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Original Research

Increased survival in non-endometrioid endometrial cancer after introducing lymphadenectomy and tailoring radiotherapy – A population-based cohort study

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Abstract ***Objective:*** To investigate recurrence and survival in non-endometrioid endometrial cancer in a population-based cohort and evaluate the implementation of the first national guidelines (NGEC) recommending pelvic and paraaortic lymphadenectomy for surgical staging and tailored adjuvant therapy.

Methods: A population-based cohort study that used the Swedish quality registry for gynaecological cancer for the identification of all women with early-stage non-endometrioid endometrial cancer between 2010 and 2017. Five-year overall (OS) and disease-free survival (DFS) were calculated using the Kaplan–Meier method. The Cox proportional hazards regression model was used to evaluate the effect of age, FIGO stage, primary treatment and lymph node dissection on DFS.

Results: There were 228 patients included in the study cohort and 67 (29%) patients had a recurrence within five years. In the recurrence cohort, the OS was 13.4% (95%CI:7.3–24.7) compared to 88.5% (95%CI:83.4–93.9) if no recurrence occurred (log-rank $p < 0.001$). The DFS for the complete cohort was 61.9% (95%CI:55.7–68.7).

The OS before implementation of NGEC was 57.3% (95%CI:48.2–68.1) and the DFS was 52.1% (95%CI:43.0–63.1) compared to an OS of 72.0% (95%CI:64.2–80.7; log-rank $p = 0.018$) and a DFS of 70.1% (95%CI:62.4–78.7; log-rank $p = 0.008$) after implementing NGEC. Patients received adjuvant radiotherapy in 92.7% before and 42.4% after NGEC implementation ($p < 0.001$). In the multivariable regression analysis, age, FIGO stage and lymph node dissection were found to be significant prognostic factors, where having a lymph node

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dissection decreased the risk of recurrence or death with a HR of 0.58 (95%CI:0.33–1.00).
Conclusion: In this population-based cohort of preoperative early-stage non-endometrioid EC, a significant improvement in survival was seen after NGEC implementation where lymph node staging for tailoring adjuvant therapy was introduced and less pelvic radiotherapy was given.

1. Introduction

The most frequent gynaecological malignancy is endometrial cancer (EC) with an incidence of 400,000 worldwide [1]. In Sweden, around 1400 women are diagnosed with EC annually and the prognosis is overall favourable with an 84% 5-year survival rate [2,3]. Non-endometrioid ECs, defined as serous, clear cell cancer and carcinosarcoma, represent 15–20% of all EC and are categorized as high-risk [4] and associated with a poorer prognosis than endometrioid EC [5–7].

Adjuvant treatment with chemotherapy and/or radiotherapy has been shown to reduce recurrences for high-risk EC, in both endometrioid and non-endometrioid EC [8], although studies have not taken nodal status into consideration when evaluating adjuvant treatment. However, adjuvant treatment with chemotherapy and/or radiotherapy is recommended for non-endometrioid EC in most guidelines [4,9–11]. Furthermore, for all EC diagnosed in advanced stages, FIGO III and IV, a survival benefit of adjuvant chemotherapy has been shown [12].

Pelvic and/or paraaortic lymphadenectomy in preoperative early-stage EC has not shown a survival benefit but is considered a staging procedure [13,14], and recently, there has been a shift towards sentinel node procedure for this purpose [15,16]. For high-risk EC, including non-endometrioid ECs, lymph node staging has been incorporated in most guidelines [4,9–11].

In 2012, the first Swedish national guidelines for EC (NGEC) were introduced, recommending pelvic and paraaortic lymphadenectomy (PPLND) for the high-risk group, including non-endometrioid ECs [17]. Before NGEC implementation, the treatment recommendation, according to the regional guideline [18], was primary surgery without assessment of lymph nodes followed by chemotherapy and radiotherapy.

The NGEC implementation was a major change in the surgical approach involving a more extensive surgical procedure with PPLND. Valid registries provided an opportunity to perform a population-based cohort study evaluating this alteration in the treatment of non-endometrioid ECs.

The primary aim of the present study was to investigate the recurrence rate, disease-free survival (DFS) and overall survival (OS) rates in women diagnosed with non-endometrioid EC in a complete population-based cohort. Second, to compare oncological outcomes before and after the implementation of NGEC, which introduced PPLND and tailored the adjuvant therapy, in women with non-endometrioid EC.

2. Methods

This is a regional population-based cohort study of all women diagnosed with non-endometrioid EC between 2010 and 2017 using the Swedish Quality Registry for Gynaecological Cancer (SQRGC) for identification of the study cohort.

