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Maintained survival outcome after reducing lymphadenectomy rates and optimizing adjuvant treatment in endometrial cancer

D. Forsse [a,b], H.F. Berg [a,b], O. Bozickovic [a,b], H. Engerud [a,b], M.K. Halle [a,b], E.A. Hoivik [a,b,d], K. Woie [b], H.M.J. Werner [b,1], I.S. Haldorsen [c,d], Trovik J. [a,b,2], C. Krakstad [a,b,*,2]

[a] Department of Clinical Science, Centre for Cancer Biomarkers CCBIO, University of Bergen, Bergen, Norway
[b] Department of Gynecology and Obstetrics, Haukeland University Hospital, Bergen, Norway
[c] Department of Radiology, Mohn Medical Imaging and Visualization Centre, Haukeland University Hospital, Bergen, Norway
[d] Section for Radiology, Department of Clinical Medicine, University of Bergen, Bergen, Norway

HIGHLIGHTS

- A cohort of 1308 endometrial cancer patients was assessed for outcome related to treatment changes over the last two decades.
- The rate of lymphadenectomy was reduced from approximately 80% to 50% without affecting survival or recurrence rates.
- Omitting adjuvant radiotherapy for a chemotherapy alone policy in high risk patients did not worsen survival or recurrence.

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ABSTRACT

Objective. Main controversies in endometrial cancer treatment include the role of lymphadenectomy and optimal adjuvant treatment. We assessed clinical outcome in a population-based endometrial cancer cohort in relation to changes in treatment management over two decades.

Methods. All consenting endometrial cancer patients receiving primary treatment at Haukeland University Hospital from 2001 to 2019 were included (n = 1308). Clinicopathological variables were evaluated for year-to-year changes. Clinical outcome before and after discontinuing adjuvant radiotherapy and individualizing extent of lymphadenectomy was analyzed.

Results. The rate of lymphadenectomy was reduced from 78% in 2001–2012 to 53% in 2013–2019. The rate of patients with verified lymph node metastases was maintained (9% vs 8%, $p = 0.58$) and FIGO stage I patients who did not undergo lymphadenectomy had stable 3-year recurrence-free survival (88% vs 90%, $p = 0.67$). Adjuvant chemotherapy for completely resected FIGO stage III patients increased from 27% to 97% from 2001 to 2009 to 2010–2019, while adjuvant radiotherapy declined from 57% to 0% ($p < 0.001$). These patients had improved 5-year overall- and recurrence-free survival; 0.49 [95% CI: 0.37–0.65] in 2001–2009 compared to 0.61 [0.45–0.83] in 2010–2019, $p = 0.04$ and 0.51 [0.39–0.68] to 0.71 [0.60–0.85], $p = 0.03$, respectively. For stage I, II and IV, survival rates were unchanged.

Conclusions. Our study demonstrates that preoperative stratification by imaging and histological assessments permits a reduction in lymphadenectomy to around 50%, and is achievable without an increase in recurrences at 3 years. In addition, our findings support that adjuvant chemotherapy alone performs equally to adjuvant radiotherapy with regard to survival, and is likely superior in advanced stage patients.

1. Introduction

Endometrial cancer is the most common gynecological cancer in industrialized countries, with a cumulative lifetime risk of 2–3% in women [1,2]. The prognosis in endometrial cancer is generally good due to detection at an early stage where surgery is likely curative [3]. Thus, selecting an appropriate level of treatment that balances the risk of recurrence with the risk of iatrogenic morbidity is a major challenge.

* Corresponding author at: Department of Gynaecology and Obstetrics, Haukeland University Hospital, Jonas Lies vei 72, 5020 Bergen, Norway.
E-mail address: camilla.krakstad@uib.no (C. Krakstad).
[1] Current address: Department of Obstetrics and Gynecology Maastricht University Medical Center, Maastricht, the Netherlands and GROW—School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, the Netherlands
[2] Shared last author.

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Currently, main controversies include the mode and extent of lymph tissue dissection for staging and selecting optimal adjuvant treatment regimens [4,5]. As an extensive research effort is ongoing to address these topics, oncological centers develop local, national or international guidelines, based on their respective evaluation of scientific evidence, available resources and clinical tradition.

During the last decade, several changes in patient treatment have been implemented for endometrial cancer patients in our region. In 2009 national guidelines were changed; adjuvant radiotherapy (external beam +/− brachytherapy) was no longer recommended for patients with high-risk tumors, defined as FIGO (International Federation of Gynecology and Obstetrics) stage IB grade 3 endometrioid, all stage I non-endometrioid, and completely resected stage II-III [6]. Instead adjuvant platinum based chemotherapy was advocated for all high-risk tumors, motivated by emerging data suggesting better survival outcome when opting for chemotherapy in the adjuvant setting [7]. In 2009 and 2011 respectively, pelvic magnetic resonance imaging (MRI) and fluorodeoxyglucose-positron emission tomography/computed tomography (PET/CT) were gradually integrated in preoperative diagnostics at Haukeland University Hospital. Finally, in October 2015, the MoMaTEC2 study (Molecular Markers in the Treatment of Endometrial Cancer, ClinicalTrials.gov Identifier: NCT02543710) was launched, evaluating the implementation of estrogen and progesterone receptor (ER/PR) expression in preoperative biopsies in combination with histological subtyping and imaging, with the intent to reduce the rate of patients undergoing lymphadenectomy.

The aim of this study was to assess effects and outcome when discontinuing adjuvant radiotherapy and reducing the rate of patients undergoing lymphadenectomy through more extensive preoperative patient stratification. Additionally, we explored trends in clinical and pathological variables that could affect patient outcome during the observed period.

2. Methods

2.1. Ethical considerations

The study was approved by the Western Regional Committee for Medical and Health Research Ethics (REK 2009/2315, 2018/594, and 2019/1020). All included patients signed an informed consent.

2.2. Patient series

Haukeland University Hospital serves approximately 10% of the Norwegian gynecological population as a full-scale gynecological oncology center, providing treatment for all endometrial cancer for local patients. Additionally, the center receives high-risk/advanced stage patients from neighboring counties, comprising approximately 15% of the cohort. The population of Hordaland is demographically representative of the Norwegian population, with similar distributions of age, gender, and body mass index (BMI) [8].

