvant EBRT (OR 0.85; 95% CI 0.59-1.24) (3, 5, 21) - The addition of all high-risk data from GOG 99 to this analysis does not favour EBRT (OR 0.97; 95% CI 0.69-1.35) (4, 20) - Death specifically from high-intermediate-risk endometrial cancer in the PORTEC trial was lower in women who received EBRT (12% vs. 14%), but deaths from all causes at 10 years were higher after EBRT (actuarial percentage 39.2% vs. 36.5%) (3, 21) - This negative effect on survival from adjuvant radiotherapy does not apply to high-risk cancer: prophylactic EBRT might be associated with a 10% absolute reduction in death from cancer (OR 0.59; 95% CI 0.30-1.17) (4, 5, 20) - Inclusion of the Argentinean trial data to the meta-analysis	*Toxicity* - In 339 women who started with radiotherapy : 1 woman died of an exacerbation of Crohn's disease soon after radiotherapy; 9 cases of grade 3 gastrointestinal late toxicity requiring surgery (3 for sigmoid stenosis; 6 small-bowel) (3, 21) - In 190 women who received radiotherapy: 2 died of related intestinal damage; 15 women suffered grade 3 or 4 intestinal toxicity compared with 2 in the surgery-only arm (4, 20) - In 55 women who received intracavity radiation: 6 major complications (2 cases of fatal acute hepatic necrosis, operative injury to ureter causing fistulae, wound dehiscence, viral hepatitis and a case of severe radiation cystitis) (22) - In 50 women who received external-beam radiation: 5 serious complications (2 cases of severe radiation enteritis, small-bowel infarction, bowel perforation, and a case of radiation fistulae)(22) - In 263 women who received radiotherapy: 2 died of pelvic radiotherapy complications (1 unspecified complications, 1 ileal resection for obstruction and adhesions complicated by fistulae and death from sepsis), 1 other woman required bladder resection for radiation necrosis (5)	- The data involve heterogeneous cohorts, and subgroup analysis is ad hoc - The RCTs studied span 25 years of research, and the pathology reporting of endometrial carcinoma operative specimens has changed over this time - Over this period, the aetiology of endometrial cancer has evolved due to the changing use of oestrogen hormone replacement therapy, increasing tamoxifen use and increasing lifespan and obesity - Data from intermediate-risk cancers are limited by a relatively small sample size but suggest that the disadvantages of adjuvant EBRT may balance the advantages	A1

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		emphasizes the disease-free survival advantage from 69% to 80% associated with prophylactic radiotherapy (OR 1.76; 95% CI 1.07-2.89) (6) *Recurrence* - Pelvic EBRT reduces the risk of pelvic recurrent disease in all types of invasive endometrial cancer (OR 0.27; 95% CI 0.16-0.44) - This risk reduction does not translate to improved survival from lower risk cancers - The risk of distant metastasis does not seem to be reduced by prophylactic radiotherapy (OR 1.58; 95% CI 1.07-2.35) → Adjuvant EBRT should not be used for low-risk (IA, IB G1) or intermediate-risk (IB G2) cancer, but it is associated with a 10% survival advantage for high-risk (stage IC G3) endometrial cancer. This challenges the role of a staging lymphadenectomy			
4	- Overall survival - Locoregional recurrence - Distant recurrence - Endometrial cancer death - Morbidity - Acute and late side-effects of pelvic radiation	*Death from all causes* - No difference in the deaths from all causes with the RR from additional pelvic radiotherapy of 1.01 (95% CI 0.71-1.43; p=0.97) - Test of heterogeneity not significant (χ^2=5.9, df=3; p=0.12; I^2=49.1%) (3-6) *Endometrial cancer death* - RR 1.22 (95% CI 0.88-1.68; p=0.23) - Test for heterogeneity was not significant (χ^2 =1.14, df=2; p=0.57; I^2=0%) (3-5) *Locoregional recurrence* - External beam pelvic radiotherapy following surgery reduced local regional recurrence, with a RR of 0.28 (95% CI 0.17-0.44; p<0.00001) - 72% reduction in risk of locoregional relapse (95% CI 56%-83%) - Absolute risk reduction (risk difference) 6% (95% CI 4% -8%) - NNT to prevent 1 locoregional recurrence was 16.7 patients (95% CI 12.5-25) - All 4 trials showed positive effect of pelvic radiotherapy on locoregional recurrence. Test of heterogeneity was not significant (χ^2=0.96, df=3, p=0.81; I^2=0%) (3-6) *Distant recurrence* - No statistically significant difference in the distant recurrence rate between the 2 arms, with a RR of 1.28 for the treatment group (95% CI 0.89-1.83; p=0.18) - Test for heterogeneity was not significant (χ^2=2.66, df = 3; p=0.45; I^2=0%) (3-6)	*Complications and side-effects* - In PORTEC 1, the 5-year actuarial rates of late complications (all grades) were 26% in the pelvic radiotherapy group vs. 4% in control group (p<0.0001). Majority of patients experienced mild symptoms; ~3% of treated patients had severe complications (3) - In GOG study, the majority of treated patients also experienced mild symptoms (63% experienced grade 1 or 2 GI side-effects; only 5% experienced grade 3 or 4 GI side-effects). 6 women in the radiotherapy arm experienced grade 3 or 4 intestinal obstruction vs. 1 in control group. 2 women in the radiotherapy arm died from complications involving intestinal injury thought to be radiation related (4) - In the Aalders study, of the patients who received intravaginal radium brachytherapy alone, 1 patient developed a rectovaginal fistula and 1 developed a urethral stricture. Of the patients who received additional pelvic radiotherapy, 2 women had severe complications related to radiotherapy and 1 woman developed radiotherapy-related bladder necrosis necessitating a partial bladder resection (5)	- Heterogeneous group of patients with different prognostic factors, ranging from stage IB/IC to occult stage II and tumour grade 1 to grade 3	A1

