Uitgangsvraag 1

Geeft lymfadenectomie bij patiënten met endometriumcarcinoom een betere (ziektevrije) overleving en/of betere kwaliteit van leven dan chirurgie zonder lymfadenectomie?

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 (Kitchener et al.) (1)	RCT	*Funding* Public research fund (Medical Research Council) and government (National Cancer Research Network) *Conflicts of interest* None declared	85 centres in 4 countries (UK, South Africa, Poland, New Zealand)	UK, South Africa, Poland, New Zealand	- Investigation if pelvic lymphadenectomy could improve survival of women with endometrial cancer - Improvement in 5-year overall survival from 80% in the standard surgery group to 90% in the lymphadenectomy group (hazard ratio 0.47)	*Inclusion* - Women with histologically proven endometrial carcinoma that was thought preoperatively being confined to the corpus and who were able to undergo both systematic lymphadenectomy and external radiotherapy - Women with node enlargement found by CT or MRI were not excluded *Exclusion* - Women with FIGO stage IIIC	- Calculated were 1,400 women - Actual number of randomly assigned women n=1,408: • 704 standard surgery group • 704 lymphadenectomy group ○ 9 withdrawals
2. Benedetti Panici et al., 2008 (2)	RCT	*Funding* University grant (Università di Roma La Sapienza, Rome), private non profit organisation (Mario Negri Institute, Milan) *Conflicts of interest* NR	30 centres in Italy, 1 centre in Chile	Italy, Chile	- Investigation if addition of systematic pelvic lymphadenectomy to standard hysterectomy with bilateral salpingo-oophorectomy improved overall survival and disease-free survival in patients with preoperative stage I endometrial cancer	*Inclusion* - Preoperative FIGO stage I disease - All patients with proven endometrial cancer with myometrial invasion - ≤ 75 years - Karnofsky performance status ≥ 80 - No previous chemotherapy or radiation therapy - No previous malignant neoplasia other than basal cell carcinoma or nonmelanoma skin cancer *Exclusion* - Patients whose intraoperative pathological assessment showed a well-differentiated tumor whose depth of myometrial invasion was <50% (FIGO stage IB, grade 1)	- Calculated were 524 patients - Actual number of randomly assigned women n=537 - 23 patients not eligible intra-operatively • 273 allocated to pelvic systematic lymphadenectomy ○ 9 ineligible intraoperatively 264 available for intention-to-treat-analysis ○ 38 protocol violoations (< 20 nodes resected) • 264 allocated to NO-lymphadenectomy ○ 14 ineligible Intraoperatively 250 available for intention-to-treat-analysis ○ 17 protocol violations (≥ 20 nodes resected)
3. Chan and Kapp, 2007 (3)	Systematic review	NR	NA	USA	Comparing the benefits and risks of a complete versus selective lymphadenectomy in patients with endometrioid corpus cancer	*Search terms* Endometrial cancer in combination with the terms node metastases, adjuvant radiotherapy, intraoperative pathology, vascular space invasion, myometrial depth *Inclusion* - Studies published in English between 1966 and 2006	NR