All consenting patients referred to Haukeland University Hospital for primary treatment of endometrial cancer from 2001 to 2019 were included. Patients were surgically staged according to FIGO 2009 criteria; patients treated prior to 2009 were reclassified according to the 2009 criteria as previously described [9]. Clinical and pathological variables were collected from the medical records. Radiological findings were recorded based on the radiology report. The surgery- and multidisciplinary tumor board reports were also reviewed to record how radiological findings had been perceived prior to surgery and to identify reasons for performing or not performing lymphadenectomy. The imaging protocols employed at our institution are largely in line with recommended European guidelines for preoperative imaging in endometrial cancer [10].

2.3. Treatment

Standard treatment was hysterectomy with bilateral salpingo-oophorectomy. Indications for lymphadenectomy changed over the study period (see below). Omentectomy was performed in patients with serous and clear cell tumors. All hysterectomies were performed by laparotomy until the introduction of robotic-assisted laparoscopic hysterectomy in 2010 and conventional laparoscopy in 2013 for selected patients (manageable comorbidity, no presumed extrauterine disease, and para-aortic lymphadenectomy not planned for). In the palliative setting, treatment options included debulking, hysterectomy for symptom control, or primary non-surgical therapy (chemotherapy, radiotherapy, or hormonal therapy). Treatment decisions were made at tumor board meetings including specialists in gynecological oncology, oncology, radiology, and pathology.

2.4. Indications for lymphadenectomy

Indications for lymphadenectomy changed during the observation period from a general pelvic sampling policy (sampling pelvic nodes at the surgeon's discretion unless deemed not tolerable or restricted access perioperatively) to a selective policy based on preoperative risk assessment. Preoperative low-, intermediate-, and high-risk groups were defined by histological assessment of curettage/endometrial biopsy and radiological findings according to the European Society of Medical Oncology (ESMO) guideline [11]. Low risk was defined as endometrioid endometrial cancers grade 1–2 with <50% myometrial invasion (MI) assessed by MRI, intermediate risk as endometrioid grade 1–2 with MI > 50%, or grade 3 endometrioid with MI <50%. Endometrioid grade 3 tumors with MI > 50% and all non-endometrioid cancers were classified as high risk. The evaluation of myometrial invasion was non-systematically performed by CT or ultrasound prior to the implementation of MRI in 2009, after which all patients were systematically grouped. Pelvic lymphadenectomy was gradually restricted (2010−2012) to the intermediate-risk group while pelvic and para-aortic lymphadenectomy was performed for the high-risk group. In 2011, PET/CT was introduced for preoperative evaluation. Any patient with PET-positive pelvic or para-aortic lymph nodes underwent lymphadenectomy, unless intolerable or complete debulking was deemed unattainable. In October 2015, preoperative immunohistochemical expression of PR and ER was included as part of a phase 4 implementation study (MoMaTEC2); in low- and intermediate-risk cases, lymphadenectomy was omitted when ER and PR expression was positive. In addition to preoperative assessment, perioperative findings (e.g. enlarged lymph nodes) could prompt lymphadenectomy. Supplementary Table 1 shows the current algorithm for extent of surgery.

2.5. Adjuvant treatment

Patients were postoperatively reclassified based on histopathological examination of the hysterectomy specimen and final FIGO stage into low-, intermediate-, or high-risk groups (endometrioid grade 3 stage IB, any stage II-IV tumors and any non-endometrioid tumors), in line with the ESMO classification [11,12]. At Haukeland University Hospital, lymphovascular space invasion status was added to the pathology report in 2018, but did not affect treatment, and is not included in our analyses. Standard adjuvant treatment in 2001–2009 was adjuvant radiotherapy (external beam +/− brachytherapy) or platinum based adjuvant chemotherapy (standard being carboplatin plus paclitaxel for six cycles) for high-risk tumors. The contemporary guidelines contained no specification for choice of modality, except for a preference for chemotherapy in serous or clear-cell tumors. From 2009, national guidelines no longer recommended adjuvant radiotherapy except for stage II patients with incomplete surgical margins. Instead, adjuvant chemotherapy was advocated for all high-risk tumors, with six cycles of carboplatin plus paclitaxel as standard treatment.

2.6. Statistical analysis

All statistical analyses were performed in SPSS 25.0 (IBM, New York) or R v3.6.1 (R Core Team 2019). Year-to-year time trends were assessed by linear regression for continuous variables and the Chi-square test for trend for proportions. Categorical variables were compared by Chi-square test or Fischer's exact test, and differences in distributions of continuous variables were assessed by the Mann-Whitney *U* test. To explore the influence of clinicopathologic variables over the observation period, a multivariable cox regression survival model was built using enter method. Age, BMI, parity, MI, histological type and grade, FIGO stage, year of treatment and adjuvant treatment modalities were analyzed in univariable analysis. Variables with hazard ratios with $p < 0.1$ were included in the adjusted multivariable analysis.

To compare different adjuvant treatment strategies the cohort was divided at 01 Jan 2010, based on the time point for national guideline change in 2009. For analysis of outcomes related to the systematic reduction in the rate of patients undergoing lymphadenectomy, 01 Jan 2013 was chosen, based on the time point where patient surgical files started containing explicit rationale for performing lymphadenectomy (gradual increase over 2010–2012).

Overall survival (OS) was defined as time from treatment to death from any cause. Disease specific survival (DSS) was defined as time from treatment to death from endometrial cancer. Recurrence-free Survival (RFS) was defined as time from surgery to first verified recurrence, and only included patients with completely resected tumors (macroscopically tumor-free). To account for differences in follow-up times due to sampling groups from different time periods, OS and DSS were reported at 5 years after primary treatment longer follow-up was blinded. RFS was analyzed at 3 years and follow-up was blinded at 3 years, as more than 70% of recurrences occur within 3 years, allowing earlier reliable assessment of RFS than OS and DSS [13]. The Kaplan-Meier method was used to visualize differences in survival between groups, using the log-rank test for comparisons between groups. For all statistical analyses, differences were considered significant at $p < 0.05$ (two-sided).