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		Subgroup analysis *Patients with at least 1 risk factor of grade 3 and stage 1C* - 3 trials showed no statistically significant difference in both deaths from all causes and endometrial cancer between the treatment group and control group (3-5) - RR of death from all causes for treatment group 1.00 (95% CI 0.80-1.26; p=0.98) - RR of endometrial carcinoma-related death 0.88 (95% CI 0.62-1.24; p=0.45) *Patients with at least 2 risk factors incl. grade 3 and stage 1C* - Trend towards a reduction in both deaths from all causes and endometrial carcinoma-related deaths although these were not statistically significant (4, 5) - RR of death from all causes for patients having radiotherapy vs. control 0.76 (95% CI 0.49-1.19; p=0.24) - RR endometrial cancer death 0.65 (95% CI 0.38-1.14; p=0.13) *Patients without risk factors grade 3 or stage 1C* - Greater risk of endometrial carcinoma-related deaths which were statistically significant with a RR of 2.65 (95% CI 1.05-6.67; p=0.04). This is because endometrial carcinoma-related deaths also included treatment-related deaths (4, 5) - Greater risk for deaths from all causes for the treatment group, RR 1.49 (95% CI 0.56-3.95; p=0.42) *Patients who had undergone pelvic and paraaortic lymphadenectomy* - External beam radiotherapy reduced all recurrences in this group of patients (RR 0.47, 95% CI 0.28-0.77; p=0.003) - No reduction in death from all causes (RR 0.72, 95% CI 0.26-1.97; p=0.52) (4, 6) → Though external beam pelvic radiotherapy reduced locoregional recurrence by 72%, there is no evidence to suggest that it reduced the risk of death. In patients with multiple high risk factors (including stage IC and grade 3) there was a trend towards a survival benefit and adjuvant external beam radiotherapy may be justified. For patients with only one risk factor, grade 3 or stage IC, no definite conclusion can be made and data from ongoing studies (ASTEC; Lukka) are awaited. External beam radiotherapy carries a risk of toxicity and should be avoided in stage I endometrial cancer patients with no high risk factors			
5	- Rate of relapse - Incidence of recurrence - Overall survival	*Postoperative pelvic external beam radiotherapy versus no further treatment* - 2 large RCTs, PORTEC and GOG (3, 4, 25), and 1 RCT (n=123)	*Tolerability* - In patients with stage I disease, postoperative pelvic radiotherapy increased the morbidity of treatment (26)		A1

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	- Rate of adverse events - Grade of severity - Intra- and postoperative complication rates	available only as an abstract (6) compared the efficacy of surgery plus adjunctive pelvic radiotherapy with surgery alone in women with stage I/II (low- and intermediate-risk) endometrial cancer - Postoperative external beam radiotherapy reduced the incidence of locoregional recurrences after surgery, although the rates of distant recurrence appeared to be generally similar between treatment groups. However, any improvements in recurrence rates seen with adjunctive radiotherapy did not confer overall survival benefits in these patient populations (overall survivall 86.0% vs. 92.0% at a median follow-up of 68 months (4); 85.0% vs. 81.0% at a median follow-up of 52 months (3); 77.0% vs. 71.0% at a median follow-up of 73 months (25); 80.0% vs. 92.0% at a median follow-up of 6 years (6)). - These findings are in agreement with the conclusions drawn by the Cochrane review (23) and the 2 systematic reviews identified by our search (29, 30) *Postoperative pelvic external radiotherapy versus chemotherapy* - 2 RCTs compared the effectiveness of adjuvant external radiotherapy with combined chemotherapy in patients with endometrial cancer classified as intermediate (stages IC, II, IIIA, IIIC; grades 1-3) and high-risk (stages IC, II; (grade 3), III) (27, 28) -Postoperative combination chemotherapy (cisplatin-doxorubicin-cyclophosphamide) conferred no advantage over external radiation therapy in terms of overall survival in these patient populations (27, 28) - A subgroup analysis performed in the trial available only as an abstract (28) suggested that, compared with radiotherapy, chemotherapy may significantly improve the overall survival of patients with high-intermediate risk endometrial cancer (stages IC [grade 3 or >70 years of age], II and IIIA [positive cytology]), although no quantitative data were reported - The rate of recurrence was generally similar in both radiotherapy and chemotherapy treatment groups in both trials (36.0% vs. 32.0% at a median follow-up of 95.5 months (27); 15.1% vs. 16.5% at a median follow-up of 60.8 months (28)). - Where reported (27), the evidence to suggest that postoperative radiotherapy may be more effective than chemotherapy in delaying local recurrences, but less effective in delaying distant recurrences in high-risk endometrial carcinoma patients, is weak since the study was not powered to detect between-group differences in this parameter → Adjuvant external beam radiotherapy reduces locoregional recurrence in stage I disease but not the risk of death. Considering the high survival rate and low recurrence risk of patients with early	- 5-year actuarial rate of primary treatment late complications (all grades) was higher in patients who received radiotherapy than in those who received no further treatment (26% vs. 4%; p<0.0001) (26) - Most complications were of the gastrointestinal tract and mild in severity; however, only radiotherapy recipients experienced severe (grade 3 or 4), albeit few (3%), complications (26) - All radiation techniques were equally well tolerated, although acute radiotherapy toxicity appeared to increase the risk of late complications (26) - The adverse events gastrointestinal (67.4% vs. 6.9%), haematological (35.3% vs. 9.9%), genitourinary (30.0% vs. 7.9%) and cutaneous (32.1% vs. 7.4%) toxicities were also more common when postoperative radiotherapy was given compared with no adjuvant treatment, in patients with intermediate-risk endometrial adenocarcinoma. Most symptoms were mild (4) → Adjunctive pelvic radiotherapy significantly increases the morbidity of treatment in endometrial cancer, increasing late complications, particularly of the gastrointestinal tract, with possible increases in other adverse events including those haematological, genitourinary and cutaneous in nature. However, further comprehensive studies are needed in order to generate a more complete tolerability profile of this therapy		