ID	Duration of the study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/comparator (including duration, dose)
1	- Start/end date of study 1 July 1998-31 March 2005 - Median follow up 37 months	- Randomisation by a telephone call to Medical Research Council Clinical Trials Unit, method of minimisation If inbalance of incision type was noticed, incision type had to be specified before randomisation - Chief investigator was blinded to treatment group when classifying the cause of death	*Standard surgery* - Median age 63 years; range 36-89 years - Median Body-mass index: 29; range 16-79 Unknown n=161 - WHO performance status 0: 74% 1: 22% 2: 3% 3: 1% 4: <1% - FIGO stage (21 women excluded because pathology details did not confirm endometrial cancer) IA 13% IB 47% IC 22% IIA 5% IIB 8% III/IV 6% Unknown n=6 *Lymphadenectomy* - Median age 63 years; range 34-93 years - Median Body-mass index: 29; range 10-69 Unknown n=177 - WHO performance status 0: 76% 1: 20% 2: 3% 3: 1% 4: <1% - FIGO stage (18 women excluded because pathology details did not confirm endometrial cancer) IA 12% IB 39% IC 28% IIA 5% IIB 8% III/IV 8% Unknown n=11 - No p-value for group comparability	*Standard surgery* - Hysterectomy and bilateral salpingo-oophorectomy (BSO), peritoneal washings, palpation of para-aortic nodes. Sampling of suspicious nodes if surgeon believed it to be in woman's best interest - Vertical incision recommended unless transverse incision was preferred due to gross obesity - Laparoscopic surgery was the alternative if it could be done safely and as thoroughly as open surgery <u>Delivered intervention</u> As previously planned *Lymphadenectomy* Standard surgery + systematic dissection of iliac and obturator nodes. If nodes could not be dissected thoroughly because of obesity/anaesthetic concern, then sampling of suspected nodes was recommended and para-aortic node sampling was at discretion of surgeon - Vertical incision recommended unless transverse incision was preferred due to gross obesity - Laparoscopic surgery was the alternative if it could be done safely and as thoroughly as open surgery <u>Delivered intervention</u> 58 (8%) women had no nodes removed because of anaesthetic concerns (n=22), obvious extra- uterine disease (12), obesity (9), withdrawal at patient request (9), or unknown reasons (6). The number of lymph nodes removed was obtained from the pathology report. 72 (12%) had 1-4 nodes removed and 396 (65%) women had ≥10 removed (median 12 nodes) 99% of women in both groups had a total abdominal hysterectomy and BSO Adjuvant treatment (both groups) To control for postsurgical treatment, women with early-stage disease at intermediate or high risk of recurrence were randomised (independent of lymph-node status) into the ASTEC radiotherapy trial	Standard surgery

ID	Duration of the study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/comparator (including duration, dose)
2	- Inclusion of patients 1 October 1996-31 March 2006 - Median follow up time 49 months	- Randomization to one of the 2 trial arms by block arrangement that balanced the treatment assignment within each site. Randomization took place at the end of endoperitoneal surgical procedures and after confirming myometrial invasion, grading, and tumor histology by frozen section analysis - Intraoperative random assignment was performed centrally by telephone at the Mario Negri Institute, Milan - Unblinded trial	*Pelvic systematic lymphadenectomy* - Median age 63 years (IQR 56-68) - Median BMI 26.6 (IQR 23.7-30) - FIGO stage determined by pathological analysis IA 0.0% IB 33.0% IC 39.4 IIA 4.5% IIB 3.8% IIIA 3.4% IIIC 13.3% IVB 1.1% Missing 1.5% Higher proportion of patients with FIGO stage IIIC was related to the lymph node dissection itself, which increases the detection of lymph node metastases. *No lymphadenectomy* - Median age 61 years (IQR 55-68) - Median BMI 26.9 (IQR 23.8-30) - FIGO stage determined by pathological analysis IA 3.2% IB 42.8% IC 32.0% IIA 2.4% IIB 6.0% IIIA 7.6% IIIC 3.2% IVB 1.2% Missing 1.6% - No p-value for group comparability	For both groups primary surgery included standard hysterectomy+BSO *Pelvic systematic lymphadenectomy* - External iliac lymph nodes Removal of the lympho-fatty tissue located above the external iliac vessels between the iliac bifurcation, the inferior epigastric vessels, and psoas muscle laterally - Superficial obturator lymph nodes (included the interiliac lymph nodes) Removal of the lymph nodes located below the external iliac vessel and above the obturator nerve, between the iliac bifurcation, the psoas muscle laterally, the obturator muscle caudally, and the virtual plane passing through the umbilical artery and bladder medially - Common iliac lymph nodes Completion of lymphadenectomy with removal of the lymph nodes located above and laterally to the common iliac lymph nodes between the aortocaval bifurcation and the iliac bifurcation Pelvic systematic lymph node dissection was considered to have been performed appropriately and according to protocol when at least 20 pelvic lymph nodes were removed and analyzed by the pathologist. Single or multiple aortic lymph node samplings or systematic lymphadenectomy was performed at the discretion of the surgeon *No lymphadenectomy* At the end of primary surgery, no lymphatic tissue in the retroperitoneal region was removed other than bulky (>1 cm) lymph nodes, if they were detected at gross intraoperative inspection by palpation of lymph node sites *Adjuvant therapy for both treatment groups* After surgery, patients at higher risk of recurrence based on the histopathologic analysis of surgical specimen (i.e, patients with different combination of risk factors such as FIGO stage IIB-IVB, poorly differentiated tumors, and positive surgical margins) could be administered adjuvant therapy at the discretion of the treating physician. Platinum- or taxol-based chemotherapy, pelvic radiotherapy with possible extended field therapy to aortic lymph nodes, and brachytherapy, either alone or in combination, were considered suitable adjuvant approaches. Adjuvant regimens had to be initiated within 1 month from surgery	No lymphadenectomy
3	1966-2006	NA	- Women with endometrial cancer	NA	NA