The Western Sweden health care region (1.9 million inhabitants) has one tertiary centre and four county hospitals involved in the treatment of EC and almost 300 women are diagnosed with EC annually. The NGEC was introduced in December 2013 according to a decision by the regional health authority.

The EC part of the SQRGC was started in 2010. Reporting to the SQRGC is performed by the treating surgeons and oncologists prospectively and continuously. Consent to participate is presumed, but patients can opt-out from registration. The coverage of the SQRGC reaches nearly 100% when compared to the Swedish National Cancer registry [19]. The SQRGC has been validated [20] with a 72–98% agreement with core variables, described in previous studies [21–23]. The regional ethical review board of Gothenburg University approved the study (Dnr: 871-17).

2.1. Data collection

Data for all women registered in the SQRGC with non-endometrioid ECs was retrieved. Women who underwent surgery as primary treatment followed by chemotherapy and/or radiotherapy according to the current guidelines and in complete remission, with no evidence of disease at the start of follow-up were included in the study. Exclusion criteria were metastatic disease identified by preoperative computed tomography, concurrent ovarian or other cancer diagnoses, palliative treatment and surgery after neoadjuvant chemotherapy. Data retrieved included age, histology, grade, stage, details on surgery, adjuvant therapy and information on recurrences. The medical records were reviewed to validate the retrieved data and to complete the study database with missing information regarding follow-up and details on recurrences. The date of recurrence was defined as the date of biopsy

confirming recurrence or if no biopsy was made: the date of radiology confirming recurrence. The site of recurrence was grouped into vaginal, pelvic, abdominal (including carcinomatosis) or distant (lung, parenchymatous organs, skeletal, etc) and the number of recurrence localisations were noted. Patients were followed until 30th September 2020 or until death.

2.2. Study cohort and treatment protocols

The total study cohort of women diagnosed with non-endometrioid EC was divided into two.

In the early cohort (2010–December 2013), patients were treated according to the regional guidelines present at that time [18], with primary surgery consisting of hysterectomy, bilateral salpingo-oophorectomy, omentectomy and removal of lymph nodes only if grossly enlarged. All patients were recommended adjuvant therapy with both chemotherapy and pelvic radiation without investigation of nodal status. The surgical method was optional and could be open surgery or minimal invasive surgery (MIS) with conventional or robotic-assisted laparoscopy.

In the later cohort, defined as after the implementation of the NGEC [17] (December 2013–2017), all patients were recommended nodal staging with PPLND as part of the primary surgery. In case of significant comorbidities, the staging procedure was limited to pelvic lymphadenectomy. All patients were recommended adjuvant chemotherapy and pelvic radiation only if the metastatic disease was present in the lymph

