Uitgangsvraag 4

4a. Bij welk histologisch type van het endometriumcarcinoom is een complete stadiëring of debulking geïndiceerd?
4b. Zijn deze patiëntengroepen pre- of perioperatief te bepalen?
4c. Hoe uitgebreid moet de complete stadiëring of debulking zijn?
4d. Heeft het wel of niet verrichten van een complete stadiëring of debulking gevolgen voor het toepassen en de keuze van 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 Boruta et al., 2009 (1)	Review	None declared (Society of Gynecologic Oncology (SGO) review)	NA	USA	- What distinguishes UPSC from endometrioid carcinoma (EEC) and other endometrial histologic subtypes? - Based on available evidence, what is the best approach to the management of patients with UPSC?	Medline: January 1966-May 2009 *Search terms* Uterine neoplasm, endometrial neoplasm, and serous *Inclusion* English-language Medline articles	Not described
2 Olawaiye et al., 2009 (2)	Review	None declared (Society of Gynecologic Oncology (SGO) review)	NA	USA	- What are the differences between clear cell, papillary serous and endometrioid endometrial cancer? - Based on available evidence, what is the best approach to the management of patients with clear cell endometrial cancer?	Pubmed: January 1966-December 2008 *Search terms* Endometrium, cancer, clear cell, endometrial adenocarcinoma, and endometrial cancer *Inclusion* Publication in English, original report, studies with subject numbers ≥30, randomized controlled trials, prospective non-randomized trials and retrospective studies. Preference was given to articles that contain a pure population of clear cell endometrial cancer patients, and those with a subsection analysis on this select group of patients *Exclusion* Non-English publications, reviews, abstracts/ proceedings from meetings that have not been formally published in a peer review format, studies with subjects <30, and endometrial cancer papers that do not include clear cell patients	Not described
3 Alobaid et al., 2006 (3)	Review	None declared	NA	Canada	- Is surgical staging essential for all patients with uterine papillary serous carcinoma (UPSC)? - What defines adequate surgical staging? - What is optimal adjuvant therapy? - Should all patients with stage I disease receive adjuvant therapy?	Medline: 1966-September 2005 *Search terms* Serous papillary cancer, endometrial cancer, and early stage Variables of interest were the surgical and adjuvant treatments of patients with stage I UPSC	Not described
4	Guideline;	*Funding*	NA	USA	- To aid practitioners in making decisions	Medline database, Cochrane Library, and the	Not described

Study (trial) ID	Study type	Source of funding/Conflicts of interest	Setting	Country	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up
American College of Obstetricians and Gynecologists (ACOG), 2005 (4)	systematic review	American College of Obstetricians and Gynecologists (ACOG)			about appropriate obstetric and gynecologic care - To review the risks and benefits of current treatment options to optimize treatment for patients with endometrial cancer	American College of Obstetricians and Gynecologists' own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1985 and April 2005 *Inclusion* The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles *Exclusion* Abstracts of research presented at symposia and scientific conferences	
5 Look, 2002 (5)	Review	None declared	NA	USA	Critically examine the evidence of relative advantages and disadvantages of the two most widely extant therapeutic paradigms for endometrial carcinoma (extended surgical staging and radiotherapy)	OVID software search of Medline: 1975-2001 *Search terms* Endometrial neoplasm, surgery, and radiation therapy *Inclusion* English-language Medline articles were assessed with regard to (a) extent of surgical staging (b) type of adjuvant radiotherapy utilized: external vs. brachytherapy vs. combination therapy; and (c) whether the patients were treated as part of prospective trial or reported as a descriptive series reflecting an institution's practice pattern	A computerized-literature search utilizing the terms endometrial neoplasm/ surgery (n=145) and endometrial neoplasm/ radiation therapy (n=196) to review the evidence (and quality of that evidence) that supports surgical staging and/or the use of postoperative radiotherapy