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	- Primary outcome measure: overall survival (definition: time from randomisation to death from any cause; women who were known to be still alive at the time of the analysis were censored at the time of their last follow-up) - Secondary outcome measures: recurrence-free survival (definition: time from randomisation to first reappearance of endometrial cancer or death from any cause; women who were known to be alive and without recurrent disease at the time of analysis were censored at time of their last follow-up), disease-specific survival (definition: time from randomisation to death from endometrial cancer or death due to treatment)	*Survival* *Overall survival* - HR 1.16; 95% CI: 0.87-1.54; p= 0.31 (unadjusted) - HR 1.04; 95% CI 0.74-1.45; p=0.83 (adjusted) *5-year* - Standard surgery group 81% (95% CI 77-85) - Lymphadenectomy group 80% (95% CI 76-84) - Difference in 5-year overall survival: 1%; 95% CI -4.0-6.0 in favour of standard surgery *Recurrence-free survival* - HR 1.35 (95% CI 1.06-1.73) p=0.017 (unadjusted) - HR 1.25 (95% CI 0.93-1.66) p=0.14 (adjusted) *5-year* - Standard surgery group 79%; 95% CI 75-83 - Lymphadenectomy group 73%; 95% CI 69-77 - Difference in 5-year recurrence-free survival: 6%; 95% CI 1-12 in favour of standard surgery * HR <1.0 indicates a decreased risk of the event for women in the lymphadenectomy group	Median number of resected lymph nodes (IQR) *Standard surgery* (n=683)* 2 (1-6) *Lymphadenectomy* (n=686) 13 (1-38) *Disease recurrence n=704* Total recurrence n=173 (25%) *Standard surgery n=75 (11%)* Local/vaginal n=18 (25%) Pelvic n=11 (15%) Distal n=38 (53%) Local/vaginal and distal n=0 Pelvic and distal n=5 (7%) Unknown n=3 *Lymphadenectomy n=98 (14%)* Local/vnaginal n=24 (27%) Pelvic n=10 (11%) Distal n=49 (54%) Local/vaginal and distal n=3 (3%) Pelvic and distal n=4 (4%) Unknown n=8	- Biased analysis of outcome according to the number of nodes removed for individual patients, since the randomised comparison had to be broken with the same issues of selection bias (although less stage shift) - Groups seemed to be equal at baseline, but results showed that women in standard surgery were at lower risk in respect to histological features (adjusted for in analyses) - Further randomisation into the ASTEC radiotherapy trial (comparing EBRT and observation with no EBRT or systemic treatment until recurrence) was required for women with intermediate-risk and high-risk, early-stage disease, including those with positive lymph nodes. Without this second randomisation, differences in postsurgical treatment could have arisen, with women in the standard surgery group either having more radiotherapy (because their lymph-node status was unknown) or less radiotherapy (because they were less likely to have positive lymph nodes identified) than women in the lymphadenectomy group were having. Women with low-risk, early-stage disease and women with advanced disease got further treatment offered according to standard practice	A2
2	- Primary outcome measure: overall survival (definition: time from random assignment to death from any cause) - Secondary endpoints: disease-free survival (definition: time from random assignment to the earliest occurrence of	*Survival* *Overall survival* *5-year* - Lymphadenectomy 85.9% - No lymphadenectomy 90.0% - Comparison between groups: - HR for death to any cause =1.16; 95% CI 0.67-2.02; p=0.59 *Disease-free survival*	Median number of resected lymph nodes (IQR) *Lymphadenectomy* 30 (22-42) *No lymphadenectomy* 0 (0-0) =at least 1 lymph node removed *Overall survival (5-year)* *Age ≤ 65 vs >65* - HR for death to any cause =2.85; 95% CI 1.65-4.92); p=<0.001 *Tumor grade 1-2 vs 3* - HR for death to any cause =2.03; 95% CI 1.17-3.52; p=0.01 *Tumor stage I-II vs III-IV*	- The lymphadenectomy used did not systematically include para-aortic lymph nodes. 67% of endometrial cancer patients with lymph node invasion have disease in para-aortic lymph nodes. Therefore surgical effort may be incomplete and the consequent inference about prognosis inaccurate - The protocol lacked standardized	A2

