

# Systematic lymphadenectomy in patients with clinical Stage II endometrial carcinoma: a case report and review of the literature

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## Summary

**Objective:** The aim of this case report and review of the literature was to evaluate the effect of adding pelvic and/or para-aortic lymphadenectomy to hysterectomy and bilateral salpingo-oophorectomy (BSO) on the five year recurrence-free survival in patients with clinical Stage II endometrial carcinoma. **Materials and Methods:** A Pubmed, Embase, and Cochrane library search was performed to identify relevant articles. After screening, using predetermined exclusion and inclusion criteria, and critical appraisal, a final of four articles remained. **Results:** This search only revealed studies with a retrospective design. Two articles showed a significant disease-specific survival benefit in patients undergoing systematic lymphadenectomy for Stage II endometrial carcinoma. In multivariate analyses, conducted in both studies, this improvement in survival was also evident (HR 0.75, 95% CI 0.69 - 0.81,  $p < 0.001$  and HR 0.74, 95% CI 0.58 - 0.93,  $p = 0.0096$ ). The remaining studies revealed a non-significant ten-year recurrence-free survival (77% vs 65%) and five-year overall survival (72% vs 70%) in favour of patients undergoing systematic lymphadenectomy. **Conclusion:** The practise of performing a systematic lymphadenectomy in patients with clinical Stage II endometrial carcinoma as advocated in guidelines, is not based on evidence from randomised clinical trials. However, lymph node dissection seems to improve the five-year disease-specific survival in retrospective studies.

**Key words:** Endometrial cancer; Lymphadenectomy; Stage II.

## Introduction

Endometrial cancer is the most common female reproductive tract malignancy in the Netherlands with an incidence of 1,900 patients and a mortality rate of 400 each year. More specific, the five-year survival for patients with Stage II disease is 76% [1].

By the International Federation of Gynecology and Obstetrics (FIGO), Stage II endometrial carcinoma is defined as carcinoma involving both the uterus and cervix, while Stage I disease is limited to the corpus [2]. The differentiation between both stages is challenging and in one report from this region, a clinical Stage II disease was downgraded in 50% to Stage I post-surgery [3].

Over the years there has been a controversy in the surgical management of endometrial cancer regarding the therapeutic benefit of lymphadenectomy [4, 5]. It is associated with adverse events in 18% [5]. Moreover, Watanabe *et al.* concluded that parametrial involvement cannot be predicted reliably by cervical involvement, suggesting that radical hysterectomy in Stage II disease to prevent parametrial spread may be overtreatment [6].

The current Dutch guideline on endometrial cancer

states that lymph node dissection is not recommended in Stage I disease [7]. This is based on results of two randomised controlled trials. These studies, however, only included patients with clinical Stage I disease [8, 9]. The Dutch guideline recommends to perform a radical hysterectomy with bilateral salpingo-oophorectomy (BSO) and pelvic and para-aortic lymphadenectomy in Stage II disease. Pelvic lymph nodes are more often tumor-positive in clinical Stage II disease (36%) compared to Stage I (10%) [10]. However, no evidence is provided that this recommendation results in a better patient outcome [7].

This case report and review of the literature was conducted to determine if the addition of systematic lymphadenectomy to radical hysterectomy and BSO improves the five-year recurrence-free survival in patients with clinical Stage II endometrial carcinoma.

## Materials and Methods

### Case presentation

A 72-year-old woman was diagnosed with endometrial cancer with uncertainty regarding the clinical Stage (I or II). She was referred to a tertiary oncology department. After re-evaluation of a preoperative magnetic resonance imaging (MRI) the patient was referred back for surgical treatment because of clinical Stage I disease. She underwent a laparoscopic hysterectomy and BSO. No lymphadenectomy was performed. Post-operative pathologic examination revealed a Stage II endometrial carcino-

