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Original Research

Survival of patients with early-stage cervical cancer after abdominal or laparoscopic radical hysterectomy: a nationwide cohort study and literature review

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KEYWORDS
Uterine cervical neoplasms;
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Abstract ***Aim:*** Recently, the safety of laparoscopic radical hysterectomy (LRH) has been called into question in early-stage cervical cancer. This study aimed to evaluate overall survival (OS) and disease-free survival (DFS) in patients treated with abdominal radical hysterectomy (ARH) and LRH for early-stage cervical cancer and to provide a literature review.

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Laparotomy;
Laparoscopy;
Survival

Methods: Patients diagnosed between 2010 and 2017 with International Federation of Gynaecology and Obstetrics (2009) stage IA2 with lymphovascular space invasion, IB1 and IIA1, were identified from the Netherlands Cancer Registry. Cox regression with propensity score, based on inverse probability treatment weighting, was applied to examine the effect of surgical approach on 5-year survival and calculate hazard ratios (HR) and 95% confidence intervals (CIs). Literature review included observational studies with (i) analysis on tumours ≤4 cm (ii) median follow-up ≥30 months (iii) ≥5 events per predictor parameter in multivariable analysis or a propensity score.
Results: Of the 1109 patients, LRH was performed in 33%. Higher mortality (9.4% vs. 4.6%) and recurrence (13.1% vs. 7.3%) were observed in ARH than LRH. However, adjusted analyses showed similar DFS (89.4% vs. 90.2%), HR 0.92 [95% CI: 0.52–1.60]) and OS (95.2% vs. 95.5%), HR 0.94 [95% CI: 0.43–2.04]). Analyses on tumour size (<2/≥2 cm) also gave similar survival rates. Review of nine studies showed no distinct advantage of ARH, especially in tumours <2 cm.
Conclusion: After adjustment, our retrospective study showed equal oncological outcomes between ARH and LRH for early-stage cervical cancer – also in tumours <2 cm. This is in correspondence with results from our literature review.

1. Introduction

Conventional and robot-assisted laparoscopic radical hysterectomy (LRH) have been presented as alternatives to abdominal radical hysterectomy (ARH) in early-stage cervical cancer, in the previous decades. A series of retrospective studies showed similar oncologic outcomes [1–9]. In the absence of prospective randomised studies, an international phase III non-inferiority study (the Laparoscopic Approach to Cervical Cancer (LACC) trial) was executed to determine the safety of laparoscopic surgery in early-stage cervical cancer [10]. Unexpectedly, preliminary data showed inferior disease-free survival (DFS) and recurrence rates in patients treated by LRH, resulting in a premature termination of the trial [11]. Nearly simultaneously, a large observational study was published, also demonstrating favourable overall survival (OS) in ARH [12]. In addition, this study reported surgical approach as independent prognostic factor for OS in patients with a tumour ≥2 cm in diameter; it was significantly lower in those treated by LRH. In tumours <2 cm, no difference was detected between the surgical approaches.

Since the LACC trial, numerous retrospective observational studies have been published on oncological outcomes comparing ARH and LRH in cervical cancer. However, comparing observational study results is difficult owing to diversities in disease-stage, follow-up duration and statistical analysis.

The LACC trial results call into question the safety of LRH in early-stage cervical cancer. Our aim was to determine the effect of surgical approach on oncological outcomes for cervical cancer patients in the Netherlands. In addition, a literature review is provided, applying strict selection criteria for fair comparison of observational studies.

2. Materials and Methods

2.1. Study design

We performed a nationwide multicentre retrospective cohort study by analysing data from the Netherlands Cancer Registry (NCR), a population-based registry with coverage of all newly diagnosed malignancies in the Netherlands since 1989. Vital status and date of death were obtained from the municipal demography registries.