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
	relapse or death from any cause)	*5-year* - Lymphadenectomy 81.0% - No-lymphadenectomy 81.7% - Comparison between groups: - HR for relapse = 1.20; 95% CI 0.75-1.91; p=0.41	- HR for death to any cause =2.14; 95% CI 1.17-3.93; p=0.01 *Disease-free survival (5-year)* *Age ≤ 65 vs >65* - HR for death to any cause =1.49; 95% CI 0.93-2.38); p=0.09 *Tumor grade 1-2 vs 3* - HR for death to any cause =1.44; 95% CI 0.90-2.31); p=0.13 *Tumor stage I-II vs III-IV* - HR for death to any cause =2.03; 95% CI 1.18-3.50; p=0.01 *% Myometrial invasion ≤ 50 vs >50* - HR for death to any cause =1.35; 95% CI 0.82-2.22; p=0.24 *No adjuvant therapy* - Lymphadenectomy n=182 (68.9%) - No lymphadenectomy n=162 (64.8%) *Radiation therapy* - Lymphadenectomy n=44 (16.7%) - No lymphadenectomy n=63 (25.2%) *Chemotherapy* - Lymphadenectomy n=23 (8.7%) - No lymphadenectomy n=14 (5.6%) *Chemotherapy + radiation therapy* - Lymphadenectomy n=15 (5.7%) - No lymphadenectomy n=11 (4.4%) - p=0.07 for all adjuvant therapies, no single comparison was done *No recurrence* - Lymphadenectomy n=231 (87.5%) - No lymphadenectomy n=217 (86.8%) *Recurrence* - Lymphadenectomy n=34 (12.9%) - No lymphadenectomy n=33 (13.2%)	criteria for adjuvant therapies	
3	- Lymphadenectomy vs no lymphadenectomy - Preoperative and intraoperative assessment	*Survival* *Overall survival and progression free survival* - In 5 studies with low-risk patients (minimum or no myoinvasive cancer, grade 1-2 tumours,endometrioid histology, and disease limited to the corpus) it was shown in previous studies that these low-risk patients had no survival advantage associated with lymph-node dissection. Only <2% had a risk of nodal metastases (4-8) - Women with stage I and IIA endometrial uterine cancers in whom >11 pelvic nodes had been removed had an improved overall and progression-free survival compared with those with ≤11 resected nodes (9) - Those who underwent para-aortic node dissection (≥5 nodes resected) had a better progression-free survival and overall		- No description of included/excluded studies - The results must be interpreted with caution as the quality of studies available for review was variable, with many of poor methodological quality (retrospective, small sample size) that may result in the introduction of bias	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
		survival than those with less nodes removed (10) *Disease-specific survival* *5-year* - 1 study intermediate-risk and high-risk patients (stage IB, grade 3; and stages IC, II, III, and IV, all grades) underwent lymph-node resection. A more extensive lymph node resection (1, 2–5, 6–10, 11–20, and >20 lymph nodes) was associated with improved 5-year disease-specific survivals of 75.3%, 81.5%, 84.1%, 85.3%, and 86.8%, respectively across all five groups (p<0·001). After adjusting for other factors (age, year of diagnosis, stage, grade, adjuvant radiotherapy, and the presence of positive nodes) a more extensive lymph-node resection remained a significant prognostic factor for improved survival in intermediate-risk and high-risk patients (p<0.001) (8) - 1 database study found a significant better 5-year disease-specific survival in women with stage I, II, III, and IV who underwent lymphadenectomy than in women who had no lymphadenectomy (11): - Women who underwent lymphadenectomy Stage I 95.5% Stage II 90.4% Stage III 73.8% Stage IV 53.3% - Women whithout lymphadenectomy Stage I 96.6% Stage II 82.2% Stage III 63.1% Stage IV 26.9% (p>0.05 for stage I; p<0.001 for stages II-IV) - 1 study reported a better disease-specific survival of patients with stage I, grade 3 disease, who underwent lymphadenectomy than those who did not have lymphadenectomy (90% *vs* 85%; p=0.0001). No significant benefit for lymphadenectomy was identified for patients with stage I, grade 1 (p=0.26) and grade 2 (p=0.14) disease (11) (See also second comment) - 1 study found in 96 Stage IIIC patients with complete surgical staging a survival benefit associated with removal of gross nodal disease. Gross nodal disease not debulked: hazard ratio=6.85; p=0.009 for 5-year disease-specific survival (12) *8-year* - 1 study showed a significant increase in 8-year disease-specific survival to 85% from 60% when comparing patients with early-stage disease who had extensive lymphadenectomy (multiple sites: ≥4 regions) with those who did not have extensive lymphadenectomy (13)			