3. Results

3.1. Increasing age, BMI and serous histology over time

A total of 1308 patients were included in the study (Table 1), with a median follow-up time of 49 months (range 0–212). The number of treated patients showed an increasing trend over 2001–2019, mirroring the Norwegian increase in endometrial cancer incidence (Fig. 1A, Supplementary Table 2). Median age at primary treatment was 66 years (interquartile range 15), with an average 2 months/year increase ($p = 0.008$, Fig. 1B). Median BMI was 27.3 kg/m^2 (interquartile range 8), also with a slightly increasing trend over time (0.08 kg/m^2/year, $p = 0.037$, Fig. 1C). The distribution of FIGO stages showed some year-to-year variation, but no time-dependent trend was observed (Fig. 1D). The proportion of endometrioid endometrial cancer at post-operative histopathological diagnosis was stable, as well as histological grade within the endometrioid subtype (Fig. 1E and F). Distribution of non-endometrioid histological types was constant, apart from a statistically significant increasing trend in the proportion of serous endometrial cancer ($p = 0.004$, Fig. 1E). The proportion of serous tumors in 2010–2019 was 13%, compared to 9% in 2001–2009 (Fig. 1F).

In a Cox regression model (Supplementary Table 3), increasing age, stage III-IV, high grade EEC, NEEC, and deep myometrial invasion were all significant predictors of poor survival in both unadjusted analysis and after adjusting for all other variables ($p = 0.031$ for grade 3 EEC, $p < 0.001$ for the rest,). Year of primary treatment did not affect survival outcome. Any adjuvant treatment was associated with higher hazard ratio (for disease specific death) compared to no adjuvant treatment, however when adjusting for the other variables, radiotherapy remained significant with an adjusted hazard ratio of 1.9 (95% CI 1.1–3.4, $p = 0.035$), whereas chemotherapy did not (1.2, 95% CI 0.8–1.9, $p = 0.47$).

Table 1
Clinical and pathological characteristics of the cohort (n = 1308).

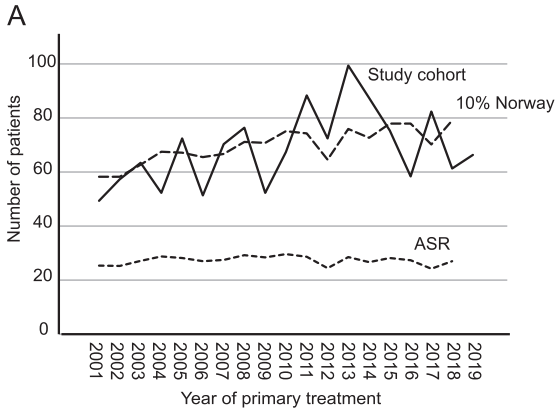
	Median	Interquartile range
Age at treatment	66	15
Body mass index	27.3	8
	n	%
Menopausal status		
Pre−/perimenopausal	130	9.9%
Postmenopausal	1177	90.1%
Parity		
Para 0	208	16.1%
Para 1+	1086	83.9%
Primary treatment		
Hysterectomy	1241	94.9%
Tumor reduction	8	0.6%
Curettage	59	4.5%
Mode of surgery (hysterectomy)		
Laparotomy	972	78.3%
Laparoscopy	92	7.4%
Robot-assisted laparoscopy	177	14.3%
Lymph node sampling		
Not performed	422	32.3%
Pelvic	742	56.7%
Para-aortic and pelvic	144	11.0%
Lymph node metastasis		
Negative	773	87.2%
Positive	113	12.8%
FIGO stage		
I	968	74.0%
II	101	7.7%
III	157	12.0%
IV	82	6.3%
Histological subtype		
Endometrioid (EEC)	1016	77.7%
Non-endometrioid	292	22.3%
Clear cell	50	3.8%
Serous papillary	148	11.3%
Carcinosarcoma	58	4.4%
Undifferentiated/other	36	2.8%
Histological Grade (EEC only)		
Grade 1–2	826	82.8%
Grade 3	172	17.2%
Adjuvant treatment		
None	863	66.0%
External radiation	81	6.2%
Brachytherapy	7	0.5%
Chemotherapy	325	24.8%
Chemotherapy + radiation	10	0.8%
Hormonal treatment	22	1.7%

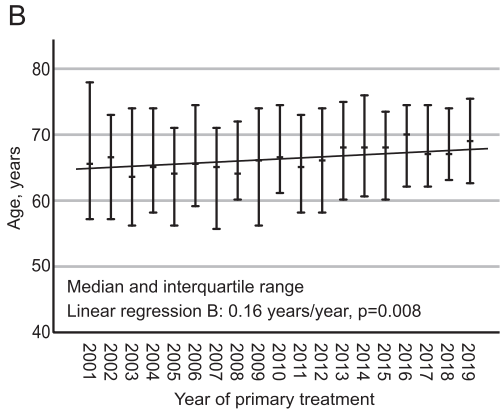
FIGO International Federation of Gynecology and Obstetrics.

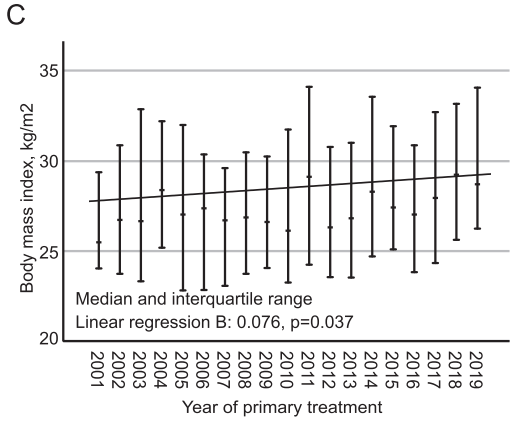
3.2. Reduction of lymphadenectomy with maintained rate of stage IIIC patients

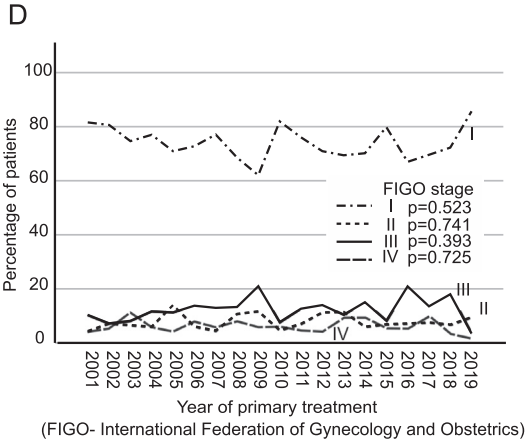
MRI and PET/CT were implemented in diagnostics during the study period (Fig. 1G), peaking in 2015–2019 with >85% of patients subjected to both examinations. The rate of lymphadenectomy decreased, with a pronounced decline in 2012–2013, and flattening out to 50–60% onwards (Fig. 1H). Thus, a significantly smaller proportion of patients underwent lymphadenectomy in 2013–2019 compared to 2001–2012 (53% versus 78%, $p < 0.001$). The rate of para-aortic procedures increased (5% to 20% of all patients, $p < 0.001$) (Table 2). The rate of patients with verified lymph node metastases was stable across the two time periods (8% vs 9%, $p = 0.576$), including para-aortic metastases (Stage IIIC2; 2% vs 2%).