ID	Duration of the study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/Comparator (including duration, dose)
1	NA	NA	Patients diagnosed with UPSC	NA	NA
2	NA	NA	Primary or recurrent clear cell endometrial adenocarcinoma	NA	NA
3	NA	NA	Stage I papillary serous endometrial cancer	NA	NA
4	NA	NA	Patients with endometrial cancer or atypical hyperplasia	NA	NA
5	NA	NA	Stage I-II endometrial adenocarcinoma	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	- Recurrence rate - Overall survival - Progression-free survival	*Surgical staging* - In most patients comprehensive surgical staging is believed to be beneficial. In addition to providing prognostic information, accurate identification of metastatic UPSC, or documentation of the lack thereof, allows for adjuvant therapy and surveillance to be appropriately tailored - International Federation of Gynecology and Obstetrics (FIGO) staging for endometrial carcinoma mandates removal of the uterus, fallopian tubes, and ovaries, along with obtaining abdominopelvic washings for cytology and performance of bilateral pelvic and paraaortic lymphadenectomy - With UPSC, performance of surgical staging selectively, based upon uterine features (e.g. myometrial invasion or lymphovascular-space invasion), is not reliable in its ability to assess for metastatic disease. Numerous investigators utilizing comprehensive staging have documented metastatic UPSC despite the absence of these features (6-13) - In 52 surgically staged patients with UPSC, similar incidence of lymph node and intraperitoneal metastases was noted in patients with either no myometrial invasion or deep invasion (36% vs. 40% and 43% vs. 35%, respectively) (7) - In patients with surgically staged UPSC lacking myometrial invasion, high rates of coincident extrauterine disease were found, ranging from 37%-63% (6;9;13) - Extrauterine disease was found in 38% of comprehensively staged patients whose uterine disease was solely present within a polyp (13) → Recommendation: Comprehensive surgical staging should be performed when feasible in all patients diagnosed with UPSC. In addition to simple hysterectomy, bilateral salpingooophorectomy, pelvic and paraaortic lymphadenectomy, and washings for cytology, performance of omentectomy and peritoneal biopsies should be considered given the propensity for UPSC to metastasize within the peritoneal cavity *Cytoreductive surgery* - An inverse correlation between survival and the volume of residual disease remaining after cytoreductive surgery in the setting of serous ovarian carcinoma has been documented. Retrospective studies suggest that cytoreductive surgery confers a survival benefit in patients with metastatic UPSC as well (14-20) - In 70 patients with stage IIIC or IV UPSC, optimal cytoreduction (defined as no gross residual disease >1 cm in diameter) was achieved in 60%, with no visible residual disease achieved in 37%. A significant difference in median time to recurrence (9 months vs. 6 months, p=0.04) and median survival (20 months vs. 12 months, p=0.02) was observed between optimally and suboptimally cytoreduced patients (20) → Optimal cytoreduction of metastatic UPSC appears to confer a survival benefit *Survival* - The prognostic significance of thorough surgical staging was emphasized by 94% overall survival in patients with tumor limited to their uteri (22 patients with 2-73 months of follow-up) (13) - In 38 patients with stage I UPSC a significant 5-year survival difference was found depending on whether complete surgical staging had been performed or not (100% vs. 61%) (21) - In 206 patients with surgical stage I-II UPSC, recurrence and progression-free survival were not associated with increasing percentage of UPSC in the histologic specimen, lymphovascular-space		- The lack of data in the form of large trials was felt to prohibit exclusion of publications reporting small pools of UPSC patients. Therefore, all peer reviewed original report publications containing the appropriate subjects were considered - Methodology not described extensively	B