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
		Extent of lymph-node assessment - 2 studies applied a lymph-node assessment including gross intraoperative inspection with palpation of lymph nodes, biopsy of suspicious nodes only (4;14) - 2 studies applied limited blind biopsies, resection of an arbitrary minimum number of pelvic and para-aortic lymph nodes (9;10) - 2 studies applied complete systematic removal of all lymphatic tissue in the retroperitoneal region (15;16) - 2 studies concluded that systematic removal of all lymphatic tissue in the retroperitoneal region might be the most accurate definition of a complete lymphadenectomy (17;18) - In 1 study investigators extended the para-aortic node dissection to 1-2 cm above the renal vessels (19) - 1 study claimed that 10 pelvic and 5 para-aortic nodes are sufficient. Patients with high-risk disease, excluding stage IV and who got ≥5 para-aortic nodes resected had a 5-year survival of 85% vs 71% in patients with <5 nodes removed (p=0.06) (10) - 1 study suggested that a systematic resection of at least 25 pelvic and 18 paraaortic nodes is needed to consider the procedure as accurate. A substantial proportion of patients with para-aortic nodal involvement had disease in the intercavoaortic region. A substantial proportion of patients with para-aortic nodal involvement had disease in the intercavoaortic region (20) - In 1 study only 27.6% of all patients with nodal metastases were diagnosed when ≤5 nodes were recovered. The largest increase in probability of detecting at least one positive node was recorded when 21-25 nodes were resected (odds ratio 1.45; 95% CI 1.08-1.94; p<0.01) (21) - Based on the GOG surgical manual, the anatomical boundaries of a pelvic and peri-aortic lymphadenectomy include the genitofemoral nerve laterally, the hypogastric artery medially, the obturator nerve posteriorly, the circumflex iliac vein inferiorly, and the origin of the inferior mesenteric artery superiorly (22) - 1 study noted an increase in the risk of retroperitoneal recurrence in those who did not undergo a biliateral pelvic and aortic lymphadenectomy (23) - 1 study with 38 women with nodal disease assessed the benefits of nodal debulking. Patients with completely resected macroscopic lymph-node metastases had a significantly longer median disease-specific survival of 37.5 months compared with only 8.8 months in those left with gross residual nodal disease (HR 4.69, 95% CI 1.55-14.17, p=0.006) (24) - In 1 study in patients with stage IIIC-IV disease with nodal metastases, the extent of node resection (1, 2-5, 6-10, 11-20, and >20 lymph nodes) was significantly associated with improved			

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
		disease-specific survival (51%, 53%, 53%, 60%, and 72%, respectively; p<0.001). The extent of lymph-node resection remained positively correlated with an improved survival after controlling for the number of nodal metastases (8) *Adjuvant therapy* - 2 studies with low-risk or intermediate-risk patients that had an absence of nodal metastases confirmed by complete lymph-node dissection concluded that the patients might be spared the costs and potential complications associated with adjuvant pelvic radiotherapy (25;26) - 2 studies showed that 20-64% of patients had substantial changes in their adjuvant treatment on the basis of lymph-node status identified at lymphadenectomy (27;28) - in 1 study 12 of 95 patients received postoperative radiation as a result of findings of para-aortic lymph-node involvement and 49 patients without nodal metastases did not receive postoperative treatment, resulting in a substantial change in adjuvant treatment in 64% of patients (28)			

NR= Not Reported; NA= Not Applicable; BSO=Bilateral Salpingo Oophorectomy; SE=Standard Error; CI=Confidence Interval; HR=Hazard Ratio; IQR=InterQuartile Range; FIGO=International Federation of Gynecology and Obstetrics; SLN=Sentinel Lymph Node; MM=Micro Metastasis; CT=Computed Tomography; MRI=Magnetic Resonance Imaging; 18F-FDG-PET=18'F-FluoroDeoxyGlucose-Positron Emission Tomography

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