All women newly diagnosed with cervical cancer between 2010 and 2017 who underwent radical hysterectomy with pelvic lymphadenectomy in one of the nine specialised medical centres, were identified from the NCR. We included patients with: International Federation of Gynaecology and Obstetrics (FIGO) 2009 stage IA2 with lymphovascular space invasion (LVSI), IB1 and IIA1; adenocarcinoma, squamous cell carcinoma or adenosquamous carcinoma; radical hysterectomy as primary treatment. Patients were excluded if: neoadjuvant chemotherapy or (chemo)radiotherapy was administered; previously diagnosed with cancer, except non-melanoma skin cancer.

Data were collected on baseline characteristics and disease-related characteristics (including follow-up time, age at diagnosis, body mass index (BMI), use of diagnostic magnetic resonance imaging (MRI), clinical tumour size, FIGO stage, surgical approach, histological subtype, differentiation grade, pathological tumour size, depth of invasion (DOI), LVSI, parametrial involvement, resection margin involvement, number of removed lymph nodes, number of positive lymph nodes, adjuvant treatment, recurrence and all-cause mortality). Surgical approach was categorised as ARH or LRH (conventional or robot-assisted LRH), categorising converted patients as LRH, in accordance with the intention-to-treat principle. Recurrence was confirmed preferably by pathological analysis (i.e. biopsy or cytology), otherwise by radiological examination.

Literature review on oncological outcomes included observational studies with analysis on tumours ≤4 cm and a median follow-up ≥30 months, corresponding to the LACC trial. In addition, at least 5 events per predictor parameter in multivariable analysis were required to prevent model overfitting [13] or, alternatively, a propensity score [14].

2.2. Ethics

This study was approved by the Privacy Review Board of the NCR (11/12/2018; K18.377).

2.3. Statistical analysis

Differences between the ARH and LRH group were assessed using Pearson's chi-squared test, independent samples t-test or Mann-Whitney U test. The primary outcomes of this study were DFS and OS. Inverse probability treatment weighting (IPTW) was applied to examine the effect of surgical approach on recurrence and all-cause mortality.

For the original model, for analyses on the full cohort, covariates were selected based on their relation with the outcome or possible confounding of the relation surgical approach with outcome, regardless of significance. Age, BMI, year of diagnosis, FIGO-stage, histological subtype, pathological tumour size, DOI, LVSI, parametrial invasion and pathological lymph nodes, were included. Missing values of pathological tumour size were replaced by clinical tumour size (reducing missing values from 15% to 4%). Weighted Cox regression, on surgical approach with propensity score as single covariate, was applied to calculate hazard ratios (HRs) and 95% confidence intervals (CIs).

Sensitivity analyses were conducted to confirm the robustness of our model. In the original model adjuvant treatment was excluded because of the possibility of being influenced by the radical hysterectomy [15]. To determine whether differences in application of adjuvant treatment between the ARH and LRH group have confounded the association of surgical approach with survival, the original model was adapted by adding adjuvant treatment. In addition, in the original model, differentiation grade was excluded due to a high rate of missing values (28%). The original model was adapted by adding differentiation grade. Furthermore, traditional multivariable Cox regression was executed with replacement of the missing values from the original model (i.e. BMI, parametrial invasion, LVSI, DOI and pathological tumour size; missing 3%–15%), by multiple imputation and without the application of IPTW.

We also conducted analyses on clinical tumour size (<2 cm vs. ≥2 cm) as previous studies have reported differences in survival between the surgical approaches on this parameter. Likewise, to examine a possible learning curve effect, we analysed the influence of period of diagnosis on DFS in two separate models (2010–2013 vs. 2014–2016). Because of limited follow-up for the 2014–2016 group and the majority of recurrences developing within two years after radical hysterectomy, two-year DFS was calculated. Detailed information on IPTW models of all analyses is presented in Supplementary Materials Methods S1. All analyses were performed using Stata/SE, version 14.2 (Stata Corporation, College Station, TX, USA). Statistical tests were two-tailed and considered significant at $p < 0.05$.