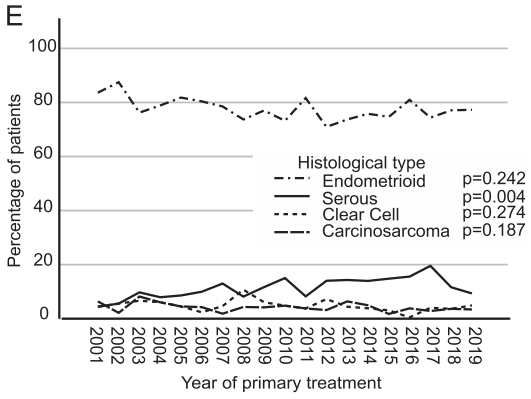
The group of patients not undergoing lymphadenectomy in 2013–2019 largely consisted of low- and intermediate-risk patients (based on preoperative histology and MI) without additional risk

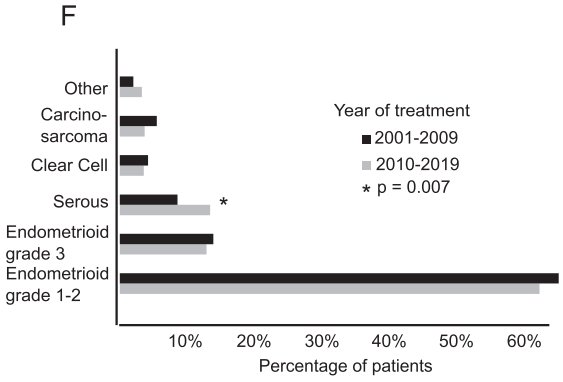

A
Number of patients
Study cohort
10% Norway
ASR
Year of primary treatment

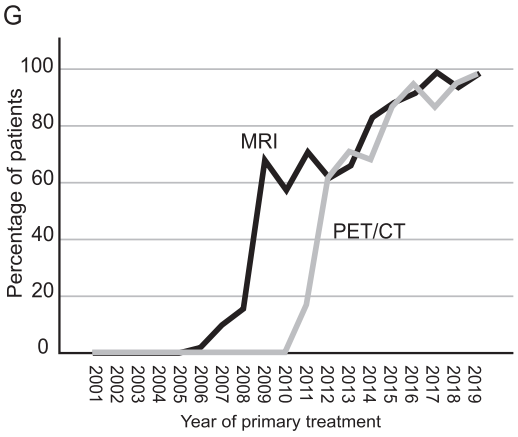

B
Age, years
Median and interquartile range
Linear regression B: 0.16 years/year, p=0.008
Year of primary treatment

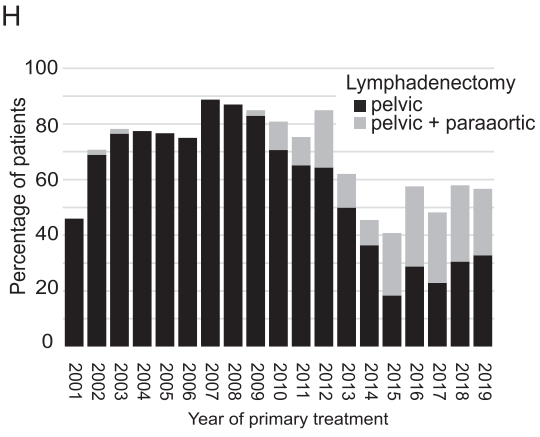

C
Body mass index, kg/m2
Median and interquartile range
Linear regression B: 0.076, p=0.037
Year of primary treatment


D
Percentage of patients
FIGO stage
I p=0.523
II p=0.741
III p=0.393
IV p=0.725
Year of primary treatment
(FIGO- International Federation of Gynecology and Obstetrics)


E
Percentage of patients
Histological type
Endometrioid p=0.242
Serous p=0.004
Clear Cell p=0.274
Carcinosarcoma p=0.187
Year of primary treatment


F
Other
Carcino-sarcoma
Clear Cell
Serous
Endometrioid grade 3
Endometrioid grade 1-2
Year of treatment
2001-2009
2010-2019
* p = 0.007
Percentage of patients


G
Percentage of patients
MRI
PET/CT
Year of primary treatment


H
Percentage of patients
Lymphadenectomy
pelvic
pelvic + paraaortic
Year of primary treatment

factors (lymphadenopathy on imaging, loss of ER/PR or clinical upstaging) (Fig. 2A). Interestingly, among patients undergoing lymphadenectomy in this period, no patients had verified lymph node metastases in the low- and intermediate-risk groups unless having additional risk factors. Among non-lymphadenectomized low-risk patients, five out of 79 (6%) experienced recurrence within 3 years, compared to one of 25 (4%) of patients undergoing lymphadenectomy in spite of not having any apparent risk factors. Corresponding percentages for intermediate-risk patients without additional risk factors were four recurrences in 41 node negative patients (10%) and three recurrences in 43 non-lymphadenectomized patients (7%).

Survival data was available for 778 patients treated between 2001 and 2012 with a median follow-up of 71 months (range 0–212) and for 530 patients treated between 2013 and 2019 in with a median follow-up of 25 months (range 0–70). Although the proportion of stage I patients not undergoing lymphadenectomy increased from 17% to 51%, 3-year RFS was maintained in this group (0.91 (95% CI 0.86–0.96) for 2013–2019 compared to 0.88 (95% CI 0.82–0.95), $p = 0.46$, Fig. 2B). For the whole cohort comparing 2001–2012 to 2013–2019, 3-year RFS was 0.84 (95% CI 0.81–0.87) vs 0.85 (95% CI 0.81–0.89, $p = 0.56$).