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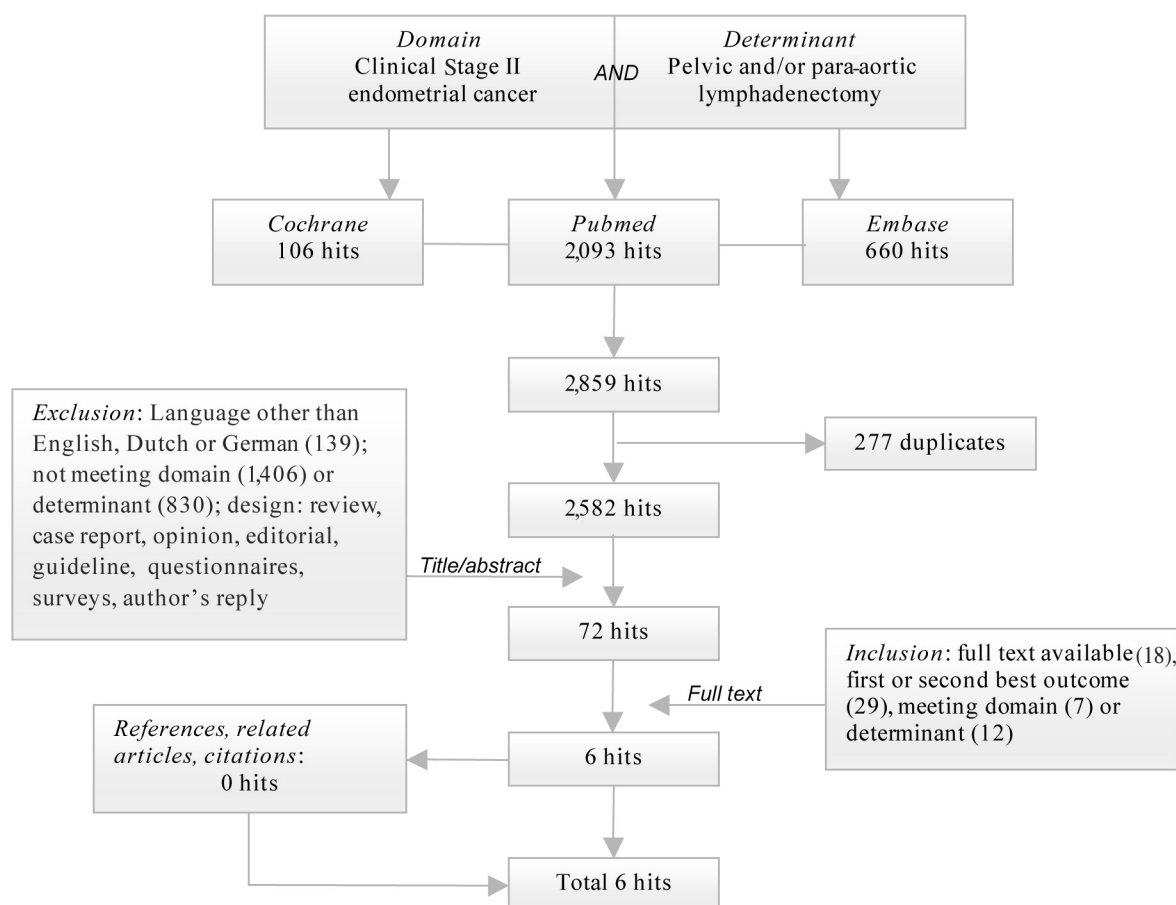


Figure 1. — (N): number of articles excluded based on the criterion. Selection was based on consensus of two authors.

ma. This case illustrates the difficulty to differentiate between clinical Stage I or II. It made the authors question 1) whether this differentiation can be clinically performed in a reliable manner, and 2) if there is evidence that a systemic lymphadenectomy in clinical Stage II endometrial carcinoma offers a benefit in terms of recurrence-free and disease-specific survival. In this report the authors limit themselves to answer the second question by performing a systematic search of the literature.

#### Search strategy and selection

A systematic search of PubMed, Embase, and Cochrane library was performed. No filter or limits were used. The search syntax (appendix) was based on synonyms of the domain and determinant of the clinical question. The search strategy is shown in Figure 1.

#### Critical appraisal

Standardized criteria were defined for critical appraisal of the relevance and validity of the selected articles (Table 1). Appraisal was performed by two authors. Studies scoring less than fifteen points were excluded from analysis based on a pre-defined scoring system by the authors.