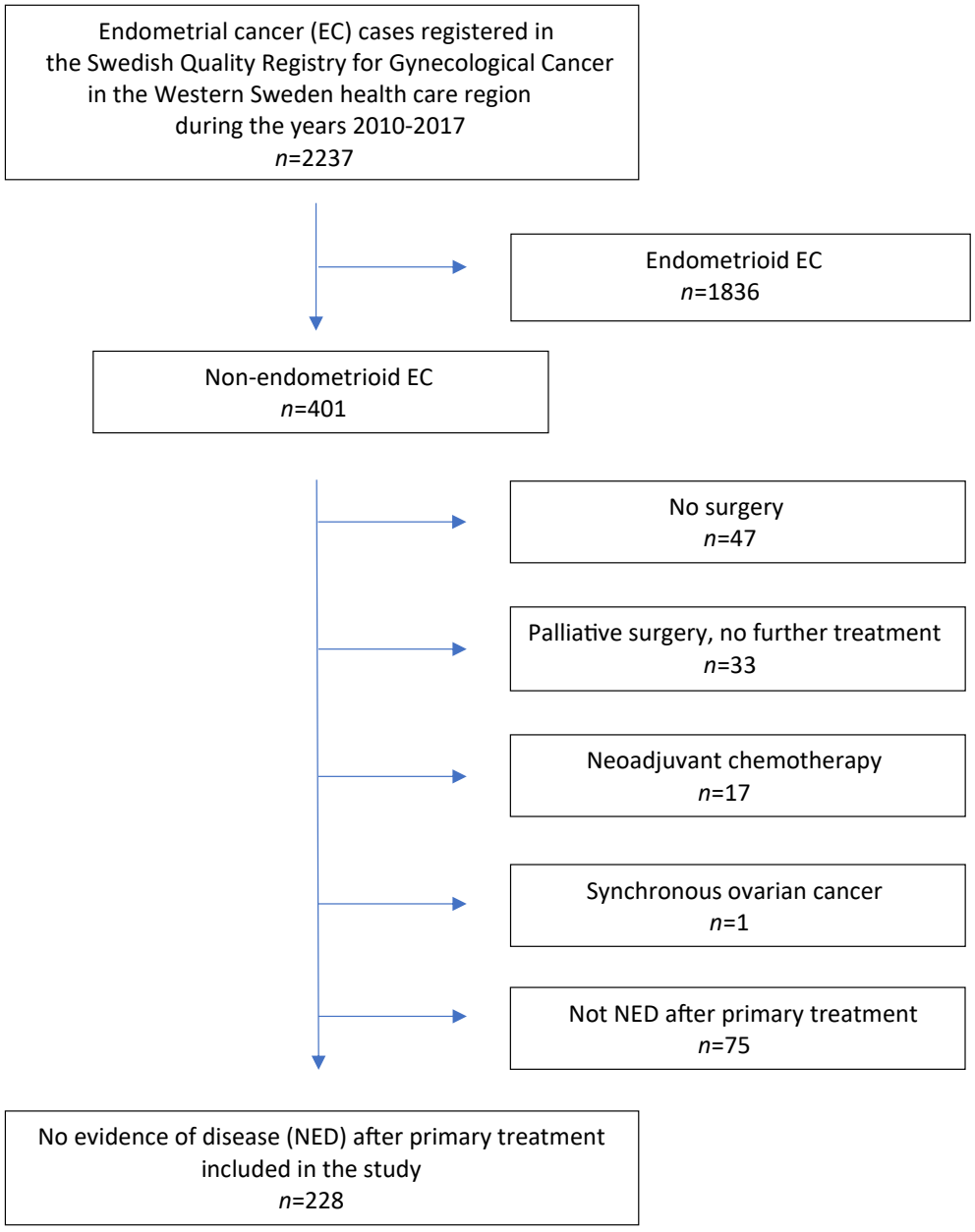

Fig. 1. Flowchart of the study population.

nodes. In the NGEC, there was a clear recommendation for MIS. Implementation of the NGEC induced a centralisation of surgery with PPLND the tertiary hospital.

3. Statistical methods

Variables were compared between the two cohorts of patients having had or not had a recurrence within 5 years after diagnosis and between the two cohorts before or after the implementation of the NGEC. For categorical variables, the Chi-squared test was used except for when any of the expected cell counts were less than 5, then the two-tailed Fisher's exact test was used. The two-tailed Student's t-test was used for the continuous variable age at diagnosis. A p-value less than 0.05 was considered significant.

To estimate OS and DFS, the Kaplan–Meier method was used. To test if there was a significant difference between the OS and DFS curves before and after the implementation of the NGEC the log-rank test was used.

Table 1
Patient and tumour characteristics (n = 228).

	Overall	**No recurrence**	**Recurrence**	***p*-value**
	n = 228 (100%)	*n* = 161 (71%)	*n* = 67 (29%)	
Age at diagnosis median (range)	71 (41–89)	70 (41–89)	73 (51–88)	0.023[b,a]
Histology; *n* (%)				
Carcinosarcoma	55 (24.1)	30 (18.6)	25 (37.3)	0.014[d,a]
Clear cell	51 (22.4)	42 (26.1)	9 (13.4)	
Serous	115 (50.4)	84 (52.2)	31 (46.3)	
Undifferentiated	7 (3.1)	5 (3.1)	2 (3.0)	
FIGO stage; *n* (%)				
IA	109 (47.8)	94 (58.4)	15 (22.4)	<0.001[d,a]
IB	33 (14.5)	19 (11.8)	14 (20.9)	
II	30 (13.2)	17 (10.6)	13 (19.4)	
IIIA	13 (5.7)	6 (3.7)	7 (10.4)	
IIIB	11 (4.8)	6 (3.7)	5 (7.5)	
IIIC	32 (14.0)	19 (11.8)	13 (19.4)	
Surgical technique; *n* (%)				
Laparotomy	159 (69.7)	109 (67.7)	50 (74.6)	0.653[d]
Robotic assisted laparoscopic	60 (26.3)	45 (28.0)	15 (22.4)	
Laparoscopic and/or vaginal	9 (3.9)	7 (4.3)	2 (3.0)	
Operating hospital; *n* (%)				
University hospital	147 (64.5)	106 (65.8)	41 (61.2)	0.504[c]
County hospital	81 (35.5)	55 (34.2)	26 (38.8)	
Primary treatment; *n* (%)				
Surgery + radiotherapy	12 (5.3)	5 (3.1)	7 (10.4)	<0.001[d,a]
Surgery + chemotherapy	83 (36.4)	73 (45.3)	10 (14.9)	
Surgery + chemo-and radiotherapy	133 (58.3)	83 (51.6)	50 (74.6)	
National guidelines implementation; *n* (%)				
Before	96 (42.1)	62 (38.5)	34 (50.7)	0.088[c]
After	132 (57.9)	99 (61.5)	33 (49.3)	
Peritoneal washing; *n* (%)				
Positive	26 (11.4)	12 (7.5)	14 (20.9)	0.001[c,a]
Negative	179 (78.5)	137 (85.1)	42 (62.7)	
Undefined/missing	23 (10.1)	12 (7.5)	11 (16.4)	
DNA flowcytometry; *n* (%)				
Diploidy	47 (20.6)	38 (23.6)	9 (13.4)	0.067[c]
Aneuploidy	113 (49.6)	75 (46.6)	38 (56.7)	
Undefined/missing	68 (29.8)	48 (29.8)	20 (29.9)	
Pelvic lymph node dissection; *n* (%)				
Yes	120 (52.6)	95 (59.0)	25 (37.3)	0.003[c,a]
lymph node count; median (range)	*18 (1–69)*	*19 (1–69)*	*17 (3–33)*	
No	108 (47.4)	66 (41.0)	42 (62.7)	
Paraaortal lymph node dissection; *n* (%)				
Yes	55 (24.1)	45 (28.0)	10 (14.9)	0.036[c,a]
lymph node count; median (range)	*7 (1–41)*	*7 (1–41)*	*11 (2–11)*	
No	173 (75.9)	116 (72.0)	57 (85.1)	
Follow-up time in months; median (range)				
	60.0 (33.3–60.0)	60.0 (33.3–60)	60.0 (60.0–60.0)	

