Gynecologic Oncology 162 (2021) 284–291

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Long-term oncological outcomes and recurrence patterns in early-stage cervical cancer treated with minimally invasive versus abdominal radical hysterectomy: The Norwegian Radium Hospital experience

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HIGHLIGHTS

- In stage IA CC, similar oncological survival outcomes were observed for MIRH and ARH.
- In stage IB1 CC, MIRH yielded a significantly shorter TTR, CSS and OS than ARH.
- In stage IB1 CC ≤2 cm, MIRH yielded a significantly shorter TTR, CSS and OS than ARH when conization was not performed.
- Intraperitoneal combined recurrences accounted for 40.0% of all recurrences after MIRH compared to 0.0% after ARH.
- No intraperitoneal combined recurrences were observed in patients who underwent conization with clean margins.

ARTICLE INFO

Article history:
Received 20 April 2021
Accepted 24 May 2021
Available online 1 June 2021

Keywords:
Early stage
Cervical cancer
Radical hysterectomy
Minimally invasive surgery
Abdominal radical hysterectomy
Oncologic outcomes

ABSTRACT

Objective. To compare long-term oncological outcomes in early-stage cervical cancer (CC) patients treated with minimally invasive radical hysterectomy (MIRH) versus abdominal radical hysterectomy (ARH), with a focus on recurrence patterns, tumor sizes, and conization.

Methods. This single-institution, retrospective study consisted of stage IA1-IB1 (FIGO 2009) squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma of the cervix, who underwent radical hysterectomy between 2000 and 2017.

Results. Of the 582 patients included, 353 (60.7%) underwent ARH, and 229 (39.3%) MIRH. The median follow-up was 14.4 years in the ARH group and 6.1 years in the MIRH group ($p < 0.0001$). Among the 96 stage IA patients, only 3 (3.1%) experienced recurrence. Among stage IB1 patients, the risk of recurrence, after adjusting for standard prognostic variables, was twofold higher in the MIRH group versus the ARH group (HR 2.73, 95% CI: 1.56–4.80), and the relative difference was similar in terms of risk of cancer-specific survival (CSS) (HR 3.04, 95% CI: 1.28–7.20) and overall survival (OS) (HR 2.35, 95% CI: 1.21–4.59). In stage IB1 ≤ 2 cm patients without conization MIRH was associated with reduced time to recurrence (TTR) (HR 4.00, 95% CI: 1.67–9.57), CSS (HR 3.71, 95% CI: 1.19–11.58) and OS (HR 3.02, 95% CI: 1.24–7.34). Intraperitoneal combined recurrences accounted for 12 of 30 (40.0%) recurrences in the MIRH group but were not identified after ARH ($p = 0.0001$).

Conclusions. MIRH was associated with reduced TTR, CSS and OS versus ARH in stage IB1 CC patients. The risk of peritoneal recurrence was high, even for tumors ≤2 cm without conization.

1. Introduction

Cervical cancer (CC) is the fourth most common cancer among women worldwide [1], with approximately 570,000 new cases and 311,000 deaths in 2018. In Norway, 355 new cases and 79 deaths from CC were registered in 2018 [2]. Norwegian Radium Hospital treats approximately two-thirds of the CC patients in Norway.

Abdominal radical hysterectomy (ARH) with pelvic lymphadenectomy remains the standard treatment for CC FIGO 2009 stages IA1 with lymphovascular space invasion (LVSI), IA2, IB1, and IIA ≤2 cm [3]. Since the first laparoscopic radical hysterectomy was reported in 1992 [4] and the first robot-assisted radical hysterectomy was reported in 2006 [5], several retrospective studies have reported that both robotic and laparoscopic minimally invasive radical hysterectomy (MIRH) are

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https://doi.org/10.1016/j.ygyno.2021.05.028

associated with reduced operative morbidity, shorter hospital length of stay and similar oncological outcomes compared to ARH in patients with early-stage CC [6–8]. However, more recent retrospective studies have shown inferior oncological outcomes with the MIRH approach [9–14]. The results from the first prospective, randomized clinical trial of stage IA1-IB1 CC were published in 2018. This multicenter, phase III trial [Laparoscopic Approach to Cervical Cancer (LACC)] with CC stage IA1-IB1, recruited patients from 2008 to 2017 and had disease-free survival (DFS) at 4.5 years as the primary endpoint. The results showed significantly lower DFS and overall survival (OS) after MIRH versus ARH [15]. However, most patients (91.9%) had stage IB1 disease, and only 6 cases of recurrence were observed among those with tumors ≤2 cm. The trial was not designed to answer questions about the cause of the inferior outcomes of MIRH. At the same time, an epidemiologic study also demonstrated that MIRH was significantly associated with shorter OS than ARH among CC patients with stage IA2-IB1 malignancy [16].