## Results

#### Methodological results

The search retrieved 2,859 articles. After removing duplicates and applying exclusion and inclusion criteria, a final of six articles were qualified for critical appraisal (Table 1). Four articles were considered eligible for analysis.

#### Clinical results

An overview of the results is shown in Table 2. All four articles describe retrospective studies.

The study of Leminen *et al.* [11] analysed the effect of abdominal simple hysterectomy and BSO versus Wertheim's radical hysterectomy including pelvic lymphadenectomy. The outcome measurement was ten-year recurrence-free survival in patients with clinical Stage II endometrial carcinoma. Although not significant, the ten-year disease-free survival was 65% and 77% respectively. Even in multivariate analyses, no statistical significant difference was found.

Chan *et al.* [12] performed a study in 39,396 women with all stages of endometrial cancer to assess the effect

Table 1. — *Critical appraisal.*

Criteria	Study					
	Leminen 1995 [11]	Chan 2007 [12]	Selvaggi 2010 [13]	Smith 2008 [14]	Trimble 1998 [15]	Sartori 2001 [16]
Relevance	Patients	+	±	+	+	±
	Intervention	±	+	±	±	±
	Comparison	+	+	+	+	+
Validity	Outcome	+	±	±	±	±
	Design	-	-	-	-	-
	Selection	+	+	+	+	+
	Missing data	+	+	+	+	+
	Equal treatment	-	-	-	-	-
	Baseline	-	-	-	-	-
	Association measure	+	+	+	±	+
	Analysis	+	+	±	+	-
	Applicable	+	+	+	+	+
	SCORE	17	16	15	15	14

Patients: + clinical Stage II endometrial carcinoma, ± surgical Stage II, - other; Intervention: + pelvic and para-aortic lymph node dissection (LND), ± pelvic LND, - other; Comparison: + no LND, - other; Outcome: + recurrence-free survival, ± overall survival, - other; Design: + randomised controlled trial, ± prospective, - retrospective; Selection: adequate inclusion of patients; + bias unlikely, - bias likely; Missing data: + 0-10%, ± 10-20%, - > 20%; Equal treatment: aside from allocated treatment; + yes, - no Baseline: similarity of intervention and comparison; + no significant differences, - significant or not mentioned; Association measure: + mean (difference), ± hazard ratio/relative risk/odds ratio/absolute risk HR/RR/OR/AR, - other; Analysis: + multivariate, ± univariate, - other; Applicable: feasible for Dutch setting; + yes, - no.

Score: + = 2, ± = 1, - = 0 (max. 24).

Table 2. — *Results.*

Study	LDN vs no LND <sup>1</sup>	Lymph nodes <sup>2</sup> (range)	Histologic type	Ten year RFS			Five-year DSS			Univariate analysis	Multivariate analysis
				LND	No LND	p value	LND	No LND	p value		
Leminen 1995	60 vs 60	Unknown	All types	77%	65%	N.S.	-	-	-	RR 1.6, CI 0.8-3.3, N.S.	RR 1.1, CI 0.5-2.4, N.S.
Chan 2007	1211 vs 1833	Median 10	Endometrioid	-	-	-	90.4%	82.2%	< 0.001	-	HR 0.75, CI 0.69 - 0.81, p < 0.001
Selvaggi 2010	15 vs 30	Mean 14 (1-29)	Endometrioid	-	-	-	72%	70%	0.894	-	-
Smith 2008	1981 vs 1383	Median 12 (1-98)	Adenocarcinoma	-	-	-	-	-	-	-	<sup>3</sup> HR 0.71, CI 0.54 - 0.94, p = 0.0175 <sup>4</sup> HR 0.76, CI 0.58-1.01, p = 0.0579 <sup>5</sup> HR 0.74, CI 0.58-0.93, p = 0.0096

LND = lymph node dissection; RFS = recurrence-free survival; DSS = disease-specific survival; N.S. = not significant; RR = relative risk; CI 95% = confidence interval; HR = hazard ratio; <sup>1</sup> Number of patients; <sup>2</sup> Number of lymph nodes removed; <sup>3</sup> > 11 lymph nodes dissected; <sup>4</sup> 1-11 lymph nodes dissected; <sup>5</sup> presence of LND.

of surgical staging on the five-year disease-specific survival. In women with surgical Stage II disease, lymphadenectomy was associated with an improvement in survival from 82.2% to 90.4% ( $p < 0.001$ ). In multivariate analysis, lymphadenectomy appears to be an independent prognostic factor for improved survival.