Categories that are 'Undefined/missing' are not included in the significance tests.
Median follow-up was calculated using the reverse Kaplan–Meier.
[a] Statistically significant at the 5% significance level.
[b] Student's t-test.
[c] Chi-squared test.
[d] Fisher's exact test.

The Cox proportional hazards regression model was used to evaluate the effect of age at diagnosis, FIGO stage, primary treatment and lymph node dissection on DFS. In all the statistical analyses, the follow-up was truncated to 5 years after diagnosis.

R statistical software version 3.6.3 was used for the statistical analysis. The 'survival' package version 3.1–12 was used for estimating OS, DFS and fitting the Cox proportional hazards regression model.

4. Results

In total, there were 2237 patients diagnosed with EC during the study period of which 401 were classified as non-endometrioid (17.9%). In the final study cohort, 228 (56.9%) patients with complete remission at the end of treatment were included. A flow chart is presented in Fig. 1 and patient and tumour characteristics are described in Table 1.

4.1. Recurrences

In total, there were 67 (29.4%) recurrences diagnosed within the follow-up period of five years. The median time to recurrence was 18.5 months (range 6.1–54.9). Recurrences were biopsy or cytology verified in 71.6%.

Table 2
Recurrences description (n = 67).

	Recurrence within 5 years after diagnosis (n = 67)
Histology verified; *n* (%)	
Yes	48 (71.6)
No	19 (28.4)
Number of recurrence localisations; *n* (%)	
1	36 (53.7)
2	22 (32.8)
≥3	9 (13.4)
Reccurrence localisation:	
Only vaginal; *n* (%)	
Yes	5 (7.5)
No	62 (92.5)
Vaginal; n (%)	
Yes	14 (20.9)
No	53 (79.1)
Pelvic (incl lymphnodes); *n* (%)	
Yes	17 (25.4)
No	50 (74.6)
Paraaortic lymphnodes; *n* (%)	
Yes	11 (16.4)
No	56 (83.6)
Abdominal (incl carcinomatosis); *n* (%)	
Yes	35 (52.2)
No	32 (47.8)
Distant; *n* (%)	
Yes	33 (49.3)
No	34 (50.7)
Time from diagnosis to recurrence (months); median (range)	18.5 (6.1–54.9)

Details concerning the recurrences, are described in Table 2, with one site of recurrence in 53.7% and 'vaginal only' localisation in no more than 7.5%. Two or more sites of recurrence were noted in 46.3% of the patients. Abdominal recurrence was the most frequent localisation, in 52.2% of the patients.

The total study cohort was divided into the cohorts 'no recurrence' and 'recurrence' as shown in Table 1. The patients with recurrence were significantly older, had higher stage disease, more positive peritoneal washings and more often carcinosarcoma or serous cancer than clear cell cancer. There were no differences between the cohorts with recurrence or no recurrence regarding surgical technique, operating hospital or follow-up time.