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		stage disease, postoperative adjuvant radiotherapy should perhaps be limited to patients with high risk of recurrence, particularly since such radiotherapy is associated with increased long-term complications and toxicity → Adjuvant chemotherapy has so far failed to demonstrate any improvement over radiotherapy in terms of overall survival			
6	- Survival - Pelvic control - Ultimate pelvic control (overall pelvic control after salvage treatment) - Toxicity	*External beam radiotherapy vs. no treatment* *GOG 99 (4)* - 392 surgically staged women randomized to receive either EBRT (50.4 Gy) or no treatment (control) - 2-year cumulative incidence of pelvic recurrence 3% in treatment and 12% in control group (relative hazard 0.42; p=0.007) - 4-year survival rates not statistically different between groups (92% for EBRT group and 86% for control group) *PORTEC (3, 21)* - 714 women with early stage endometrial cancer who underwent TAH+BSO and biopsy of any suspicious lymph nodes randomized to EBRT (46 Gy) or no treatment (control) - At 5 years pelvic recurrence rates significantly lower for patients who received EBRT vs. no treatment (4% vs.14%; p<0.001) (3) - At 10 years, with revised pathology data, identical difference in favor of ERBT was maintained (5% vs. 14%; p<0.001) (21) - Rates of distant recurrence not significantly different between EBRT and control group (7% vs. 4% at 5 years; 8% vs.4% at 10 years) - 105 deaths (EBRT n= 57; control n=48); 64 deaths (61%) unrelated to endometrial cancer; 31 deaths (30%) due to metastatic disease. Incidence of non-endometrial cancer deaths makes it difficult to draw conclusions regarding effectiveness of radiotherapy in treatment of endometrial cancer (3) *Intracavitary radiotherapy vs. no treatment* - 1 RCT compared ICRT to no treatment. Patients randomized in: preoperative ICRT, surgery alone or adjuvant post-op ICRT (31) - 47% of patients <50% myometrial invasion, and 70% had grade 1 disease - No significant benefits for pelvic control, disease-free survival, overall survival at 5 or 10 years in surgery vs. adjuvant ICRT group *External beam & intracavitary radiotherapy vs. intracavitary alone* - 540 endometrial cancer patients underwent TAH+BSO and ICRT, then randomized in EBRT (40Gy) or no treatment (control) - EBRT significantly associated with greater pelvic control (EBRT + ICRT 1.9% vs. ICRT alone 6.9%; p<0.01), but not in 5-year (89%	*Subgroup analysis from 3 RCTs (3-5)* *GOG 99 (4)* - High-intermediate risk (HIR) n=132: 1. >70 years old with 1 other risk factor, 2. >50 years old with 2 other risk factors, 3. any age with 3 risk factors - Low-intermediate risk (LIR) n=260: all other patients - 13% of HIR women who received radiotherapy had pelvic recurrences vs. 29% of the women without radiotherapy (HR 0.42, 95% CI 0.21-0.83) -No significant difference in relapse in LIR group (HR 0.46, 95% CI 0.19-1.11) - No significant differences in survival between treatment and control groups in either subgroup *PORTEC (3)* - Unpublished data suggested no difference in cancer-related survival regardless of risk of recurrence subgroup - Pelvic recurrence rate at 10 years lower in intermediate-risk patients receiving EBRT (5.8% vs.16.1%; p<0.01) - When subgroups were analyzed according to age, no consistent trends in survival or recurrence were identified between the randomized groups *Aalders et al. (5)* - No significant differences in survival between treatment and control groups. 20% of women at high risk (grade 3 and <50% myometrial invasion) in the ICRT arm had pelvic recurrences compared to 5% of women in the EBRT + ICRT arm. No difference in the arms in survival for subgroups according to age, weight, and vascular invasion (5) → 3 studies were consistent in reporting differences in pelvic recurrences among women at intermediate to high risk of recurrence in favor of the radiotherapy group over the control group. However, none of the RCTs prospectively designed their subgroup analyses, and none of the subgroup analyses were powered to detect significant differences in survival or recurrence. Results should be interpreted with caution and should be considered to be hypothesis generating	- Difficulty drawing conclusions due to limited number of studies, variety of comparisons, small numbers, reporting of analyses, lack of pathology review, and lack of power in subgroup analyses *GOG 99 (4)* - Limitations in terms of eligibility criteria, final data presented and subgroup analysis - "Intermediate"-risk patients (included patients with any degree of myometrial invasion with adenocarcinoma of any grade and no evidence of lymph node involvement with stages IB, IC, IIA (occult), IIB (occult)) not directly comparable to low, intermediate- and high-risk groups in non-surgically staged patients, though some overlap - While investigators estimated risk of recurrence 20-25% at 5 years, in reality, the rate of recurrence was 11.2% after 12 years, and the results reported were "estimated at 2 and 4 years" despite enrolment between 1987-1995 results published in 2004 *PORTEC (3)* - Original published results based on reporting of recurrence rates from the initial pathology report. Study included patients with low-risk disease (grade 2 <50% myometrial invasion). Review of the pathology resulted in a shift of patients from intermediate- to low-risk disease. Based on revised pathology 381 of the 714 patients randomized had intermediate-risk disease - Subgroup analysis in review of Lukka	A1

