Uitgangsvraag 6
Wat is de invloed van follow-up controles op het opsporen van recidieven, de (ziektevrije) overleving (en de kwaliteit van leven) bij patiënten met endometriumcarcinoom die na een curatieve behandeling klinisch ziektevrij zijn?

6a. Waaruit moeten de follow-up controles bestaan en in welke frequentie moeten de controles worden uitgevoerd?
6b. Verschilt het follow-up traject bij verschillende behandelvormen en bij verschillende vormen van endometriumcarcinoom?

Outcomes of interest: **Recurrence rate** **Survival (disease free/overall)** **Quality of Life** **Surgical staging**

Study (trial) ID	Study type	Source of funding/Conflicts of interest	Setting	Country	Hypotheses	Eligibility criteria	Sample size/ Lost to follow up
1 Fung-Kee-Fung et al., 2006 (1)	Systematic review	Public research fund (Cancer Care Ontario), government (Ontario Ministry of Health and Long-term Care)	NA	Canada	To determine the optimum follow-up of women who are clinically disease-free following potentially curative treatment for endometrial cancer	*Search terms* (Uterine neoplasms or cervical neoplasms or endometrial neoplasms or (cervix or endometrium or endometrial and cancer or carcinoma)) and (surveillance.ti. or follow$.ti. or strategy.ti. or routine.ti.) for the following study designs: practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, non-randomized comparative cohort studies, prospective single-cohort studies, and retrospective single-cohort studies. *Inclusion* - Published 1980-October 2005 in Medline and Embase - Published in issue 3, 2005 in the Cochrane Library - Published in the Canadian Medical Association Infobase and the National Guideline Clearinghouse - Relevant abstracts published 1999-2005 in the proceedings of the meetings of the American Society of Clinical Oncology and 1999–2003 in the American Society for Therapeutic Radiology and Oncology. - Scanning of reference lists of papers that were eligible for inclusion - Follow-up strategies for patients who had received potentially curative treatment for endometrial cancer and were clinically disease-free at study point. Specifically, studies were to describe the follow-up program, define the entry criteria for the study population, and report outcome data on survival, the number of recurrences found	16 retrospective studies (2-17) 2 systematic reviews based on retrospective data (18;19)

						during screening, or on patient preferences. - Practice guidelines, meta-analyses, or systematic reviews explicitly based on evidence related to the guideline question *Exclusion* Case reports, letters, editorials, and papers published other than English	
2 Kew et al., 2005 (20)	Systematic review	NR	NA	UK	To determine whether or not routine follow-up was justified in order to develop evidence-based guidelines for follow-up practice	*Search terms* - MeSH terms: (Genital Neoplasms or Female) AND (Follow-up studies Aftercare or Population surveillance or Primary health care or Ambulatory care facilities - Free text: (cervi$ or endometr$ or ovary or ovarian$ or vulva$ or fallopian$ or vagina$ or uterus or uterine or meig$ or gynaecolog$ or gynecolog$) adj3 (neoplasm$ or cancer$ or carcinoma$ or adenocarcinoma$ or malignan$ or sarcom$) AND (Followup or follow up or aftercare or after care or surveillanc$Primary care or general practic$ or gp$ or family practic$ or clinic$ or nurse$) AND (hospital$ or secondary or routine or usual or consultant$) *Inclusion* - Published 1966 to July 2004 in Medline, Premedline, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, Cochrane Controlled Trials Register, the American College of Physicians journal club databases. - Abstracts of national and international meetings between 1999 and 2003 - Hand search of references of all articles identified - Articles pertaining to follow-up after any gynaecological malignancy that considered detection of recurrence *Exclusion* - Narratives and descriptive articles - Articles that only provided information on detection of recurrence	8 articles (3-6;8;9;11;12), 1 letter (21)