3. Results

A total of 1109 patients met the inclusion criteria (Fig. 1) and were selected for this study. Baseline and disease-related characteristics are presented in Table 1 and Table 2, respectively. We observed more patients with large tumours (clinical diameter ≥2 cm; 59%) than with small tumours (<2 cm; 41%). ARH was performed in the majority of patients (67%). Of the LRH group (33%), most patients were treated by robot (73%). In 2010–2013, 27% was treated by LRH and in 2014–2016 this increased to 34% ($p = 0.009$).

Exploring postoperative differences between the ARH and LRH groups, patients in the ARH group more frequently had intermediate and high-risk factors

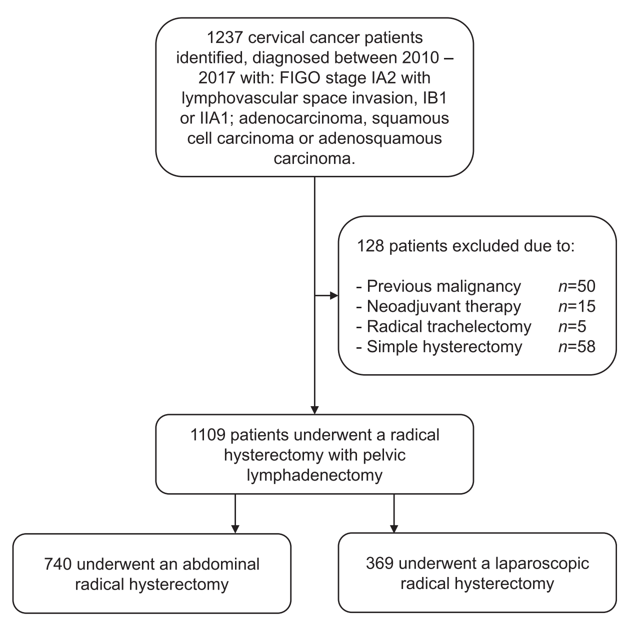

Fig. 1. Patient selection flowchart.

for recurrence (Table 2) and tumours ≥2 cm (61% vs. 36%, $p < 0.001$). Correspondingly, patients in the ARH group more often received adjuvant radiotherapy or chemoradiation (28% vs. 15%, $p < 0.001$), Table 3. Recurrence was seen more often in the ARH compared with the LRH group (13% vs. 7%, $p = 0.004$). Most of the recurrences ($n = 76$, 61%) occurred within two years after radical hysterectomy.

3.1. Survival analyses

Median follow-up duration for DFS and OS were 35 months (range: 0–100) and 56 months (range: 1–109), respectively, with longer follow-up in the ARH group (Table 1), $p < 0.001$. Eighty-seven patients (8%) have died at time of analysis of which 70 (9%) underwent ARH and 17 (5%) LRH, $p = 0.005$. Survivor functions of the primary outcomes are presented in Fig. 2, whereas HRs and CIs for full cohort, sensitivity, and subgroup analyses on survival are presented in Fig. 3.

Full cohort unadjusted analysis showed a lower 5-year DFS (82.8% vs. 91.0%) and 5-year OS (91.1% vs. 95.2%) in ARH compared with LRH. After adjustment by means of IPTW, weighted Cox regression analysis showed DFS was 89.4% and 90.2% in the ARH and LRH group, respectively (HR: 0.92; 95% CI: [0.52–1.60]). OS was 95.2 and 95.5% in the ARH and LRH group, respectively (0.94 [0.43–2.04]).

3.2. Sensitivity analyses

Sensitivity analysis with adjustment for treatment and differentiation grade, respectively, gave similar HRs and 95% CIs for DFS (0.92 [0.53–1.61] and 0.91 [0.51–1.60]) and OS (0.94 [0.43–2.04] and 0.98 [0.45–2.14). Replacing missing values by multiple imputation, also provided similar results for DFS (0.88 [0.53–1.41]) and OS (0.88 [0.46–1.69]).