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		vs. 91%) or 9-year overall survival (87% vs. 90%) (5) → Adjuvant radiotherapy is not recommended in low-risk patients (stages IA, IB, grades 1 and 2). It is reasonable to consider EBRT for intermediate risk subgroup patients (stage IC, grades 1 and 2, or stages IA, IB, grade 3), regardless of surgical staging, to reduce the risk of pelvic recurrence. EBRT is recommended for high-risk patients (stage IC, grade 3). The benefits of EBRT need to be weighed against the toxicity of treatment. Patients should be informed of the benefits and risks of EBRT	*Toxicity* *GOG 99 (4)* - Grade 3 and 4 toxicities EBRT group: gastrointestinal (5%), gastrointestinal obstruction (3%) and cutaneous (3%) - Grade 3 and 4 toxicities control group: cardiovascular (2%), hematologic (<1%), and cutaneous (<1%) *PORTEC (3)* - Most of the complications were grade 1 - EBRT: 84 patients (25%) some late toxicity; 6 (2%) grade 3 - Control group: 22 cases (6%) of late toxicity; 1 (0.3%) grade 3 *Aalders et al. (5)* - Treatment group: 3 patients (1.6%) severe late complications - Control group: 2 patients (2%) severe late complications	et al. based on pathology review of the specimen *Piver et al. (31)* - Small number of included patients does not allow conclusions to be drawn - Study used clinical staging (FIGO 1971) *Aalders et al. (5)* - Included low-, intermediate- and high-risk patients (~50% intermediate- or high-risk disease) - Study reported in 1980, radiotherapy techniques have improved over the last 25 years	
7	- Death due to any cause - Death due to relapse of disease - Death due to intercurrent disease - Relapse of disease	*Influence of adjuvant progestagen therapy on all deaths* - Meta-analysis of trials demonstrates no significant effect on overall survival for women using adjuvant progestagen therapy. The direction of effect is towards more deaths in the progestagen treated women OR 1.05; 95% CI 0.88-1.24 (12-14, 16, 17, 33) *Influence of adjuvant progestagen therapy on endometrial cancer deaths and disease relapse* - Meta-analysis shows an OR of 0.88; 95%CI 0.71-1.1, progestagens might reduce endometrial cancer deaths - The same effect is demonstrated with a reduced relapse rate in progestagen women OR 0.81; 95% CI 0.65-1.01 (12-14, 16, 33) *Influence of adjuvant progestagen therapy on intercurrent death* - 5 trials reported the incidence of intercurrent deaths in the treatment and control groups. None of the individual trials reached statistical significance, and the final meta-analysis demonstrated a significant adverse effect with adjuvant progestagen therapy; OR 1.33; 95%CI 1.02-1.73 (12-14, 16, 33) - OR for deaths due to cardiovascular disease (cerebrovascular accident, thrombo-embolism, and cardiac failure) derived from data from MacDonald (14), De Palo (12), Vergote (13) and COSA-NZUK (33) are 0.87 (95%CI 0.28-2.7), 0.84 (0.3-2.3), 1.49 (0.75-2.9) and 1.2 (0.67-2.18) respectively - Overall survival was not improved by adjuvant progestagen therapy (OR 1.05; 95%CI 0.88-1.24) - Non-endometrial cancer related deaths were more common in women treated with progestagens (OR 1.33; 95% CI 1.02-1.73)		*Risk of bias in included studies* - In only 1 trial (14) was the method of randomisation specifically stated and this was truly randomised - The trials by De Palo (12), Lewis (17) and COSA-NZ-UK (33) were multi-centre studies using centralised randomisation and therefore treatment allocation was almost certainly concealed from investigators - The trials included in this review are predominantly based on low risk patients where adequate statistical precision is hard to attain	A1

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		→ Progestagens have established place in the palliative treatment of women with advanced disease. Meta-analysis based on the currently available good quality trials failed to demonstrate that adjuvant progestagen therapy has a significant beneficial effect on endometrial cancer related deaths. The trials included in this review are predominantly based on low risk patients where adequate statistical precision is hard to attain. The available evidence points towards the conclusion that progestagens have no role in the primary treatment of endometrial cancer			
8	- Recurrence rate - Overall survival - Disease-free survival - Toxicity	*Recurrence rate* - During the 5-year follow-up time 32 patients (20.5%) had recurrent disease - Radiotherapy: 18.0%; radio- and chemotherapy: 22.6%(p=0.496) - Pure locoregional recurrence rate in the whole study population was low (3.2%) and evenly distributed among the groups - 27 patients had metastases in distant locations including extrapelvic abdominal cavity, para-aortic lymph nodes, liver parenchyma, lungs, bone and brain - Chemotherapy was not able to prevent the distal spread of disease: the distal recurrence rate 13.8% (radiotherapy) vs. 20.2% (radio- and chemotherapy) - As calculated from the operation, the median time to recurrence was 15 (range 6-37) months (radiotherapy) vs. 20 (range 8-60) months (radio- and chemotherapy) (p=0.170) *Survival* - 26 of the 32 patients with recurrent disease (81.2%) died of endometrial carcinoma: radiotherapy n=11; radio- and chemotherapy n=15 - Disease-specific 5-year survival was 84.7% (radiotherapy) vs. 82.1% (radio- and chemotherapy). Kaplan-Meier analysis showed no survival difference between the 2 therapies - Median time interval from the recurrence to death was 8 (range 3-11) months (radiotherapy) vs. 9 (range 2-22) months in (radio- and chemotherapy) - Among the surviving patients, only 2 patients (1 in each group) with a local recurrence were free of disease at the end of follow-up - Patients succumbing in the radiotherapy group lived a median 23 (range 15–44) months vs. 37 (range 13-50) months in the radio- and chemotherapy group (p=0.148) - Median disease-free survival was 18 months (range 9-36) (radiotherapy) vs. 25 months (range 12-49) (radio- and chemotherapy) (p=0.134) - In Cox proportional hazards models only age-adjusted invasion through the myometrium to the serous layer significantly increased the relative risk of death with a HR 4.29 (95% CI 1.11-16.54)	*Toxicity radiotherapy* - During both treatment periods, the patients in the radio- and chemotherapy group were more often anemic and their erythrocyte sedimentation rates were higher. However, the rate of leucopenia did not differ between the groups - All other laboratory parameters that included liver and kidney functional tests, were similar in both groups *Toxicity chemotherapy* - Chemotherapy was tolerable. Though 6, 13 and 14 patients during the consecutive courses, respectively, experienced grade 3 and 4 leucopenia altogether, none of them suffered from Grade IV infection - 2 cases of sepsis and 8 patients had Grade 3 infections - Nausea/emesis occurred frequently but Grade 3 and 4 diarrhea was quite uncommon during the consecutive courses - Mucosal symptoms occurred infrequently - Alopecia proved to be an increasing problem, worsening throughout even though an ice cap was used - Liver and kidney functional test results remained within normal range throughout the chemotherapy *Intestinal complications* - A total of 10 patients developed intestinal complications demanding surgery: radiotherapy n=2 (2.7%); radio- and chemotherapy n=8 (9.5%)	- Blinding not possible - While designing the trial, it was presumed that the 5-year survival rate in the radiation-only group would be ~60%, based on Finnish material from the late 70's.The largest difference between the older material and the present study lies in the surgical staging that was adequate in our study only. We should have taken into account that the thorough surgical staging would probably increase survival in both groups and we should have increased the sample size accordingly. In other words, a smaller than 20% survival benefit for chemotherapy cannot be ruled out	A2