ID	Duration of the study	Randomization method	Patient characteristics and group comparability	Interventions and compliance	Control/Comparator (including duration, dose)
1	NA	NA	Women who had received potentially curative treatment for endometrial cancer and who were clinically disease-free at study point	NA	NA
2	NA	NA	Women with endometrial cancer but were disease free at the end of treatment	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	- Time frame for when recurrences tend to occur (pooled) - Survival for women who had recurrence - Intervals for follow-up for patients who were treated	*6 Recurrences* Results of pooled data: - Overall recurrence rate 13% (95% CI, 11-14%) - 77% (95% CI 74-81%) of recurrences presented with symptoms - 23% (95% CI 19-26%) of recurrences were asymptomatic - 39% (95% CI 35-44%) of recurrences were local - 61% (95% CI 56-65%) of recurrences were distant - 1-3% recurrence rate for patients at low risk for recurrence(not pooled) - 5-16% recurrence rate for patients at high risk for recurrence (not pooled) ➡ The majority of patients who were followed did not experience a recurrence regardless of follow-up; especially for patients at a low risk of recurrence. It seems reasonable that patients at a lower risk of recurrence be followed differently than those at a higher risk of recurrence. *6 Follow-up and recurrences* - No pooled data on median follow-up time, median time to recurrence and amount of recurrences diagnosed after surgery because of lack of data - 10 studies reported a median follow-up time varying between 26 months and >120 months (2-5;7-12) - 7 studies found a median time to recurrence varying between 13 months and 22 months (2;4-6;10-12) - 9 studies detected 68-100% of recurrences 2.0-3.2 years after surgery (2;3;5;8-13) - 5 studies detected 86-100% of recurrences 5.0-5.6 years after surgery (2;4;6;11;13) - 12 studies found that 41-100% of patients with recurrences were symptomatic (2-13) - 1 study reported 20-32 follow-up visits within 5 years. 86% of all recurrences were detected as symptomatic recurrences (7) - In 1 study the median follow-up time was 18 months (range 12-36 months). 86% were recurrence free throughout follow-up. 11% had recurrences (14) - In 1 study the median follow-up time was 39 months (range 4-54 months). 12% of the recurrences were detected among patients treated by surgery (15) - 1 study found 12% recurrences of the total population after a median follow-up of 54.5 months. 80% of recurrences were diagnosed 3 years after surgery (5) ➡ At about 3 years or less after primary potentially curative treatment, 70-100% of recurrences had occurred. For the majority of patients, follow-up in year 4, 5 or beyond, detected very few recurrences, and would seem to be of questionable benefit. About 60-75% of all recurrences were detected through symptoms alone. Recurrence detection would have occurred regardless of follow-up strategy. Counseling of recurrence symptoms is therefore useful. *6 Survival and recurrence*	*6a Accuracy of the follow-up tests being used* Detection of asymptomatic recurrences ranged from: - 5-33% of patients with physical examination - 0-4% with vaginal vault cytology - 0-14% with chest X-ray - 4-13% with abdominal ultrasound - 5-21% with abdominal/pelvic CT scan - 15% in selected patients with CA 125	All data are from retrospective 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
		- 1 study reported a median survival of 9.5 months after recurrence. Recurrences were detected after a median follow-up of 54.5 months (5) - In 1 study detected recurrences were 10% (after median follow-up of 64 months), 77% of the women with recurrence had died of disease, 15% of these women were alive with disease, and 8% of these women were alive without signs of disease (10) ➡ Follow-up programs identified in this series were not particularly effective in improving patient outcomes related to survival. If a patient does experience a recurrence, the data indicate that approximately 60% of the time the recurrence will be distant. The prognosis for patients with a distant recurrence is generally not favorable regardless of timing of disease detection. For these patients, it is unlikely that early detection through follow-up would result in any survival benefits. *6 Quality of life* No studies addressed quality of life. *6a How follow-up visits were performed* - 1 study used pelvic examinations, Pap smears and CA 125 levels to diagnose recurrences during follow-up visits (14) - 1 study used pelvic examination, Pap smear, chest X-ray and CA 125 levels as being part of follow-up visits (15) ➡ The use of routine examinations or diagnostic interventions in asymptomatic patients resulted in inconsistent outcomes. Only physical examination showed some utility in detecting recurrence. This supports the idea that physical examination including a pelvic rectal examination is useful as part of a routine follow-up strategy to detect asymptomatic recurrences. Key issue is that practitioners be skilled in the performance of a pelvic rectal examination and assessment grounded in an understanding of the natural history of the disease. *6a Intervals for follow-up* - 1 study applied 20-32 visits within 5 years. 6-12 follow-up visits were in 1st and 2nd year, 4 visits in 3rd year, 2 visits in 4th and 5th year (7) - 1 study implemented follow-up visits every 3-4 months within 3 years. Median follow-up time was 18 months (range 12-36 months) (14) - 1 study applied follow-up visits every 3-4 months for the first 2 years, every 6 months for the next 3 years and yearly thereafter. Median follow-up time was 39 months (range 4-54 months) (15) - 1 study measured CA 125 levels every 3 months for a median follow-up time of 63 months (range 21-90 months) (17) ➡ No discernable differences in outcomes were detected between any of the follow-up programs (follow-up schedules ranging from 8-32 visits over 5 years).			
2	Recurrence rates, survival, and quality of life	*6 Follow-up and recurrences* - 5 studies detected in women with early stage or stage I-III 58.5-82% of recurrences in year 2 of follow-up (3,6,8,11,12).		- All articles were retrospective case series analyses - One article is in form of a letter	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
		- 3 studies detected in women with stage I-II or stage I-III 70-82% of recurrences in year 3 of follow-up (5,9,11). - 1 study (weak methodology) that detected in women with stage I-III 65% of all recurrences in year 2 of follow-up, detected 100% of recurrences in year 5. In total 15% of patients had recurrences of which 24% were asymptomatic. (6) *6 Survival and recurrence* - 1 study (weak methodology) concluded a survival benefit from detection of recurrence at an asymptomatic stage (p=0.048) (6) - 8 studies did not find benefit in survival from detection of asymptomatic recurrence at routine follow-up, as opposed to symptomatic recurrence or interval detection. During follow-up (5 or 10 years or until death) In total 8.5-19% of patients had recurrences of which 8.5-54% experienced asymptomatic recurrences (3-5;8;9;11;12;21) ➡ Follow-up may not provide any survival benefit in women who have been treated for endometrial cancer. *6a Intervals for follow-up* - All 9 studies showed large variations in follow-up frequencies and use of routine investigations. Years of follow-up were 5 or10 years or until death, the number of follow-up visits ranged from 8-14 in the first 5 years (3-6;8;9;11;12;21)		- Articles are heterogeneous, comparison between them is difficult - Stage of disease varies, strategies for follow-up (both the frequency and the use of routine investigations) show large variation	

NR=Not Reported;NA=Not Applicable; CI=Confidence Interval

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