4.2. Study cohorts before and after implementation of national guidelines

The study cohort was divided into two, before and after implementation of the NGEC. The early cohort consisted of 96 patients and the later cohort of 132 patients, described in Table 3.

There were no differences seen in age, histology distribution or surgical technique between the two cohorts. Upstaging occurred to a larger proportion of FIGO stage IIIC (18.9% versus 7.3%) after adding lymphadenectomies. Postoperative treatment shifted towards less radiotherapy, where 92.7% of the patients received radiotherapy before and 42.4% after the implementation of NGEC ($p < 0.001$). Peritoneal washings neither showed difference between the periods nor did DNA flowcytometry.

4.3. Survival

In the complete study cohort, the 5-year OS was 65.4% (95%CI:59.3–72.2) (Fig. 2A) and the 5-year DFS was 61.9% (95%CI:55.7–68.7) (Fig. 2C). For patients with a recurrence, the 5-year OS was 13.4% (95%CI:7.3–24.7), and for no recurrence, the 5-year OS was 88.5% (95% CI:83.4–93.9) and a significant difference was found with a log-rank of $p < 0.001$ (Fig. 2A).

Patients diagnosed with carcinosarcomas had a 5-year OS of 49.6% (95%CI:37.4–65.8), serous carcinoma had a 5-year OS of 66.5% (95%CI:58.1–76.0) and clear cell carcinoma had a 5-year OS of 79.8% (95% CI:69.3–91.9) (Supplementary Fig.S1). For FIGO stage I, the 5-year OS was 77.5% (95%CI:70.7–85.0), for FIGO stage II, the 5-year OS was 48.2% (95% CI:32.2–70.8), and for FIGO stage III, the 5-year OS was 44.2% (95%CI:32.5–60.0) (Supplementary Fig.S2).

4.4. Survival before and after implementation of national guidelines

When analysing survival comparing the two cohorts, a statistically significant improvement in both OS and DFS was found in the later study period as shown in

Table 3
Patient and tumour characteristics before/after implementation of national guidelines.

	Overall	Before	After	*p*-value
	n = 228 (100%)	n = 96 (42%)	n = 132 (58%)	
Age at diagnosis median (range)	71 (41–89)	70.5 (41–88)	71 (49–89)	0.944[b]
Histology; *n* (%)				
Carcinosarcoma	55 (24.1)	29 (30.2)	26 (19.7)	0.184[d]
Clear cell	51 (22.4)	23 (24.0)	28 (21.2)	
Serous	115 (50.4)	41 (42.7)	74 (56.1)	
Undifferentiated	7 (3.1)	3 (3.1)	4 (3.0)	
FIGO stage; *n* (%)				
IA	109 (47.8)	47 (49.0)	62 (47.0)	0.010[d,a]
IB	33 (14.5)	12 (12.5)	21 (15.9)	
II	30 (13.2)	13 (13.5)	17 (12.9)	
IIIA	13 (5.7)	8 (8.3)	5 (3.8)	
IIIB	11 (4.8)	9 (9.4)	2 (1.5)	
IIIC	32 (14.0)	7 (7.3)	25 (18.9)	
Surgical technique; *n* (%)				
Laparotomy	159 (69.7)	72 (75.0)	87 (65.9)	0.371[d]
Robotic assisted laparoscopic	60 (26.3)	21 (21.9)	39 (29.5)	
Laparoscopic and/or vaginal	9 (3.9)	3 (3.1)	6 (4.5)	
Operating hospital; *n* (%)				
University hospital	147 (64.5)	46 (47.9)	101 (76.5)	<0.001[c,a]
County hospital	81 (35.5)	50 (52.1)	31 (23.5)	
Primary treatment; *n* (%)				
Surgery + radiotherapy	12 (5.3)	8 (8.3)	4 (3.0)	<0.001[c,a]
Surgery + chemotherapy	83 (36.4)	7 (7.3)	76 (57.6)	
Surgery + chemo- and radiotherapy	133 (58.3)	81 (84.4)	52 (39.4)	
Recurrence within 5 years after diagnosis.; *n* (%)				
No recurrence	161 (70.6)	62 (64.6)	99 (75.0)	0.088[c]
Recurrence	67 (29.4)	34 (35.4)	33 (25.0)	
Peritoneal washing; *n* (%)				
Positive	26 (11.4)	13 (13.5)	13 (9.8)	0.468[c]
Negative	179 (78.5)	76 (79.2)	103 (78.0)	
Undefined/missing	23 (10.1)	7 (7.3)	16 (12.1)	
DNA flowcytometry; *n* (%)				
Diploidy	47 (20.6)	23 (24.0)	24 (18.2)	0.736[c]
Aneuploidy	113 (49.6)	52 (54.2)	61 (46.2)	
Undefined/missing	68 (29.8)	21 (21.9)	47 (35.6)	
Pelvic lymph node dissection; *n* (%)				
Yes	120 (52.6)	17 (17.7)	103 (78.0)	<0.001[c,a]
No	108 (47.4)	79 (82.3)	29 (22.0)	
Paraaortal lymph node dissection; *n* (%)				
Yes	55 (24.1)	1 (1.0)	54 (40.9)	<0.001[c,a]
No	173 (75.9)	95 (99.0)	78 (59.1)	
Time from diagnosis to recurrence in months; median (range)				
	18.5 (6.1–54.9)	18.2 (6.1–54.9)	19.1 (8.7–44.8)	0.716[e]
Median follow-up in months; median (range)				
	60.0 (33.3–60.0)	60.0 (56.6–60.0)	60.0 (33.3–60.0)	