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		- Age-adjusted sequential radio- and chemotherapy as compared to radiotherapy alone did not alter the risk of death HR 1.21 (95% CI 0.56-2.65) - In a multivariate model comprising of age, stage, grade, the depth of invasion, histological subtype and treatment only increasing age was a predictive factor for death with a HR 1.08 (95% CI 0.999-1.18) → Chemotherapy added to the standard treatment, or surgery and radiotherapy, failed to improve overall survival in patients with early-staged high-risk endometrial carcinoma. It tended to prolong the disease-free survival time of patients who would later die of disease in that it postponed the appearance of recurrent disease. The combination of standard treatment and chemotherapy as used in this study was generally well tolerated but appeared to increase the risk of intestinal complication			
9	- Overall survival - Progression-free survival - Incidence of toxicity	*Survival* - PFS rate at 5 years was 83.5% in PRT group; 81.8% in the CAP group. Hazard ratio 1.07 (95% CI 0.65 1.76; p=0.726) - OS rate at 5 years was 85.3% in PRT group; 86.7% in the CAP group (p=0.462). Hazard ratio 0.72 (95% CI 0.40-1.29; p=0.268) *Recurrence* - 30 recurrences (15.5%) occurred in the PRT group; 33 recurrences (17.2%) occurred in the CAP group - The patterns of recurrence were similar in both treatment groups. Specifically, the incidence of intrapelvic recurrence sites, such as the pelvis or vagina, was 6.7% (13/193) in the PRT group and 7.3% (14/192) in the CAP group, while the incidence of extrapelvic recurrence sites, such as the peritoneal cavity, liver, lung, paraaortic lymph nodes, and others, was 13.5% (26/193) and 16.1% (31/192) respectively *Prognostic factors* - Statistically significant univariate prognostic factors predicting worse PFS were age (≧60 years vs. b60 years), co-morbidity, clinical staging (IIIA vs. II vs. IB vs. IA), tumor grade (G2/3 vs. G1), myometrial invasion (beyond serosa vs. serosa vs. ≧2/3 to b serosa vs. ≧1/2 to b2/3), pelvic lymph node metastasis, adnexal involvement, cervical involvement, peritoneal cytology, and surgical staging (IIIC vs. IIIAvs. IIB vs. IIA vs. IC) - For OS, the statistically significant univariate prognostic factors were age, co-morbidity, clinical staging, tumor grade, myometrial invasion, pelvic lymph node metastasis, lymphovascular space invasion, and surgical staging	*Adverse effects* - G3 and G4 toxicities were experienced in 1.6% (3/193) of the PRT and 4.7% (9/192) of the CAP groups - Bowel obstructions were the main complication in the PRT group, and myelosuppression was detected in the CAP group - No treatment-related deaths occurred in either group *Deaths* - 48 patients died, of whom26 had been assigned to the PRT group and 22 to the CAP group - PRT: 21 deaths were related to endometrial cancer, 1 death to another cancer, and 2 deaths to other diseases - CAP: 13 deaths were related to endometrial cancer, 4 deaths to other cancers, and 4 deaths to other diseases *Subgroup analysis based on risk* - Low- to intermediate-risk (LIR): stage IC patients under 70 years of age and with G1/2 endometrioid adenocarcinoma - Among 190 LIR patients, PFS rates at 5 years in the PRT and CAP groups were 94.5% and 87.6% (p=0.110) and OS rates at 5 years in the PRTand CAP groups were 95.1% and 90.8% (p=0.281) - High- to intermediate-risk (HIR): 1. stage IC patients over age 70 years or having G3 endometrioid adenocarcinoma or 2. stage II or IIIA (positive cytology) patients with deeper than 50% myometrial invasion in the corpus - Among these 120 patients, the CAP group had significantly higher PFS rate (83.8%) (hazard ratio 0.44, 95% CI 0.20-0.97; p=0.024) and OS rate (89.7%) (hazard ratio 0.24; 95% CI 0.09-	- Blinding not possible - In this trial, the dosage of doxorubicin was lower than in other trials using AP. Due to this relatively low dose, G3 and G4 adverse effects were rare (4.7%), and protocol compliance was very high (95.3%) in the CAP group. The number of CAP courses was relatively small (median: 3 courses). Cisplatin-based chemotherapy may be a feasible alternative to adjuvant pelvic radiation therapy for patients with intermediate-risk endometrial cancers. However, validation of a true efficacy of adjuvant chemotherapy for early-stage endometrial cancer, especially for LIR patients, requires a randomized controlled trial of no-treatment versus chemotherapy	A2