<table>
<tr><th>ID</th><th>Primary Outcome Measure(s)
Secondary outcome(s)</th><th>Effect size-Primary Outcome(s)
Effect size-Secondary outcome(s)</th><th>All other outcomes, endpoints</th><th>Critical appraisal of study quality</th><th>Level of evidence</th></tr>
<tr><td></td><td></td><td>invasion, or tumor size. Patients with UPSC in their uterine specimens were at a significant risk for recurrence (21% overall) and poor survival outcomes regardless of the percentage of total tumor comprised of UPSC (22)
→ The traditional uterine features used to predict prognosis in patients with early-stage EEC cannot substitute for thorough surgical staging in patients with UPSC, including those with only a small fraction of their total tumor comprised of UPSC histology

Adjuvant therapy
Summary outcomes of patients with surgically staged stage I UPSC according to type of adjuvant therapy administered and substage (n respondents/n total (%)) (9;10;20;23-31):

<table>
<tr><th>Final stage</th><th>Overall RR</th><th>Observation only RR</th><th>Adjuvant XRT RR</th><th>Adjuvant CT±XRT RR</th></tr>
<tr><td>IA</td><td>24/177 (13.6%)</td><td>14/115 (12.2%)</td><td>10/40 (25.0%)</td><td>3/56 (5.4%)</td></tr>
<tr><td>No residual disease</td><td>0/13 (0%)</td><td>0/10 (0%)</td><td>0/1 (0%)</td><td>0/2 (0%)</td></tr>
<tr><td>Polyp only disease</td><td>1/19 (5.3%)</td><td>1/9 (11.1%)</td><td>0/3 (0%)</td><td>0/7 (0%)</td></tr>
<tr><td>Polyp only/no residual</td><td>1/31 (3.2%)</td><td>1/19 (5.3%)</td><td>0/4 (0%)</td><td>0/9 (0%)</td></tr>
<tr><td>Other IA</td><td>11/67 (16.4%)</td><td>2/27 (14.8%)</td><td>4/12 (33.3%)</td><td>2/28 (7.1%)</td></tr>
<tr><td>IB</td><td>10/64 (15.6%)</td><td>7/25 (28.0%)</td><td>3/26 (11.5%)</td><td>5/66 (7.6%)</td></tr>
<tr><td>IC</td><td>9/30 (30.0%)</td><td>3/6 (50.0%)</td><td>5/16 (31.3%)</td><td>4/24 (16.7%)</td></tr>
<tr><td>IB and IC combined</td><td>59/212 (27.8%)</td><td>25/67 (37.3%)</td><td>26/71 (36.6%)</td><td>12/107 (11.2%)</td></tr>
<tr><td>All stage I combined</td><td>78/389 (20.0%)</td><td>41/190 (21.6%)</td><td>23/106 (21.7%)</td><td>18/165 (10.9%)</td></tr>
</table>

→ The relatively favorable prognosis of patients with stage IA UPSC with no residual uterine disease after comprehensive surgical staging may justify close observation alone. However, adjuvant chemotherapy and vaginal brachytherapy should be considered in other stage IA patients</td><td></td><td></td><td></td></tr>
<tr><td>2</td><td>- Incidence of extrauterine disease
- Overall survival
- Progression-free survival</td><td>Surgical staging
Recommendation: Comprehensive surgical staging including simple hysterectomy, bilateral salpingo-oophorectomy, pelvic, para-aortic lymphadenectomy, omentectomy and cytologic evaluation of the abdominal/pelvic peritoneum should be performed in all medically fit patients diagnosed with clear cell endometrial cancer to allow for planning of appropriate adjuvant treatment and surveillance

Cytoreductive surgery
- Patients with extra-uterine disease may benefit from maximum cytoreductive effort. Patients with stage IIIC to IV disease who were completely cytoreduced had a superior progression free and overall survival compared with patients with residual disease at the end of surgery (32)

→ Comprehensive surgical staging and optimal cytoreduction of metastatic disease appears to benefit women with clear cell endometrial cancer and should be considered the first step in most treatment programs