3.3. Changes in adjuvant treatment with discontinuation of radiotherapy

Administration of adjuvant radiotherapy was reduced from 12% of all patients in 2001–2009 to 1% in 2010–2019 ($p < 0.001$, Fig. 3A), while the proportion of patients receiving adjuvant chemotherapy increased from 10% to 31% ($p < 0.001$). In stage I high-risk patients, 79% received chemotherapy in 2010–2019 compared to 28% in 2001–2009 ($p < 0.001$), representing the main contribution to the overall increase in use of adjuvant therapy (Fig. 3B). For (postoperative) low- and intermediate-risk patients in stage I, adjuvant therapy rates were low and stable. In stage II patients, the reduction in radiotherapy was comparable to the increase in chemotherapy, thus with a stable overall rate of adjuvant treatment in this group (62% to 58%, $p = 0.7$). The proportion of patients with stage III (macroscopically tumor-free) receiving adjuvant chemotherapy increased significantly from 27% to 95% ($p < 0.001$). The proportion not receiving any adjuvant treatment in this group decreased from 16% to 5% ($p < 0.05$).

The median follow-up time was 73 months (range 0–212) for the 2001–2009 group and 35 months (range 0–95) for the 2010–2019 group. No differences in 5-year OS or DSS between groups were found, nor for 3-year RFS (Fig. 4A). In subgroup analysis, 5-year OS improved significantly in completely resected stage III patients from 0.49 (95% CI: 0.37–0.65) to 0.61 (0.45–0.83, $p = 0.04$, Fig. 4B). RFS at 3 years in stage III was also significantly better in 2010–2019 (0.71 (95% CI: 0.39–0.68)) compared to the 2001–2009 group (0.51 (0.39–0.68, $p = 0.03$)). OS, DSS and RFS in stage I and II were similar before and after 2009. Outcome was also stable for stage I high-risk patients in spite of a substantial increase in adjuvant chemotherapy in this group (Supplementary Fig. 1). The 3-year recurrence rate for all patients for the whole observation period was 17%, with distant recurrences in 9%, pelvic in 2% and vaginal recurrences in 6% (Fig. 4C). In completely resected stage III patients the rate of distant recurrences decreased from 38% in 2001–2009 to 28% in 2010–2019, vaginal recurrences from 9% to 3% and pelvic recurrences increased from 5% to 8%, but the changes were not statistically significant.

Table 2
Comparison of extent of disease and extent and outcome of lymphadenectomy before and after 1 Jan 2013.

	2001–2012 (n = 778) n (%)	2013–2019 (n = 530) n (%)	*p* (chi-square)
FIGO Stage			0.899
I	581 (75)	384 (73)	
II	60 (8)	41 (8)	
III	91 (12)	66 (13)	
IIIc1	49 (6)	30 (6)	
IIIc2	14 (2)	9 (2)	
IV	46 (6)	35 (7)	
Lymphadenectomy (LA)			**<0.001**
Not performed	171 (22)	251 (47)	
Pelvic	567 (73)	175 (33)	
Para-aortic and pelvic	40 (5)	104 (20)	
Lymph node metastasis			0.576
Negative + unknown	708 (91)	487 (92)	
Positive	70 (9)	43 (8)	

FIGO: International Federation of Obstetrics and Gynecology.
Numbers in bold signify p-values < 0.05.

4. Discussion

Major research efforts are being deployed into uncovering the optimal ways to stage and treat endometrial cancer. Main points of controversy are the role of lymphadenectomy and matching optimal adjuvant therapy regimes to subgroups. We have performed a broad analysis in a population based Norwegian cohort to retrospectively assess the effects of national and local changes to optimize the rate of patients undergoing lymphadenectomy on one hand, and the discontinuation of adjuvant radiotherapy on the other. We describe a successful reduction of the rate of endometrial cancer patients undergoing lymphadenectomy, with maintained identification rates of stage IIIC patients and consistent low recurrence rates in unstaged patients. In addition, we have analyzed outcome after discontinuing radiotherapy as an adjuvant option and implementing adjuvant chemotherapy alone as standard treatment in high-risk patients, and find maintained overall survival outcome and improved survival in stage III patients.

Sentinel node (SN) mapping is on the rise in endometrial cancer, due to high sensitivity and negative predictive value [14]. Nevertheless, in a recent survey, 50% of gynecological oncologists in Europe and USA did not use this technique, implying that for many institutions a better risk-stratification of patients prior to surgical staging is still an important issue [15]. At our institution, where sentinel node mapping is not implemented, the rate of patients undergoing lymphadenectomy has decreased over the last 6–7 years. This is due to a shift from universal sampling to selective lymphadenectomy, following an incorporation of imaging and molecular biomarkers into the diagnostic work-up. We show that in spite of a marked reduction in lymphadenectomies, we still identify metastatic nodes at the same rate, and there is no indication of increased recurrence rates in the non-staged patients. For institutions using sentinel node techniques, these results may also be of interest, especially when failed mapping mandates a full- or hemipelvic lymphadenectomy [16]. Even when successful, sentinel node procedures add significant time and cost to surgery compared to no lymph node removal, and should be omitted when unnecessary [17].

Fig. 1. Time trends in clinicopathological characteristics 2001–2019. A) Number of endometrial cancer patients receiving primary treatment at Haukeland University Hospital. The stippled lines show the incidence in Norway divided by 10 and the Norwegian age-standardized rate per 100,000 person years (ASR) based on 2014 age weights [2]. Full numerical data in Supplementary Table 1. B) Age at primary treatment, median and inter-quartile range with linear regression $y = Bx + k$. C) Body mass index, median and inter-quartile range with linear regression $y = Bx + k$. D) Trend in distribution of FIGO stages. Trends analyzed with chi-square test for trend. E) Trend in distribution of histopathological subtypes in final surgical specimen. Trends analyzed with chi-square test for trend. F) Distribution of histologic types in final surgical specimen split by decade. Other includes undifferentiated and rare histological subtypes. G) Changes in the use of magnetic resonance imaging (MRI) and positron emission tomography/computerized tomography (PET/CT). MRI was included in routine management from 2009, PET/CT from 2011. H) Changes in rates of lymphadenectomy, and extent of procedure.