3.3. Clinical tumour size

Analysis on clinical tumours <2 cm showed 5-year DFS was 91.4% and 96.0% in the ARH and LRH group, respectively (0.44 [0.16–1.27]). Five-year OS was 96.4% and 98.5% (0.39 [0.08–1.86]). In tumours ≥2 cm DFS was 85.0% and 82.5% in the ARH and LRH group, respectively (1.18 [0.64–2.21]). Five-year OS was 94.2% and 92.8% (1.26 [0.53–2.99]).

3.4. Period of diagnosis

Analysis on patients diagnosed between 2010 and 2013 showed 2-year DFS was 95.8% and 91.7% in the ARH and LRH group, respectively (2.01 [0.82–4.98]). Between 2014 and 2016 DFS was 90.3% and 94.7% in the ARH and LRH group, respectively (0.53 [0.20–1.40]).

3.5. Literature review

Nine studies conducted at least one analysis meeting our selection criteria for fair comparison of observational studies (Table 4) [12,16–23]. Seven reported at least one analysis with no significant association between surgical approach and oncological outcome [17–23]. Four of these found no difference in DFS between the surgical approaches [17,18,21,23]. Three examined all-cause mortality and observed no difference [17,22,23]. Jensen *et al.* [19] examined DFS, OS and disease-specific survival before and after the introduction of robot radical hysterectomy and reported no difference on any of the outcomes.

Four studies reported significantly higher survival rates in patients with ARH compared with LRH

Table 1
Baseline characteristics of 1109 patients with cervical cancer (FIGO stage IA2 with LVSI, IB1 and IIA1) treated with radical hysterectomy between 2010 and 2017 in the Netherlands.

Characteristics, n (%)	Missing	Full cohort ($N = 1109$)	ARH ($n = 740$; 67%)	LRH ($n = 369$; 33%)	P
Age, years*		45 (11)	46 (12)	44 (10)	0.003
BMI, kg/m^2*	32 (3)	25 (5)	25 (5)	25 (4)	0.380
Follow-up OS, months†		56 (1–109)	60 (1–109)	46 (9–109)	<0.001
Follow-up DFS, months†		35 (0–100)	37 (0–100)	29 (1–94)	<0.001
Use of diagnostic MRI		723 (65)	450 (61)	273 (74)	<0.001
Clinical tumour size	181 (16)				<0.001
<2 cm		384 (41)	218 (34)	166 (56)	
≥2 cm		543 (59)	414 (66)	129 (44)	
FIGO stage					0.137
IA2 with LVSI		7 (1)	3 (0)	4 (1)	
IB1		1069 (96)	711 (96)	358 (97)	
IIA1		33 (3)	26 (4)	7 (2)	

* mean (SD).
† median (range).

Table 2
Disease-related characteristics of abdominal and laparoscopic radical hysterectomy.

Characteristics, *n* (%)	Missing	Full cohort (*N* = 1109)	ARH (*n* = 740; 67%)	LRH (*n* = 369; 33%)	*P*
Histological subtype					0.711
Squamous cell carcinoma		738 (67)	490(66)	248 (67)	
Adenocarcinoma		321 (29)	214 (29)	107 (29)	
Adenosquamous carcinoma		50 (5)	36 (5)	14 (4)	
Differentiation grade	311 (28)				0.147
1		90 (11)	57 (11)	33 (11)	
2		408 (51)	242 (49)	166 (55)	
3		300 (38)	198 (40)	102 (34)	
Pathological N+, yes		165 (15)	135 (18)	30 (8)	<0.001
Pathological tumour size	171 (15)				<0.001
<2 cm		434 (46)	251 (39)	183 (64)	
2–4 cm		425 (45)	329 (51)	96 (33)	
>4 cm		79 (8)	71 (11)	8 (3)	
Depth of invasion	62 (6)				<0.001
≤5 mm		396 (38)	216 (31)	180 (51)	
6–10 mm		387 (37)	262 (38)	125 (35)	
>10 mm		264 (25)	216 (31)	48 (14)	
Lymphovascular space invasion, yes	61 (6)	473 (45)	325 (47)	148 (41)	0.086
Parametrial involvement, yes	51 (5)	44 (4)	33 (5)	11 (3)	0.250
Surgical margin involvement, yes	45 (4)	33 (3)	28 (4)	5 (1)	0.031
Closest distance (mm)*	391 (35)	6.0 (4.4)	5.8 (4.2)	6.3 (4.7)	0.097
Recurrence, yes		124 (11)	97 (13)	27 (7)	0.004
Local		36 (29)	26 (27)	10 (37)	
Regional		24 (19)	17 (18)	7 (26)	
Distant		64 (52)	54 (56)	10 (37)	
All-cause mortality		87 (8)	70 (9)	17 (5)	0.005