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		- Significant prognostic factors were used to perform a multivariate analysis with a Cox regression model: age (≧60 years) and tumor grade (G2/3) were the most important poor prognostic factors for both PFS and OS → In patients with early-stage endometrial cancer and deeper than 50% myometrial invasion, adjuvant platinum-based combined chemotherapy and pelvic radiation therapy each led to a good prognosis. In patients with HIR endometrial cancers, the aforementioned chemotherapy improved the prognosis significantly compared to pelvic radiation. Additional phase III randomized controlled trials are required to establish a standard adjuvant chemotherapy regimen including anthracyclin, taxane or platinum for intermediate-risk or high-risk endometrial cancer	0.69; p=0.006) versus the PRT group (66.2% and 73.6%) - High-risk: other stage IIIA patients with factors other than a positive peritoneal cytology and stage IIIB and IIIC patients - For 75 cases in high-risk group, OS rates and PFS rates were not statistically different between PRT group and CAP group. The OS rate at 5 years was 75.8% in the PRT group and 71.1% in the CAP group (p=0.667). The hazard ratio was 1.123 (95% CI 0.42-3.04; p=0.819). The PFS rate at 5 years was 78.6% in the PRT group and 64.4% in the CAP group (p=0.169). The hazard ratio was 1.847 (95% CI 0.73-4.65; p=0.193)		
10	- Recurrence - Progression-free survival - Overall survival	*Recurrence* - WAI: 109 patients (54%) had documented tumor recurrence. Initial site of recurrence was limited to the pelvis in 27 patients (13%), within the abdomen in 33 patients (16%), and extra-abdominal or liver metastases in 45 patients (22%) - AP: 97 patients (50%) had documented tumor recurrence. Initial site of recurrence was limited to the pelvis in 34 patients (18%); 27 patients (14%) experienced disease recurrence within the abdomen, and, in 34 patients (18%), the first recurrence included extra-abdominal or liver metastases *Survival* - At the time of final analysis, 76 patients (38%) on the WAI arm were alive compared with 98 patients (51%) on the AP arm - Progression hazard ratio relative to the WAI arm, adjusted for stage, was 0.71 (95% CI 0.55-0.91; p=0.007). This adjusted relative hazard ratio was associated with a predicted increase in PFS at 60 months of 12% (50% for AP vs. 38% for WAI) - Hazard ratio of death relative to the WAI arm, adjusted for stage, was 0.68 (95% CI 0.52-0.89; p=0.004). This adjusted relative hazard estimate was associated with a predicted increase in OS at 60 months of 13% for patients on the AP arm vs..WAI patients (55% vs. 42%) - Unadjusted Kaplan-Meier estimates of 5-year PFS and OS were 42% and 53%, respectively, in the AP arm compared with 38% and 42%, respectively, in the WAI arm *Prognostic factors* - Stage IV disease was a very strong indicator of shorter PFS and OS when compared with stage III disease - In exploratory multivariate analysis, grade 3 tumor, older age,	*Adverse effects* - Most common acute grade 3 to 4 toxicities were hematologic. Comparisons of grade 3 to 4 hematologic toxicities between WAI and AP are as follows: WBC (4% vs. 62%), absolute neutrophil count (1% vs. 85%), platelets (3% vs. 21%), and maximum hematologic toxicity (defined as percentage of patients who developed at least one grade 3 or 4 hematologic toxicity of any type; 14% vs. 88%) - Second most commonly reported acute toxicity was grade 3 to 4 GI toxicity (WAI 13% vs. AP 20%), and hepatic toxicity (3% vs. 1%) - Grade 3 to 4 cardiac toxicities (WAI 0% vs. AP 15%) and neurologic toxicities (WAI <1% vs. AP 7%) *Deaths* - Treatment probably contributed to 8 deaths on the AP arm (2 patients had sepsis, 2 patients had congestive heart failure, and 1 patient each had sepsis plus left ventricular/aortic thrombus, hypoglycemic shock with myelosuppression, stroke secondary to congestive heart failure, and renal failure with severe thrombocytopenia) and 5 deaths on the WAI arm (1 patient each had veno-occlusive liver disease, disease progression with hepatomegaly, aspiration and liver necrosis, renal and liver failure secondary to sepsis with severe ascites, and sepsis and liver failure) - The age range of patients suffering treatment-related deaths was 48-68 years (median 62 years) and 50-76 years (median,68.5 years) in the WAI and AP arms - Initial performance status was 0 to 1 in all patients experiencing treatment-related deaths, except for 1 patient on the AP arm who had a performance status of 2	- Blinding not possible - The data do not permit definitive subset analyses assessing heterogeneity of the treatment effect within smaller groups of patients. However, there is no evidence to suggest that the study conclusions apply only to a subset of patients - WAI may not be the most effective RT approach	A2

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		serous histology, and African American race were associated with shorter PFS and OS. Gross residual disease was associated with significantly shorter PFS but not OS. 14% and 24% of patients did not undergo optional pelvic or para-aortic nodal evaluation, respectively. The effects of positive versus negative PLN or PALN on PFS and OS were not analyzed → Patients with surgical stage III or IV endometrial carcinoma treated with AP experienced a statistically significant improvement in survival when compared with patients who received WAI, but they also experienced more frequent and more severe acute toxicity. Clearly, greater efficacy and less toxicity are needed. Avenues for further progress remain to be explored	*Subsequent treatment* - WAI: 132 patients (65%) received no subsequent treatment. Patients treated with initial salvage therapy subsequent to protocol treatment included 42 patients (21%) various chemotherapy regimens, 13 patients (6%) further RT, 14 patients (7%) hormonal therapy (HT) only, and 1 patient (0.5%) who received surgery only - AP: 107 (55%) received no further treatment. 41 (21%) chemotherapy, 24 (12%) RT, 17 (9%) HT only, and 5 (3%) were treated with surgery only after initial relapse. 1 patient who received HT and surgery is included in the HT only group *Subgroup analyses* - The treatment effects given by the AP death hazard ratio relative to that of WAI within subgroups of stage were as follows: IIIA, 0.47; IIIB, 0.54; IIIC, 0.75; and IV, 0.68. For combined subcategories of stage III, the relative hazard ratio was 0.68		
11	- Quality of life (QOL): - Fatigue Scale (FS) - Peripheral Neuropathy Scale (APN) - Functional Alterations due to Changes in Elimination (FACE) - Functional Assessment of Cancer Therapy-General (FACT-G)	*FS assessment* - AP: FS was initially stable but decreased (representing improved QOL) at the 3-month (mean change=-1.9; p=0.039) and 6-month (mean change=-3.2; p=0.001) time points - WAI: significant increase in the FS score from the pre-treatment to EOT assessments (mean change=5.6; p<.001). This increase disappeared by 3 months post-treatment. The FS score at 6 months post-treatment was even lower (representing a better QOL) than the pre-treatment score, although this change score did not reach significance (mean change=-1.5; p=0.100) - The only difference between the groups occurred at EOT, when patients treated with WAI demonstrated significantly higher FS scores than those treated with AP (mean difference=3.1; p=0.015) - In terms of the clinical meaning of these findings as demonstrated by the RCI, both arms showed a clinically reliable FS score increase (worsening of fatigue-related QOL) at EOT (38% of WAI compared with 26% of AP patients). Fatigue remained clinically problematic in 18% of WAI and in 13% of AP patients 6 months posttreatment *Peripheral neuropathy (APN) assessment* - AP: APN score increased at EOT (mean change=3.4; p<0.001) and increased again at the 3-month post-treatment time point (mean change=5.8; p<0.001) compared to the pre-treatment assessment. Neurologic toxicity was still at a high level 6 months posttreatment. - WAI: slightly higher change in APN at 3 months posttreatment (mean change=1.1; p=0.033) and at 6 months post-treatment (mean change=1.5; p=0.005) relative to the pre-treatment score		- Blinding not possible - WAI may not be the most effective RT approach - 1st limitation: QOL assessment period (pre-treatment through 6 months post-treatment) did not capture some of the late effects of therapy. Future studies should consider continuation of QOL assessments as long as possible, although compliance in late stage disease is particularly challenging - 2nd limitation: QOL instruments used in this study. In 1989 the National Cancer Institute directed the Clinical Trials Cooperative Groups to begin assessing QOL. In 1990, when GOG 122 was in development, the state-of-the science related to many of the QOL instruments commonly used today in cancer research was in its infancy. For example, several instruments that were subsequently developed and validated, such as the Piper Fatigue Scale or the Multidimensional Fatigue Inventory did not come into popular use until the mid- to late-1990s - Regardless of the evolution of state-of-the-science QOL instruments, we found the performance of the	A2