Adjuvant therapy
- Without knowledge of surgical stage, adjuvant treatment decisions must be made upon uterine pathology alone. Given that patients with clear cell endometrial cancer are known to be at high risk of extra-uterine disease compared to lower grade endometrioid histologies (33), management with</td><td></td><td>- Because of the rarity of this cancer, there are no prospective trials with a study population comprised solely of patients with clear cell endometrial cancer. Available data from prospective studies was derived from subsection analysis of large studies wherein the majority of study subjects had more common endometrial cancer histologies, namely endometrioid and papillary serous. Data from small, retrospective studies reporting only patients with clear cell endometrial cancer were available. While useful, they are limited in their strength of conclusion due to well known limitations of such studies
- Thomas et al. is the only study that addressed the role of surgery in a homogenous population of clear cell</td><td>B</td></tr>
</table>

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
		aggressive adjuvant therapy may be recommended. In cases wherein disease is truly confined to the uterus, some of the treatment may be overzealous, resulting in unnecessary cost and potential morbidity. Extra-uterine disease that goes undiscovered due to failure to perform complete surgical staging may lead to inadequate adjuvant treatment resulting in a missed opportunity for improved survival - 50% of patients with clear cell endometrial cancer with disease truly confined to the uterus were managed without adjuvant therapy and underwent close surveillance only. No hematologic, lymphatic or peritoneal failures were detected at a median follow-up of 44 months (32). Thomas et al. suggested that adjuvant chemotherapy may not be necessary in thoroughly surgically staged clear cell endometrial cancer patients with disease truly confined to the uterus. A definitive conclusion cannot be made from this single study		endometrial cancer patients (32) - Methodology not described extensively	
3	- Incidence of extrauterine disease	*Is surgical staging essential for all patients with UPSC?* Several studies have demonstrated the importance of complete surgical staging in apparently early stage disease: - Extrauterine disease was observed in 72% of 50 patients with clinical stage I UPSC at the time of surgery (7) - In 16 patients with non-invasive tumours (apparent stage IA), 6 had 'true' stage IA, 10 had metastatic disease and 2 had isolated omental disease (6) - Complete surgical staging, including omentectomy, was performed in 12 patients with non-invasive UPSC: half of them had extrauterine disease. Moreover, 25% of the patients with no invasive uterine lesion and no intraoperative evidence of macroscopic omental involvement had microscopic isolated omental metastasis (8) - 13 of 32 patients (38%) with UPSC superficial disease had extrauterine spreading. In 69% of these patients, the disease involved the omentum, and 19% had lymph-node metastases (9) → Although all series had a limited number of patients, they clearly demonstrate that UPSC has a tendency to manifest with extrauterine disease, even for tumours which appear to be limited to the endometrium. Consequently, incomplete surgical staging would understage a significant number of UPSC patients, who would then be incorrectly managed as having stage I disease *What defines adequate surgical staging?* - As in epithelial ovarian cancer, microscopic omental or peritoneal implants may be the only evidence of extrauterine disease in UPSC. Therefore, UPSC patients should undergo similar surgical staging procedures as patients with ovarian cancer, and traditional endometrial cancer staging including peritoneal cytology, TAH, BSO, PLN and PALN, should be completed with omentectomy and multiple peritoneal biopsies (8;34) → At present, there is no evidence that complete surgical staging, including omentectomy and peritoneal biopsies, reduces mortality. However, until this evidence will be available, we believe that complete surgical staging should be performed, to define the extent of the disease and to correctly identify patients whose survival may be improved by adjuvant therapy. This information allows more appropriate patient counseling and permits the accurate identification of patients for participation in clinical trials		- Studies with limited number of patients - Methodology not described extensively	B