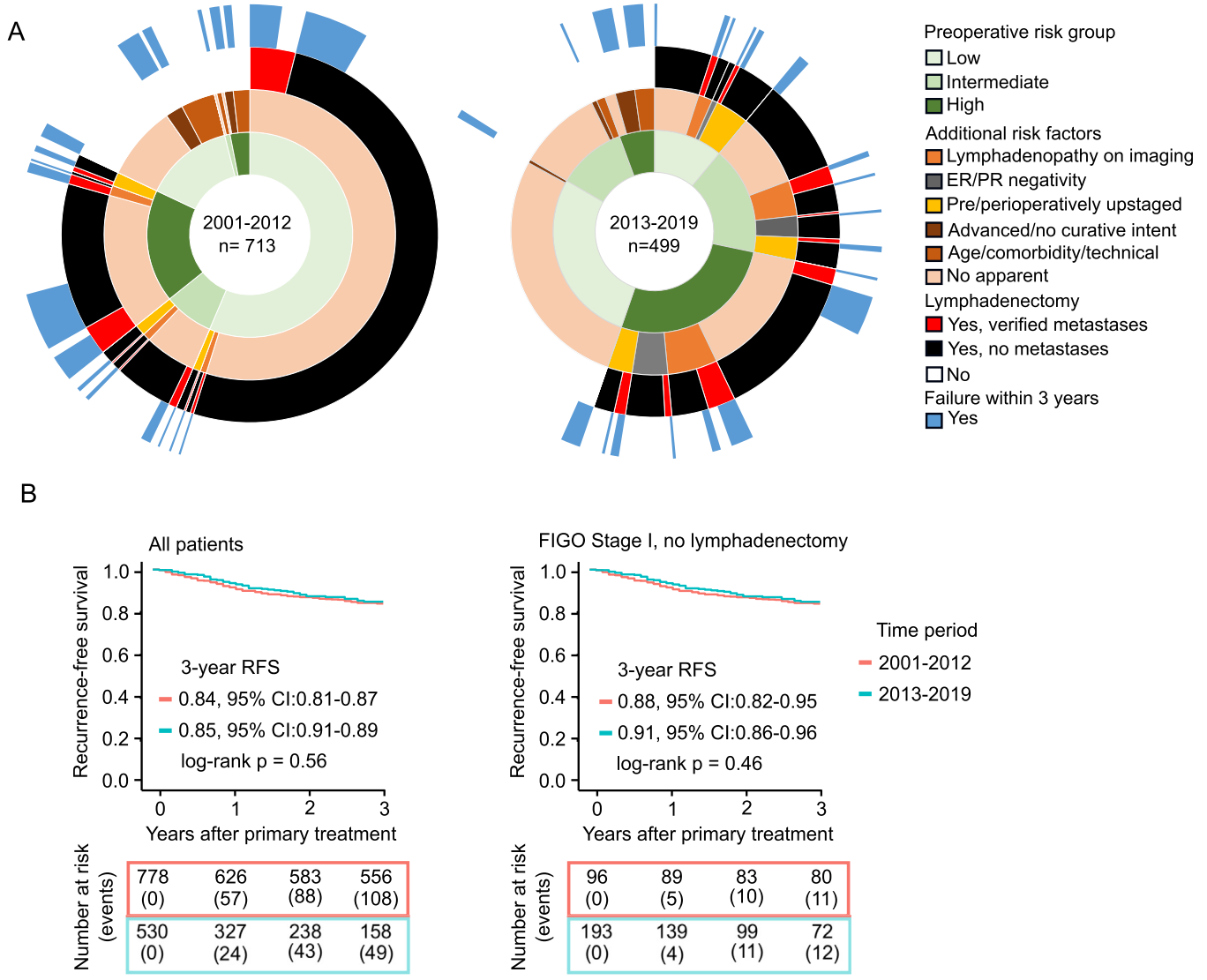


Fig. 2. A) Preoperative characterization of hysterectomized patients, before and after 01 Jan 2013, with a preoperative endometrial cancer assessment (excluding incidental findings after benign diagnosis and surgery for presumed ovarian cancer). Inner circle displays risk groups based on histologic assessment of preoperative biopsy/curettage and imaging: Low: endometrioid grade 1–2 with <50% myometrial invasion (MI) or MI unknown. Intermediate: endometrioid grade 1–2 with >50% MI or grade 3 with <50% MI. High: endometrioid grade 3 with >50% MI or MI unknown and all non-endometrioid cancers. Patients missing preoperative histological info were excluded (n = 31). Second circle displays the additional risk factor most important for explaining whether patients underwent LA, based on patient file review. Third circle displays prevalence of metastatic lymph nodes where LA was performed. Outer circle displays recurrences or progression occurring within 3 years. All sectors correspond to proportions of patients included. ER Estrogen Receptor, PR Progesterone Receptor, pre/perioperatively upstaged signifies imaging or clinical findings corresponding to stage>I (other than lymphadenopathy), technical signifies perioperative technical issues due to adhesions, bleeding, also including patient's wish. B) Kaplan-Meier survival curve showing 3-year recurrence free survival before and after reduction of lymphadenectomies in 2013. FIGO: International Federation of Gynecology and Obstetrics.

We report an increase in use of adjuvant chemotherapy in high-risk patients (stage I high-risk + stage II and III), and a concomitant cessation of adjuvant radiotherapy. Although adjuvant therapy for high-risk patients is in line with current international recommendations, the optimal treatment algorithm is under debate, especially concerning the respective roles of radiotherapy and systemic chemotherapy. The ESMO consensus favors external beam radiation therapy for stage I high-risk patients when staged and node negative, and supports consideration of brachytherapy, but states that the role of systemic chemotherapy is insufficiently investigated [12]. In trials with stage I high-risk patients where chemotherapy alone has been compared with radiotherapy, no differences in OS or RFS have been shown, although pelvic recurrence rates were lower after radiotherapy and distant recurrences lower after chemotherapy [18,19]. Our study shows that omitting radiotherapy in stage I patients has not produced poorer outcome, when substituted with chemotherapy. Advantages with this approach is avoidance of radiotherapy related side effects and saving radiotherapy for salvage treatment of vaginal and small pelvic recurrences in patients if they do occur. We report a vaginal recurrence rate of 6% in the whole population-based series, which seems comparable to 5–10% in previously published chemotherapy only-studies reporting high-risk cases [18–20]. We do note that the substantial increase in adjuvant chemotherapy in stage I patients does not seem to improve outcome. The ongoing ENGOT-EN2-DGCG/EORTC55102 study (clingov ID NCT01244789), comparing adjuvant chemotherapy with observation for low-stage high-risk patients will hopefully provide additional data to optimize treatment strategies for this group. Molecular subtyping provides prognostic information independent of classical histopathological stratification and could improve tailoring of treatment [21].