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		- Comparing the 2 arms, the AP group showed significantly higher APN scores at EOT (mean difference=2.4; p<0.001), at 3 months (mean difference=4.5; p<0.001), and at 6 months (mean difference=4.1; p<0.001) compared to WAI. Clinically, the reliable change in APN was notably high in the AP arm at every time point, with 41% of patients experiencing a clinically reliable increase in score (worsening of peripheral neuropathy-related QOL) at EOT. This proportion increased by 20% at the 3-month time point and was still high (56%) at 6 months post-treatment *FACE* - AP: no significant difference in FACE scores between pre-treatment and EOT assessments. However, statistically significant decrease in FACE at 3 months compared to pre-treatment (mean change=-1.4; p=0.032) - WAI: increase in total FACE score from pre-treatment to EOT (mean change=3.3; p<0.001). However, it returned to the pre-treatment level at 3 months posttreatment. According to subscale scores, both urinary and bowel symptoms were increased at EOT compared to pre-treatment (p<0.001), but they returned to pre-treatment levels 3 months post-treatment - Significant differences in FACE scores between the WAI and AP arms at EOT (mean difference=3.7; p<0.001) and the 3-month posttreatment time point (mean difference=2.3; p=0.004). FACE urinary subscale scores in the AP arm showed no significant change in urinary function at EOT or post-treatment compared to pre-treatment. Among AP patients, bowel subscale scores decreased from pre-treatment to 3 months post-treatment, but they returned to pretreatment levels 6 months post-treatment. Compared to the AP arm, urinary subscale scores were higher in WAI patients at EOT (p=0.001), and bowel subscale scores were higher among WAI patients at EOT (p<0.001) and 3 months posttreatment (p=0.004). The clinical importance of these findings as defined by the RCI indicated that almost one-third of WAI patients experienced a clinically reliable increase in FACE (associated with worsening of problems with elimination) at EOT, but this was reduced to 16% and 18%, respectively, at the 3- and 6-month time points. For AP patients, a small number reported a reliable increase in FACE at EOT, 3 months, and 6 months post-treatment (13%, 10% and 16%, respectively) *FACT-G* - AP: FACT-G score was not significantly changed at the EOT, but increased somewhat at 3 months (mean change=3.9; p=0.009) and 6 months posttreatment (mean change=4.1; p=0.006) - WAI: decrease in the FACT-G score from pretreatment to EOT		instruments used in this study satisfactory and the information gained useful in achieving the study objectives	

ID	Primary Outcome Measure(s) Secondary outcome(s)	Effect size-Primary Outcome(s) Effect size-Secondary outcome(s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
		(mean change=-6.5; p<0.001), which returned to the pre-treatment level at 3 months post-treatment. It appears this change was mostly due to a decrease in the physical well-being domain score - No significant differences between the treatment groups in FACT-G scores at any assessment time point; however, the physical well-being (PWB) subscale showed a between-group difference at EOT, when WAI patients demonstrated lower PWB scores than AP patients (mean difference=-2.8; p=0.001). The RCI indicated that 21% of patients on the WAI arm and 18% of patients on the AP arm had clinically meaningful decreases in FACT-G scores at the 6-month posttreatment time point → The trade-off for increased survival with AP is its potential for clinically significant peripheral neuropathy. This should be discussed with patients, particularly those who work with their hands or on their feet, in weighing therapeutic choices. Further research is needed to manage side effects having an enduring impact on QOL			
12	- Recurrence-free survival - Local-regional recurrences - Distant recurrences - Adverse events - Quality of life *(Ntx scores)*	*Recurrence* - 218 RFS events with a median follow-up of 47 months among living patients without evidence of recurrence - 62% of CD patients were alive, recurrence free 36 months following randomization compared to 64% of CDP patients(p=0.21) - Ratio of the hazard of recurrence or death relative to the CD arm stratified by stage is 0.90 (95% CI 0.69-1.17) - Median follow up time among those alive, recurrence-free is 46 months for CD and 47 months for CDP - Nearly 30% of patients had a distant recurrence and 10% had a local-regional recurrence *Subgroups* - p-value for the test for homogeneity of treatment effects within the subgroups defined by residual disease (none or microscopic vs. gross) at study entry was 0.076 - 50% reduction in the risk of recurrence or death (HR 0.50; 95%CI 0.27-0.92) in the CDP arm among those with gross residual disease (GRD) compared to the CD arm - Among patients with no GRD who did not receive EFRT, the effect of treatment favors the CDP regimen. The effect of treatment among those with no GRD who did receive EFRT does not favor CDP, it slightly favors CD - CDP appears to be favored among those with GRD regardless of the radiation field used. Among the 77 patients who had one, negative, or no PA nodes sampled and did not receive EFRT, the treatment effect appears to favor CDP	*Acute adverse events* - Compared to the CD group there were more acute adverse events in the CDP group for the categories: leucopenia, neutropenia, thrombocytopenia, anemia, infection/fever, febrile neutropenia, sensory neuropathy, pain, myalgia *Late adverse events* - The cumulative probability of a late grade 3 or higher treatment related gastrointestinal adverse event was 5% *Deaths* - Majority of deaths are due to disease, but 3 of the randomized patients died as a result of complications due to small bowel obstructions related to radiation effects; 1 patient who was never randomized had radiation interrupted by nausea and vomiting and died 3 weeks later; 1 patient died as a result of multiple events related to chemotherapy including acute renal failure *Patient-Reported Neurotoxicity(Ntx scores)* - Baseline Ntx scores did not differ between the 2 regimens - After adjusting for baseline score, the fitted linear mixed model estimates indicated that the treatment effect on the Ntx scores were not constant within 4 weeks of last cycle and at 6 month post last cycle (p<0.001 for interaction between treatment and assessment times) - Within 4 weeks of last cycle, the mean Ntx score was 32.9 points; 5.2 pointsworse (95% CI: 4.0-6.5; p<0.001) in the CDP arm than that in the CD arm (38.1 points)	- No blinding - Given the caveats of subset analyses, the data from this study suggests that if there is any benefit due to paclitaxel, it is primarily observed among those patients with gross residual disease and possibly those with no gross residual disease who do not receive EFRT. It is possible that the treatment-by-gross residual disease (GRD) interaction result is spurious, however; the results of GOG 177 support the subgroup analysis results of improved RFS for gross residual disease in this study. The vast majority of patients in this study had no GRD. The results in this subgroup not treated with EFRT would need to be evaluated further in other studies	B