Categories that are 'Undefined/missing' are not included in the significance tests.
Median follow-up was calculated using the reverse Kaplan–Meier.
[a] Statistically significant at the 5% level.
[b] Student's t-test.
[c] Chi-squared test.
[d] Fisher's exact test.
[e] MannWhitney U test.

Figs. 2B and C. The 5-year OS was 57.3% (95% CI:48.2–68.1) and the 5-year DFS was 52.1% (95% CI:43.0–63.1) for the cohort before the implementation of the NGEC compared to a 5-year OS of 72.0% (95% CI:64.2–80.7) and 5-year DFS 70.1% (95% CI:62.4–78.7) after the NGEC implementation. The *p*-value of the log-rank test comparing the survival curves was $p = 0.018$ for OS and $p = 0.008$ for DFS.

4.5. Regression analysis

The DFS was further explored with univariable and multivariable analysis using the Cox proportional hazards model for possible explanatory factors which included age, FIGO stage, primary treatment, lymph node dissection and before/after implementation of NGEC (Table 4). An event was recurrence or death. In

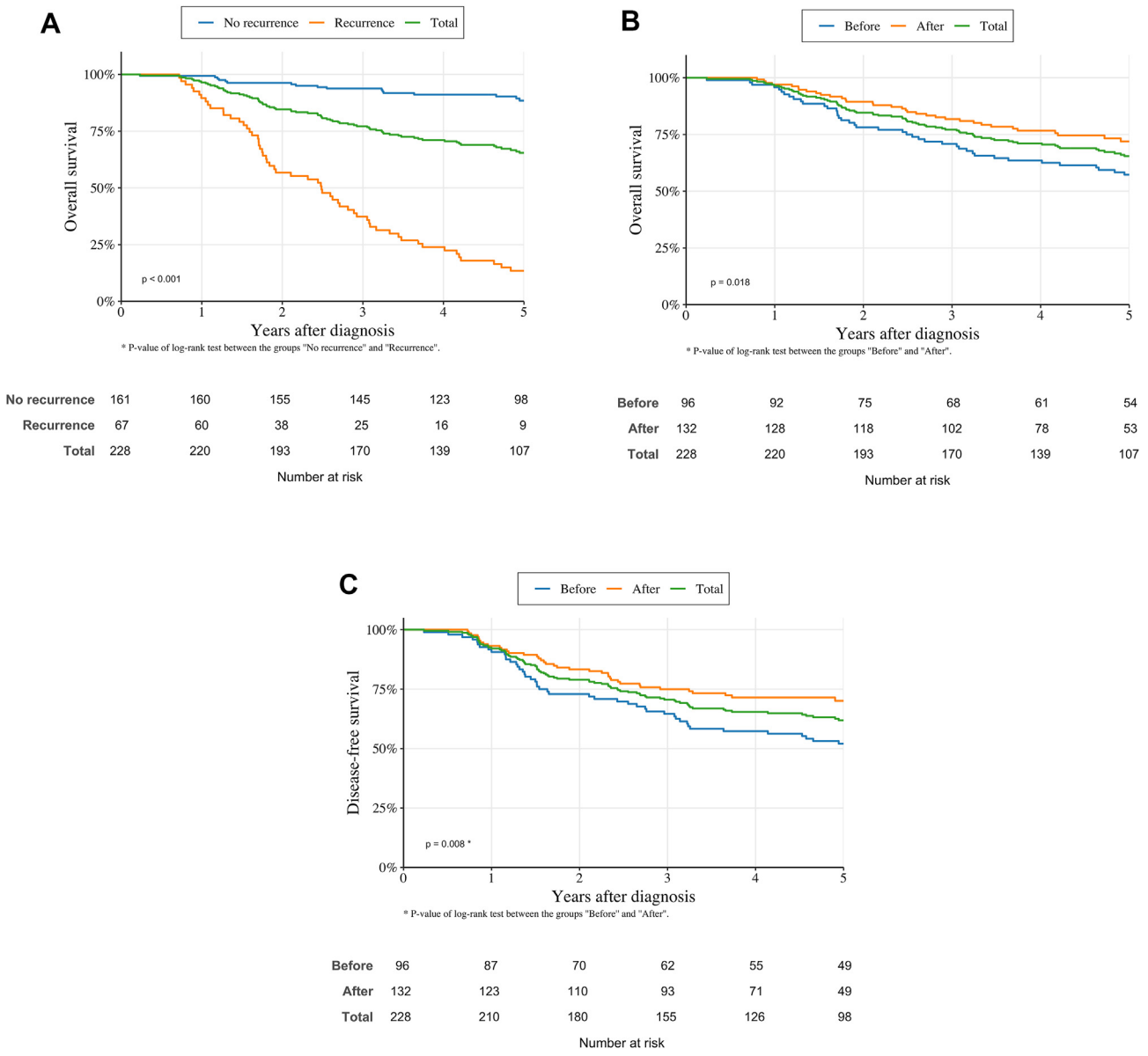

Fig. 2. **A**) Overall survival (OS) for the total cohort and the cohorts with recurrence and no recurrence. The 5-year OS for the total cohort was 65.4% (95%CI:59.3–72.2), for the cohort with recurrence 13.4% (95%CI:7.3–24.7) and with no recurrence 88.5% (95%CI:83.4–93.9). The *p*-value was <0.001 for the log-rank test comparing the OS curves for no recurrence and recurrence. B) Overall survival (OS) for the total cohort and the cohorts before and after the implementation of national guidelines for endometrial cancer (NGEC). The 5-year OS for the total cohort was 65.4% (95%CI:59.3–72.2), for the cohort before 57.3% (95%CI:48.2–68.1) and after NGEC 72.0% (95% CI:64.2–80.7), respectively. The *p*-value was 0.018 for the log-rank test comparing the OS curves before and after the implementation of NGEC. C) Disease-free survival (DFS) for the total cohort and the cohorts before and after implementation of national guidelines of endometrial cancer (NGEC). The 5-year DFS for the total cohort was 61.9% (95%CI:55.7–68.7), for the cohorts before 52.1% (95% CI:43.0–63.1) and after NGEC 70.1% (95%CI:62.4–78.7) respectively. The *p*-value was 0.008 for the log-rank test comparing the DFS curves before and after the implementation of NGEC.