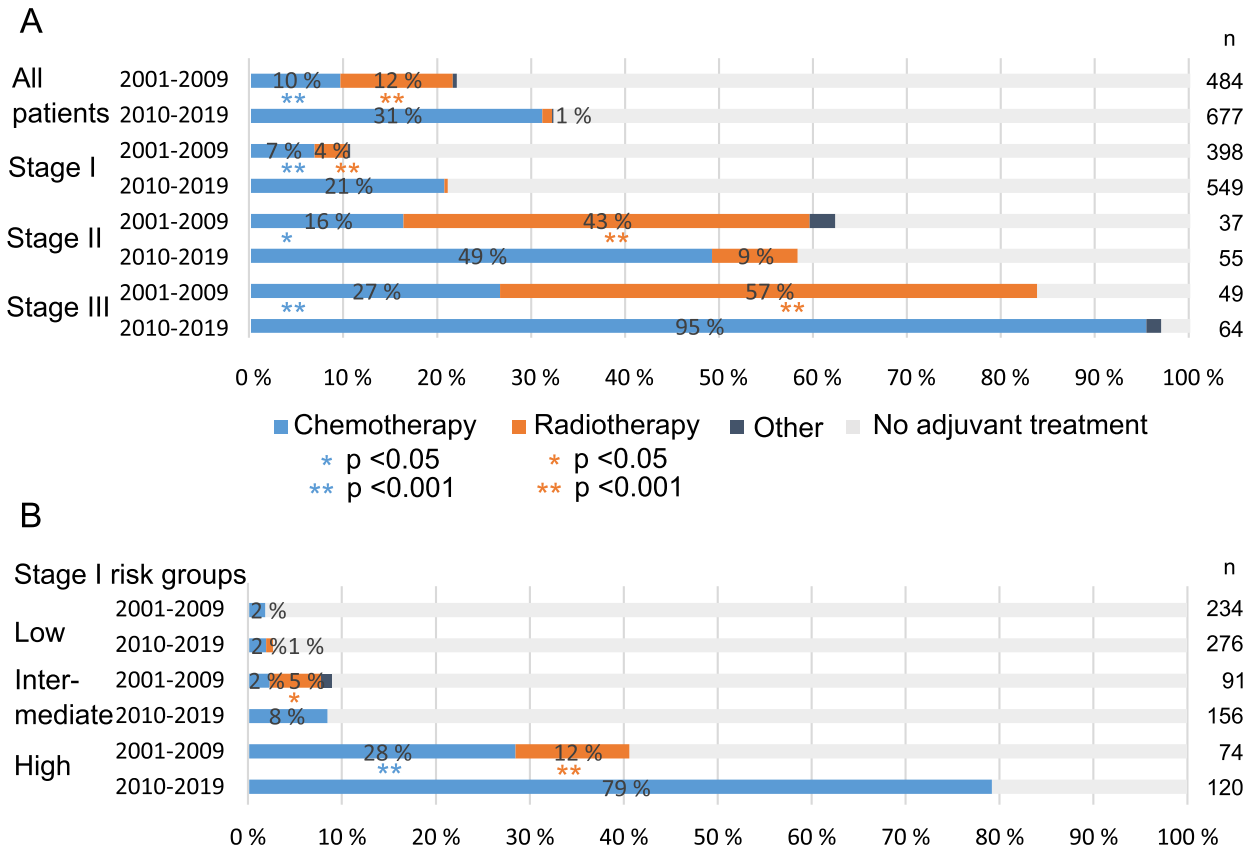


Fig. 3. A) Changes in administration of adjuvant treatment between 2001 and 2009 and 2010–2019. Hysterectomized patients with macroscopically resectable tumors included. Other includes hormonal treatment (n = 5), brachytherapy alone (n = 2) and chemoradiation (n = 1). Statistical comparison between use of chemotherapy/radiotherapy in the different time periods by Chi-square or Fischer's exact test (2-sided) where appropriate. B) Stage I risk groups based on histologic assessment of preoperative biopsy/curettage: low; endometrioid grade 1–2 with <50% myometrial invasion (MI) or MI unknown, intermediate; endometrioid grade 1–2 with >50% MI on imaging or grade 3 with <50% MI, and high; endometrioid grade 3 with >50% MI or MI unknown and all non-endometrioid cancers. FIGO: International Federation of Gynecology and Obstetrics.

As of yet, no published prospective data regarding management of endometrial cancer by molecular subtype is available.

Unlike early stage endometrial cancer, for advanced endometrial cancer patients there is strong evidence in favor of adjuvant chemotherapy. In the GOG-122 trial, chemotherapy demonstrated superior OS and progression-free survival to radiotherapy for stage III-IV patients, and was non-inferior to the combination of chemotherapy and radiotherapy in GOG-258, although the pelvic recurrence rate was higher for chemotherapy alone [7,22]. In the present study, improvement in OS and RFS for stage III patients was observed, coinciding with an overall increase in adjuvant treatment, and at the same time a cessation of radiotherapy. Similar survival and recurrence rates have been demonstrated in a separate Norwegian high-risk cohort [20]. The low rate of vaginal recurrences in stage III patients is interesting. However, a low number of stage III patients could affect this result, and the drop from 9% to 3% was not statistically significant. Preoperative MRI and PET/CT could increase the proportion of stage IIIC patients with limited uterine disease, and thus lower the risk for local recurrence as observed in our study, but this needs to be confirmed in future studies. The PORTEC-3 trial recently demonstrated improved OS and failure-free survival when combining chemotherapy and radiotherapy compared to radiotherapy alone in high-risk patients, mainly driven by improved results in stage III patients and with an increased rate of adverse events and persisting morbidity [23]. Adjuvant chemotherapy alone was not explored in PORTEC-3, thus the available evidence today does not support a benefit of adding radiotherapy when adjuvant chemotherapy constitutes the management strategy for advanced stage endometrial cancer, again reflected in the analysis of the present population based series.