ARH, abdominal radical hysterectomy; LRH, laparoscopic radical hysterectomy.
* mean (SD).

Table 3
Adjuvant treatment.

Characteristics, *n* (%)	Full cohort (*N* = 1109)	ARH (*n* = 740; 67%)	LRH (*n* = 369; 33%)	*P*
Adjuvant treatment, yes	265 (24)	209 (28)	56 (15)	<0.001
Chemoradiation	121 (11)	95 (13)	26 (7)	
Radiotherapy	145 (13)	115 (16)	30 (8)	
Adjuvant treatment, no	843 (76)	530 (72)	313 (85)	

ARH, abdominal radical hysterectomy; LRH, laparoscopic radical hysterectomy.

[12,16,20,22]. Three studies [16,20,22] found significantly higher DFS in ARH. Melamed *et al.* [12] conducted the largest observational study to date and reported a significantly higher OS. Interestingly, two studies reported favourable DFS in ARH but observed no difference in OS [20,22]. Their analyses on all-cause mortality were conducted with a low absolute number of events (Paik *et al.* = 7; Uppal *et al.* = 13). Paik *et al.*

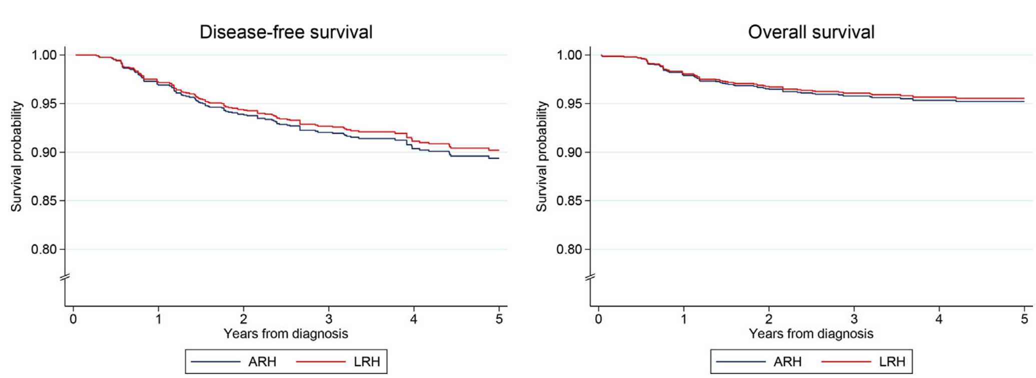

Fig. 2. Cox regression survival functions, adjusted by inverse probability treatment weighting. ARH, abdominal radical hysterectomy; LRH, laparoscopic radical hysterectomy.