the univariable regression model, all covariates were significant with a *p*-value <0.05. In the following multivariable regression analysis, age, FIGO stage and lymph node dissection were significant prognostic factors. Age (per 10 years) had a hazard ratio (HR) of 1.71 (95% CI:1.30–2.26, $p < 0.001$) and FIGO stage III compared to FIGO stage I a HR of 3.13 (95%CI:1.86–5.29, $p < 0.001$). Lymph node dissection had a HR of 0.58 (95%CI:0.33–1.00, $p = 0.048$) indicating a decreased risk of recurrence or death if a lymph node dissection was performed, keeping the other variables constant.

5. Discussion

This is to our knowledge, the first study evaluating survival and recurrences exclusively in non-endometroid ECs in a population-based cohort. Our study showed that non-endometrioid ECs in complete remission at the

Table 4
Cox regression analysis with disease-free survival (DFS) as endpoint n = 228.

	Univariable analysis		Multivariable analysis	
	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Age at diagnosis (per 10 years)	1.65 (1.27, 2.14)	<0.001	1.71 (1.30, 2.26)	<0.001
FIGO stage				
I	Ref		Ref	
II	2.54 (1.41, 4.57)	0.002	2.27 (1.21, 4.25)	0.011
III	2.69 (1.67, 4.35)	<0.001	3.13 (1.86, 5.29)	<0.001
Primary treatment				
Surgery + chemotherapy	Ref		Ref	
Surgery + radiotherapy ± chemo	3.34 (1.88, 5.93)	<0.001	1.45 (0.75, 2.83)	0.273
Lymph node dissection				
No	Ref		Ref	
Yes	0.42 (0.27, 0.66)	<0.001	0.58 (0.33, 1.00)	0.048
National guidelines implementation				
Before	Ref		Ref	
After	0.56 (0.37, 0.87)	0.009	0.79 (0.46, 1.36)	0.392

start of follow-up was associated with a high recurrence rate and a poor prognosis when a recurrence occurs. Moreover, the study showed a decreased risk for recurrence or death when lymph node dissection was performed. This is further reflected in the results of improved OS and DFS after the introduction of NGEC recommending PPLND for surgical staging and tailoring adjuvant therapy with radiotherapy only to those with lymph node metastases.