Our retrospective study is limited in its inability to establish clear cause-effect relationships, especially in evaluating contributions of different diagnostic methods towards a reduction of the overall rate of patients undergoing lymphadenectomy. We are however, at this time satisfied to point out that the rate of lymphadenectomy can be reduced, and that in our setting, no apparent detrimental effect is seen. Preoperative risk grouping to tailor surgery depends on a high concordance between the diagnostic workup and final diagnosis. We have previously shown that there is histological discordance between biopsy and hysterectomy specimen in 16%, and that the MRI diagnosis of cervical invasion and deep myometrial invasion have an accuracy of 79%–89% and 61–68% respectively, and thus additional parameters are necessary to optimize a selective lymphadenectomy algorithm [24,25]. Availability of imaging modalities including MRI and PET differs between institutions and they are not standard of care in many countries. Immunohistochemical analysis of ER and PR however, carries little extra cost and is potentially beneficial for clinics without access to advanced imaging. Improvement of the selective lymphadenectomy algorithm with focus on cost effectiveness is an important aim for future research.

Another potential bias is the shorter follow-up time for the patients treated in the most recent time period. We have attempted to compensate for this by choosing appropriate outcome for comparison. This is especially relevant for lymphadenectomy frequencies, where the most recent group has a median follow-up time of 25 months. Data maturation will enable a better estimate of the recurrence rate and survival of low-stage patients not undergoing lymphadenectomy, and will be reported when finalizing the MoMaTEC2 study. We were unable to retrospectively quantify treatment related complications in our study, as

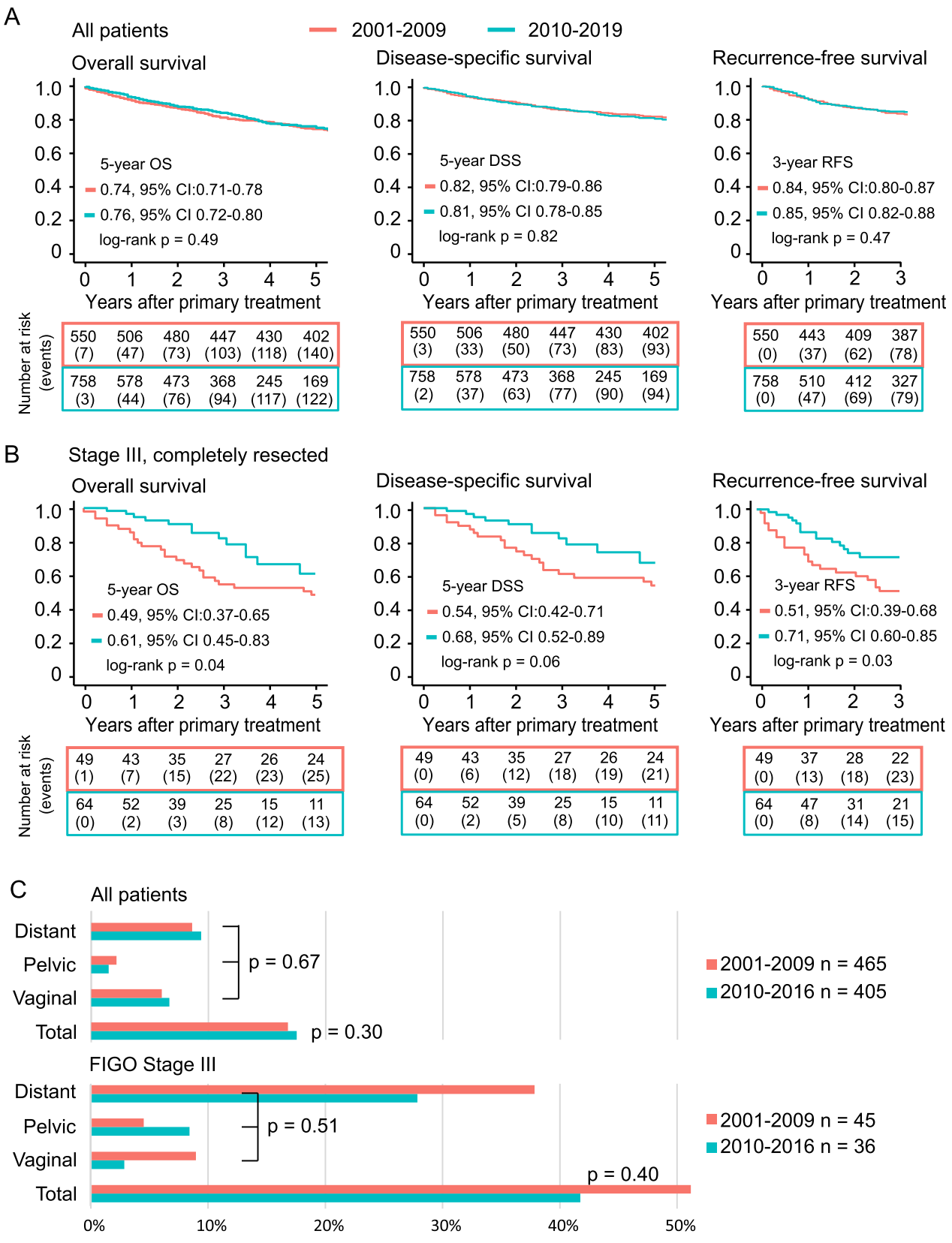


Fig. 4. Kaplan-Meier survival curves showing survival outcome before and after omitting radiotherapy as adjuvant treatment for A) all patients. B) completely resected FIGO stage III patients. C) Recurrence rate by site at 3 years in completely resected patients. Patients censored before 3 years not included. Statistical comparison of groups with chi-square. FIGO: International Federation of Gynecology and Obstetrics.

these have not been systematically registered clinically. There is a need for prospective data on patient reported outcomes for different treatment modalities, to better understand tolerability in short and long term.

In conclusion, we present data from a population based endometrial cancer cohort over the span of two decades, and show that changing to a strategy of individualized risk-based stratification for lymphadenectomy does not affect survival outcomes negatively, when compared to the previous practice based on more frequent lymphadenectomy. Additionally, our data supports that adjuvant treatment without radiotherapy is feasible with maintained survival and was even associated to improved survival for stage III patients.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2020.12.002.

Declaration of competing interest

There are no conflicts of interest to disclose.

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