Selvaggi *et al.* [13] studied the effect of performing pelvic lymphadenectomy in 410 clinical staged patients with endometrial carcinoma. In the patients with Stage II, lymph node dissection resulted in a five-year survival of 72% compared to 70% when no lymph node dissection was performed ( $p = 0.894$ ).

Smith *et al.* [14] included 42,184 patients with endometrial cancer to assess the effect of pelvic lymphadenectomy on the five-year uterine specific survival. In patients with Stage II disease (3364) 58.9% underwent lymph node dissection. Multivariate analyses showed a hazard ratio of 0.74 if lymph node dissection was performed

(95% CI 0.58 - 0.93,  $p = 0.0096$ ). Improved uterine specific survival was most pronounced if more than eleven lymph nodes were removed.

## Discussion

There are several limitations to this report. First, the search did not yield a randomised controlled trial and resulted only in retrospective studies. A retrospective design is prone to selection bias since the surgeon decides whether lymphadenectomy should be performed based on patient characteristics. This holds especially true for patients with endometrial cancer. Patients in whom lymph node sampling or lymphadenectomy may not be feasible due to comorbid factors, blood loss, or body habitus may have a much poorer prognosis *quod vitam*, compared to patients in whom lymphadenectomy is a realistic option.

Second, in all four studies, the adjuvant therapy follow-

ing surgical treatment with or without lymphadenectomy, was unequally distributed or unknown between patients.

Third, three studies defined the five-year overall survival as an outcome, instead of the five-year recurrence free survival. Therefore, this has been used as a second best outcome.

Fourth, FIGO staging changed in 2009. Stage IIA, with superficial involvement of the cervix, was downstaged to Stage I. Stage II now requires a tumour that invades cervical stroma and thus more advanced disease. The studies represented in this report have used the former FIGO staging system and therefore may also have included patients with a more favourable prognosis related to the superficial cervical involvement of Stage IIA.

Considering the individual studies, Chan *et al.* [12] only included surgically staged patients. To answer the question, studies that analysed patients with clinical Stage II endometrial carcinoma were more useful, as the decision to perform lymphadenectomy is made preoperatively and based on a clinically-defined stage. After surgical staging, not all patients will have true Stage II disease. This might result in stage migration and thereby influence the outcome. Also notable, the survival rates of this particular study are substantially higher than one could expect on the bases of other studies and even demographic data. A plausible explanation for this discrepancy could not be found.

Smith *et al.* [14] concluded that besides performing lymphadenectomy, the amount of lymph nodes removed is also of relevance for survival. This can be explained by the fact that with an increasing number of nodes removed, there is a higher statistical probability of obtaining sufficient nodes to adequately stage patients. Also, by removing micrometastatic disease within the node, a patient's survival may improve. This benefit associated with the extent of lymph node dissection is reported by more studies [4, 5, 17, 18].

Both Selvaggi *et al.* and Chan *et al.* included only patients with a histologic subtype of endometrioid endometrial carcinoma [12, 13]. Thereby, it is questionable if the results of these studies are applicable to patients with other histologic subtypes.

Moreover, the studies of Selvaggi *et al.* and Leminen *et al.* are also less to answer the question because they included small numbers of patients [11, 13]. Therefore, the answer to the question can only be based on the studies of Chan *et al.* and Smith *et al.* [12, 14].

## Conclusion

This study shows that there still is uncertainty in regards to the benefit of performing a systematic lymphadenectomy in clinical Stage II endometrial carcinoma.

Systematic lymphadenectomy seems to improve the five-year disease-specific survival in patients with clinical Stage II disease. However, the limitations of retrospective study designs prevent a strong recommendation. The individual situation of each patient should be taken in consideration when planning therapy modalities.