A most interesting and main finding in our study was the significantly improved survival found after implementation of the NGEC. Importantly, the guidelines introduced surgical staging with PPLND for non-endometrioid EC. Before the introduction of the NGEC, this patient group had only hysterectomy, bilateral salpingo-oophorectomy and omentectomy and adjuvant treatment with both chemotherapy and radiotherapy. The Cox regression multivariable analysis performed pointed towards having lymph node dissection as part of primary surgery to be an independent factor in reducing the risk of recurrence or death. It may be debated whether lymphadenectomy per se has an impact on survival. Earlier large studies on ECs have not shown this survival effect [13,14] but there may be subgroups of EC, such as the non-endometrioid group, where actually an effect of the lymphadenectomy as such may be seen. Other research groups have displayed results indicating a survival benefit in the high-risk group when adding lymphadenectomy [25,26].

Another essential factor to consider in the change of practice with the addition of PPLND was that centralisation to a tertiary centre occurred and this may have had an impact on survival. We have, in studies of advanced ovarian cancer, shown improved survival when centralised care was implemented [27,28]. In the present study of non-endometrioid EC, we were not able to perform an appropriate analysis of the effect of centralisation as such but it may be possible in future larger nationwide studies.

In the later period, after the implementation of the NGEC with surgical staging based on lymphadenectomy, radiotherapy was omitted in cases of negative nodes resulting in a smaller proportion of only 42.4% receiving radiotherapy than 92.7% in the early period. Despite this, the survival improved significantly. There was also additional benefit for the patients as they werespared the side-effects of radiotherapy on the bowel and urinary tract.

MIS, mainly robotic surgery in our study, did not show any significant difference to open when comparing the recurrence and no recurrence cohorts. This finding is in concordance with the randomised Lap2 study [29] which showed MIS to be a safe approach in early-stage EC including high-grade EC. A previous study [30] from Canada showed an association between uterine weight and recurrences in MIS surgery for high-grade EC. We did not have data on uterine size in our study, nonetheless surgical technique did not seem to have an impact.

There was no significant difference in OS between stage II and III in our study, which may be partly explained by the fact that our cohort included only patients with no evidence of disease at the start of follow up, where stage III with residual disease was excluded. Another explanation could be an under-staging of the stage II cohort from the earlier period as lymphadenectomies were not performed. However, women with stage I disease had a more favourable OS than stage II-III.

Sentinel lymph node dissection (SLN) is rapidly gaining ground replacing PPLND as it has been shown to be accurate for staging in high-grade EC [15,31,32]. During our study period, SLN had not yet been introduced. It will be interesting in the coming years to explore if the improved survival associated with PPLND staging will be maintained or even better with the SLN concept.

An important strength of our study is the completeness of the study database which is made possible due to full coverage in the national cancer registry and excellent adherence to the SQRGC. Furthermore, due to the Swedish public health care system, all women have equal opportunity to receive medical care and clinical treatment guidelines are followed to a great extent. It has previously been shown that guideline-concordant treatment gives a prognostic advantage [33]. One may argue that a weakness of our study is the retrospective design and the many years included in the study, where minor changes in treatment may have occurred. Notably, chemotherapy and radiotherapy treatment protocols have been identical during the study period. The change in the practice of surgical management was introduced sharply on Dec 1, 2013 and therefore the effects can be tracked to before and after the date and followed up accordingly. There was a relatively large proportion with non-endometrioid EC excluded during the study period because of apparent tumour spread or palliative intention of surgery as the aim of this study was to investigate the efficacy of the recommended primary treatment and recurrences after complete remission. Importantly, there was no difference in patients excluded over the studied time periods, thus the same proportion were excluded before and after the implementation of the NGEC.

6. Conclusion

In this regional population-based cohort study of preoperative early stage non-endometrioid EC, we found significantly improved survival after the shift in treatment guidelines when adequate lymph node staging was added to tailor adjuvant oncological treatment. This is promising as an adequately staged patient without lymph node metastasis may safely be spared radiotherapy with its potentially harmful long-term side-effects, which in turn favours a better quality of life.

Author contributions

Åsa Åkesson: Conceptualization, Methodology, Investigation, Data curation, Writing – review & editing, Formal analysis, Visualization, Project administration, Funding acquisition, Claudia Adok: Methodology, Formal analysis, Writing – review & editing, Visualization, Pernilla Dahm-Kähler: Conceptualization, Methodology, Formal analysis, Resources, Writing – review & editing, Funding acquisition, Supervision

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Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.04.002.

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