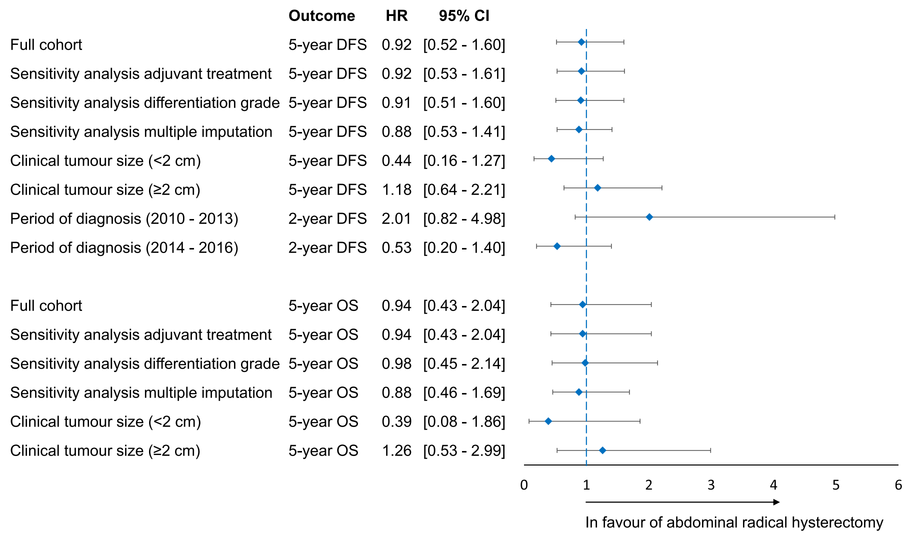

Fig. 3. Weighted Cox regression analyses with propensity score, based on inverse probability treatment weighting. DFS, disease-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval.

[20] expected the difference in OS to become statistically significant with a larger sample size. Uppal *et al.* [22] did not elaborate on the difference between their analysis on recurrence and all-cause mortality. In our analyses, with far more events, we neither found a difference in DFS nor in OS. Moreover, this was confirmed in all sensitivity analyses.

Four studies reported subanalyses on tumours <2 cm [12,17,20,21]. None of these reported higher OS in ARH. Three studies also examined DFS of which two revealed no differences [17,21]. One study conducted an analysis on a specially selected low-risk subgroup and reported significantly lower DFS in <2 cm tumours treated by LRH [20]. However, it had a low absolute number of recurrences (=7) and a wide CI (1.45–116.24), thus evidently lacking power. In a large Chinese study ($N = 1852$), only tumours ≤2 cm were examined but differences on DFS were not observed [24]. In our study, we did not detect significant differences in DFS and OS in tumours <2 cm. Two studies reported subanalyses on tumours ≥2 cm. Melamed *et al.* [12] reported significantly lower OS in LRH. Pedone Anchora *et al.* [21] reported lower DFS in LRH and similar OS, but subgroup sample size was small ($N = 130$). We did not observe statistically significant differences, although our results tend to show worse recurrence (HR: 1.18) and all-cause mortality (HR: 1.26) in LRH.

Table 4
Analyses from studies comparing abdominal and laparoscopic radical hysterectomy in tumours ≤4 cm, with ≥30 months follow-up and a multivariable Cox regression with ≥5 events per predictor parameter or a propensity score.

Authors	Year	FIGO stage (2009)	Treatment years	*N*	Recurrence (%)	Survival analysis*		*P*-value	Preferred surgical approach
Wallin *et al.*	2017	IA1–IB1, IIA1	2006–2015	304	12%	5-year	DFS	<0.05	ARH
Melamed *et al.**	2018	IA2, IB1	2000–2018	2461	–	4-year	OS	0.002	ARH
Alfonzo *et al.**	2019	IA1, IA2, IB1	2011–2017	464	12%	5-year	DFS	0.756	None
						5-year	OS	0.990	None
Kim *et al.**	2019	IB1	2000–2018	392	10%	5-year	DFS	0.100	None
						5-year	OS	0.300	None
Paik *et al.**	2019	IB1, IIA1	2000–2008	476	7%	–	DFS	0.005	ARH
						–	OS	0.624	None
Brandt *et al.*	2020	IB1	2007–2017	145	14%	5-year	DFS	0.510	None
Jensen *et al.*	2020	IA2, IB1	2005–2017	1125	7%	5-year	DFS	0.550	None
						5-year	DSS	0.100	None
						5-year	OS	0.100	None
Pedone Anchora *et al.*	2020	IA1–IB1, IIA1	? – 2016	423	17%	–	DFS	>0.05	None
Uppal *et al.**	2020	IA1, IA2, IB1	2010–2017	315	8%	–	DFS	0.019	ARH
						–	OS	0.400	None

OS, overall survival; DFS, disease-free survival; DSS, disease-specific survival; ARH, abdominal radical hysterectomy
* Use of propensity score.