## References

- [1] Dutch Cancer Registration. <http://www.ikcnet.nl/page.php?id=114>. Accessed 30 January 2011.
- [2] Pecorelli S.: "Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium". *Int. J. Gynaecol. Obstet.*, 2009, 105, 103.
- [3] Van Lankveld M.A.L., Koot N.C.M., Peeters P.H.M., Schagen van Leeuwen J., Jürgenliemk-Schulz I.M., Van Eijkeren M.A.: "Compliance to surgical and radiation treatment guidelines in relation to patient outcome in early stage endometrial cancer". *J. Eval. Clin. Pract.*, 2006, 12, 196.
- [4] Kilgore L.C., Partridge E.E., Alvarez R.D., Austin J.M., Shingleton H.M., Noojin F. *et al.*: "Adenocarcinoma of the endometrium: survival comparisons of patients with and without pelvic node sampling". *Gynecol. Oncol.*, 1995, 56, 29.
- [5] Cragun J.M., Havrilesky L.J., Calingaert B., Synan I., Secord A.A., Soper J.T. *et al.*: "Retrospective analysis of selective lymphadenectomy in apparent early-stage endometrial cancer". *J. Clin. Oncol.*, 2005, 23, 3668.
- [6] Watanabe Y., Satou T., Nakai H., Etoh T., Dote K., Fujinami N. *et al.*: "Evaluation of parametrial spread in endometrial carcinoma". *Obstet. Gynecol.*, 2010, 116, 1027.
- [7] Dutch Concept Guideline Endometrial Carcinoma. December 2010.
- [8] Kitchener H., Redman C.W., Smart A.M., Amos C.L., ASTEC Study Group. ASTEC: "A study in the treatment of endometrial cancer: a randomized trial of lymphadenectomy in the treatment of endometrial cancer". *Lancet*, 2009, 373, 9658:125.
- [9] Benedetti Panici P., Basile S., Maneschi F., Alberto L.A., Signorelli M., Scambia G. *et al.*: "Systematic pelvic lymphadenectomy vs no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial". *J. Natl. Cancer Inst.*, 2008, 100, 1707.
- [10] Mencaglia L., Valle R.F., Lurain J.: "Endometrial carcinoma and precursors: diagnosis and treatment". *Isis Medical Media*, 1999.
- [11] Leminen A., Forss M., Lehtovirta P.: "Endometrial adenocarcinoma with clinical evidence of cervical involvement: accuracy of diagnostic procedures, clinical course and prognostic factors". *Acta Obstet. Gynecol. Scand.*, 1995, 74, 61.
- [12] Chan J.K., Wu H., Cheung M., Shin J., Osann K., Kapp D. *et al.*: "The outcomes of 27,063 women with unstaged endometrioid uterine cancer". *Gynecol. Oncol.*, 2007, 106, 282.
- [13] Selvaggi L., Loizzi M., Lorusso M., Demitri P., Cormio G.: "Lymphadenectomy versus no lymphadenectomy in endometrial carcinoma: a retrospective analysis of 410 patients". *J. Gynecol. Surgery*, 2010, 26, 2.
- [14] Smith D.C., Macdonald O., Lee C., Gaffney D.: "Survival impact of lymph node dissection in endometrial adenocarcinoma: a surveillance, epidemiology and end results analysis". *Int. J. Gynecol. Cancer*, 2008, 18, 255.
- [15] Trimble E.L., Kosary C., Park R.C.: "Lymph node sampling and survival in endometrial cancer". *Gynecol. Oncol.*, 1998, 71, 340.
- [16] Sartori E., Gadducci A., Landoni F.: "Clinical behavior of 203 clinical Stage II endometrial cancer cases: the impact of primary surgical approach and of adjuvant radiation therapy". *Int. J. Gynecol. Cancer*, 2001, 11, 430.
- [17] Chan J.K., Cheung M.K., Huh W.K., Osann K., Husain A., Teng N.N. *et al.*: "Therapeutic role of lymph node resection in endometrioid corpus cancer: a study of 12,333 patients". *Cancer*, 2006, 107, 1823.
- [18] Lutman C.V., Havrilesky L.J., Cragun J.M., Secord A.A., Calingaert B., Berchuck A. *et al.*: "Pelvic lymph node count is an important prognostic variable for FIGO Stage I and II endometrial carcinoma with high-risk histology". *Gynecol. Oncol.*, 2006, 102, 92.

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