ID	Primary Outcome Measure(s) Secondary outcome(s)	Effect size-Primary Outcome(s) Effect size-Secondary outcome(s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
		- Among those who were not prescribed EFRT (only received pelvic RT), and had no gross residual disease there is little, if any, treatment difference - With the exception of GRD and extent of the radiation field, there is no other suggestion of a heterogeneous effect of treatment within subgroups *Proportional hazards regression model* - Adjusting for stage (IV vs. III), residual disease (gross vs. none or microscopic), EFRT and interactions between treatment and both GRD and EFRT; age, histology and grade, positive para-aortic nodes, pelvic metastasis, and positive cytology were statistically significantly associated with RFS - Once other factors are adjusted for, there was no statistically significant association of black racial designation and elevated CA 125 with RFS - Other factors not statistically significant at the p<0.05 level in univariate models were positive pelvic nodes (any vs. none vs. not evaluated), GOG performance status, myometrial invasion (none vs. <50%, vs. >50%), and pathologically confirmed presence of lymphovascular space involvement, vaginal metastasis, bladder metastasis, and abdominal metastasis → In patients with advanced local or regional stage III endometrial carcinoma with ≤2 cm maximum residual tumor following surgery and volume directed radiation, the addition of paclitaxel to cisplatin and doxorubicin was not associated with a significant improvement in RFS but was associated with increased morbidity. Because of the small number of patients with gross residual disease that may have benefited from the addition of paclitaxel, this should be used for hypothesis generating purposes. Three important high risk groups were identified: clear cell histology, papillary serous histology, grade 3 adenocarcinoma and patients with gross residual disease	- 6 months after completing treatment, the difference was diminished but still remained statistically significant (difference=1.6; 95% CI 0.3-2.8; p=0.014)		
13	- Overall survival - Disease-free survival - Adverse reactions - Recurrence	*Overall survival* - Overall survival curves were similar in the 2 groups, with a 5-year survival rate of 88.4% in CAP and 95.1% in EP group (p=0.3496) *Disease-free survival* - Disease-free survival rate was 80.3% in CAP and 84.8% in the EP group (p=0.4533) - Using a cutoff level of 35 IU/ml, the 5-year disease-free survival rate was 95.1% for patients with CA125 levels <35 IU/ml compared to 71.0% for patients with levels ≥35 IU/ml (p<0.05) - Disease-free survival curves show a significant advantage in favor of patients without pelvic lymph node involvement compared	*Adverse reactions* - None of the patients discontinued adjuvant chemotherapy because of adverse drug reactions, and there were no significant differences in relation to adverse drug reactions between the 2 groups *Recurrence* - Recurrence was noted in 10 patients of the CAP group and in 5 patients of the EP group. The most common recurrence site was the intrapelvic cavity followed by lymph nodes - Radiotherapy was administered to 5 patients with local recurrence, and all of them were still alive at the last follow-up	- No blinding	B

ID	Primary Outcome Measure(s) Secondary outcome(s)	Effect size-Primary Outcome(s) Effect size-Secondary outcome(s)	All other outcomes, endpoints	Critical appraisal of study quality	Level of evidence
		with those with positive pelvic lymph nodes (p=0.0338). The 5-year disease-free survival rate was 68.8 and 88.2% for patients with and without pelvic lymph node involvement. Although the 5-year survival rates were 85.2 and 93.6% for patients with and without pelvic lymph node involvement, the difference was not significant (p=0.1852) - Patients were also studied regarding positive and negative ascitic fluid cytology, grade of differentiation and cancer infiltration into the muscularis. The survival and the disease-free survival curves were not significantly different in these factors *Prognostic factors* - In a Cox's proportional hazard model statistically significant variables were preoperative CA125 and pelvic lymph node metastasis → EP chemotherapy had no significant advantage in terms of survival and disease-free survival compared to CAP, although these rates were superior in the EP compared to the CAP group			

AP=Doxorubicin-cisplatin; APN=Peripheral Neuropathy Scale; CAP=Cyclophosphamide-doxorubicin-cisplatin chemotherapy; CD=Cisplatin/doxorubicin; CDP=Cisplatin/doxorubicin/pactitaxel; CI=Confidence Interval; EBRT=External beam radiotherapy; EOT=End of treatment; EP=Etoposide and cisplatin; FACE=Functional Alterations due to Changes in Elimination; FACT-G= Functional Assessment of Cancer Therapy-General; FS=Fatigue Scale; ICRT=Intracavitary radiotherapy; NA=Not Applicable; NR=Not Reported; RFS=Recurrence-free survival; PRt=Pelvic radiation therapy;WAI=Whole-abdominal irradiation; QOL=Quality of life

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