4. Discussion

We did not observe an effect of surgical approach on DFS and OS in early-stage cervical cancer, in this nationwide multicentre retrospective observational study in the Netherlands. Besides, we did not find an effect of clinical tumour size on the outcomes of ARH vs. LRH.

Since the disclosure of the LACC trial results, numerous studies have been published on oncological outcomes comparing ARH and LRH in cervical cancer. Our literature review, including nine retrospective studies, showed no distinct advantage of ARH over LRH in tumours ≤4 cm. An effect of surgical approach on oncological outcome in tumours <2 cm was absent in the majority of studies, suggesting the safety of the application of LRH in this subgroup. In ≥2 tumours, results seem to be in favour of ARH. The exact effect of surgical approach on oncological outcomes in tumours <2 vs. ≥2 cm requires further investigation in prospective randomised trials.

Recent literature suggests that the learning curve might influence recurrence rates in LRH [25–27], whereas other studies did not find such an effect [12,17,28]. Our study focussed on 2010–2017, and this time frame includes the introduction (which started in 2006) of the laparoscopic technique in several of the centres. We observed an increase over time in survival in LRH and a decrease in survival in ARH, although statistically insignificant. Learning curve might be one possible explanation for differences between ARH and LRH, but the present studies provide inconclusive results.

Strengths of this large European study include: data on recurrence and all-cause mortality, the application of IPTW to balance distribution of covariates, a propensity score to avoid overfitting issues and therefore making treatment comparison more accurate [29], multiple sensitivity analyses to confirm model robustness and the introduction of strict selection criteria to increase comparability of studies.

Although data from individual medical centres are not presented in this article, the data suggest there are differences in diagnostic work-up (for example in determining clinical tumour size, or the use of MRI), indications for ARH and LRH, the actual execution of the radical hysterectomy (e.g. extent of parametrial resection, nerve-sparing vs. non-nerve sparing, handling preoperative suspected or intraoperative positive lymph nodes and uterine manipulator use) and the criteria for adjuvant (chemo)radiotherapy. Moreover, two centres only perform ARH. In medical centres performing both surgical approaches, high-risk patients might have been selected for open surgery more often, possibly explaining the patients in the ARH group were observed more frequently with intermediate and high-risk factors for recurrence. Pursuing uniformity on a national level will result in more accurate comparisons. However, the quantification of the required surgical parameters was not within the scope of this research project. Furthermore, low numbers of events per centre prevented us from in-depth analysis.

Observational research in general depends on the quality of data in the medical record. As there are no guidelines on reporting clinical tumour size and not all medical centres use it as selection criterion for surgical approach, there was a lack of uniformity in its definition (i.e. based on MRI or clinical examination). However, we do not expect this to have affected our results, as conducting the analyses with pathological tumour size instead, provided similar results. In addition, although the IPTW technique was applied to make a fair comparison between ARH and LRH, unmeasured confounding cannot be adjusted for and all relevant confounders might not have been included.

Our retrospective study showed equal oncological outcomes between ARH and LRH for early-stage cervical cancer, after IPTW adjustment. Moreover, we observed no effect of surgical approach on DFS and OS in tumours <2 cm. After a literature review on retrospective observational studies no distinct advantage of ARH over LRH was found, especially in tumours <2 cm. The exact role of LRH in the treatment of cervical cancer should be examined in prospective randomised trials.

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Conflict of interest statement

H.N. reports receiving grants from Aduro and DCprime and is founder and stockholder of ViciniVax. All the other authors do not have any conflict of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.04.006.

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