4	- Survival rate - Complication rate - Cost - Recurrence rate	*Recommendation based on limited or inconsistent scientific evidence (Level B)* Most patients with endometrial cancer should undergo systematic surgical staging, including pelvic washings, bilateral pelvic and paraaortic lymphadenectomy, and complete resection of all disease. Exceptions to this include young or perimenopausal women with grade 1 endometrioid adenocarcinoma associated with atypical endometrial hyperplasia and those at increased risk of			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
		mortality secondary to comorbidities			
5	- Recurrence rate - Overall survival - Progression-free survival	*Surgical staging* The Society of Gynecologic Oncology (SGO) Practice Guidelines recommends surgical staging for those with high-risk histologies (e.g. clear cell, papillary serous), high grade endometrioid lesions (grade 2-3), deep myometrial invasion, clinical evident extrauterine disease, or suspicious nodes, cervical involvement (35) *Preoperative selection for surgical staging* As only a minority of patients with endeometrial adenocarcnoma (approximately 25%) will likely have nodal metastases, various strategies involving measurement of serologic markers and/or radiologic imaging have been investigated to determine if there is predictive value that would allow the clinician to determine who needs to be sent for surgical staging and who can undergo a simple TAHBSO without an unacceptable risk of understaging → At present, the use of imaging modalities to determine depth of invasion prior to surgery is considered investigational and should not be considered as standard of care *Intraoperative selection for surgical staging* Investigators have developed strategies to evaluate the uterine primary intraoperatively using gross inspection and/or frozen section to determine whether or not nodal dissection should be performed. Parameters which have been assessed include size of the primary, depth of invasion or involvement of cervix, and lymphatic vascular spaces *Adjuvant therapy* - Patients who undergo extended surgical staging (ESS) are less likely to receive postoperative external beam radiotherapy (ERT) than those not so staged (36-38) - Proponents of ESS have posited that for those with proven negative nodes fewer, if any, will require postoperative ERT, thereby the potential morbidity and expense of radiotherapy can be limited to those patients with greatest need (39-43) In the Alabama experience 670/864 patients were surgically staged and known to be node negative (44): - 329/334 with stage IB (< 50% DOI) received no further therapy, only 5% suffered a recurrence - Of 84 patients with stage IC disease 69% received no further therapy, 8% developed recurrence - Of the 21 total recurrences, 13 were subsequently salvaged - In surgically staged patients, conservative therapy with close surveillance was a reasonable alternative to the routine use of postoperative radiotherapy, whether it be ERT or brachytherapy In the GOG trial #99, after ESS 448 patients with stages IB, IC, or IIA-IIB occult disease were randomized to no further therapy (n=200) or adjuvant radiotherapy (n=190). Papillary serous and clear cell types were excluded (45): - At a median follow-up of 56 months, there were 39 recurrences and 52 deaths (56% due to recurrence endometrial cancer) - 2-year progression-free interval was 96% in the RT arm and 88% in the NFT arm (p=0.004) - No difference in 3-year survival of 96% in the RT group and 89% in the NFT group (p=0.09)	The advantage of ESS, not claimed to be therapeutic in Ashih's decision analysis, is that it decreases the percentage of patients who require postoperative radiation from approximately 40% to 20% (46) *Complications* - Possibility of complications in patients receiving external beam therapy after ESS (47-52) - A risk in the range of 7-12% severe enteric morbidity if external beam radiotherapy is given to a field which has undergone ESS (47-49;53). However, some gynecologic oncologists believe that ERT can be withheld in patients with pathologically documented negative nodes, such that whole pelvic therapy need only be given to those with positive nodes, thus limiting the potential morbidity to those approximately 25% of patients most at risk to suffer a recurrence (39;43) - 37% rate of complications in those who received postoperative ERT following ESS vs. a 4% rate of complications in those that received postoperative brachytherapy alone (54)	- Different levels of evidence taken into account - Methodology not described extensively	B

BSO=Bilateral salpingo-oophorectomy; EEC=Endometrioid carcinoma; ERT=External beam radiotherapy; ESS=Extended surgical staging; NA=Not applicable; PALN=Para-aortic lymphadenectomy; PLN=Pelvic lymphadenectomy; TAH=Total abdominal hysterectomy;TAHBSO=Total abdominal hysterectomy and bilateral salpingoophorectomy; UPSC=Uterine papillary serous carcinoma

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