There is still conflicting evidence regarding whether the MIRH approach in patients with tumors ≤2 cm is associated with worse oncological outcomes than ARH [9–14,17]. Moreover, conization before radical hysterectomy has been reported to be associated with a lower risk of recurrence with either surgical approach [10,18]. Additionally, intraperitoneal metastasis has been suggested to be the main contributor to the worse prognosis associated with the MIRH approach [14,19,20]. However, it has not yet been studied whether and how these three observations interact with each other. We therefore aimed to investigate a cohort of early-stage CC patients treated with ARH or MIRH at our institution, which has a central pathology review, institutional treatment algorithms that result in relatively low utilization of postoperative adjuvant therapies, and uniformly compliant patient follow-up, by exploring potential associations with differences in survival between ARH versus MIRH, focusing on i) the importance of tumor size ii) the influence of preoperative conization, and iii) recurrence patterns.

2. Material and methods

2.1. Ethics and approvals

Our study was approved by the Patient Privacy Agency at The Oslo University Hospital (PA; reference code: 2017/11320) and was classified as a quality assurance/improvement study; thus, the need to obtain written informed consent was waived. Quality assurance/improvement studies at our institution do not require approval from the Regional Committee for Medical and Health Research Ethics (REC; reference code: 2017/1636).

2.2. Study population

In this retrospective longitudinal study conducted at Norwegian Radium Hospital, 651 consecutive stage IA1-IB1 (FIGO 2009) CC patients treated with ARH or MIRH were identified. Patients with rare histological types, concomitant cancers, pregnancy, or neoadjuvant chemotherapy were excluded, leaving 582 patients with squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma of the cervix as the study population (Fig. 1). Data were collected between January 1, 2000, and December 31, 2017, and the last date of follow-up was June 30, 2020. The ARH group were followed from January 2000, while MIRH patients were followed from April 2004. The time from inclusion in the study to the end of follow-up varied from 2.5 to 20.5 years.

2.3. Data sampling

Data were extracted from our quality assurance database. Starting in 2006, data on patient characteristics, treatment, histology and outcomes were entered immediately into a secured database. Patients included between 2000 and 2005 were identified retrospectively from the hospital's electronic database containing basic treatment data and CC stages. Detailed patient data for this time period were extracted from the hospital's medical records and retrospectively entered into the database, which is linked to Statistics Norway, securing correct registration of all deaths. Diagnoses were based on cervical biopsies or diagnostic cervical conizations. Tumor size was evaluated based on formalin-fixed surgical specimens measured by pathologists, including cones. In our institution, grading is only performed for adenocarcinoma. Staging of all CCs was performed using the FIGO 2009 classification, which for the involved/respective stages, was the same as the FIGO 1999 classification. All patients were followed-up according to the national guidelines. Most patients were followed-up at local hospitals, which are obliged to readmit patients with relapse, allowing the date and localization of first

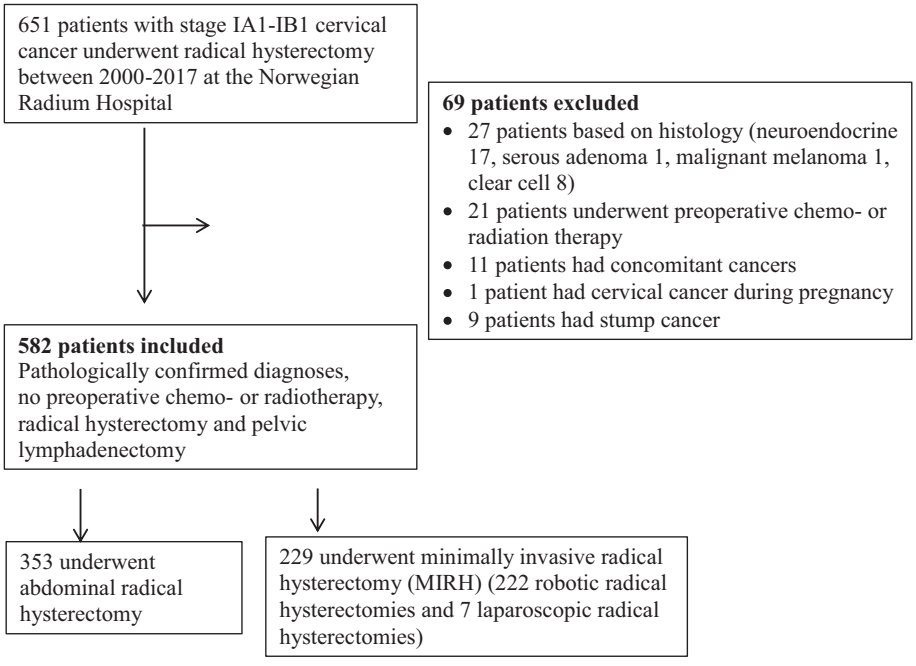

Fig. 1. Flow diagram describing the study population.

relapse to be registered in the database. Recurrences were verified with biopsies. All pathology diagnostics were performed at our institution by pathologists experienced in gynecologic oncology.

2.4. Treatment issues

In 2004, the MIRH approach was introduced to our institution with laparoscopy and then with the robotic platform in 2005, which resulted in a decline in ARH cases from 2006 and an accelerated decline after 2013 (Supplementary Fig. 1). Patients were allocated to either radical hysterectomy or primary chemoradiation based on preoperative findings on MRI and CT and examination under anesthesia. According to our departmental practice, patients with signs of parametrial infiltration or stromal infiltration to the outer third of the cervical stroma together with a diameter > 2 cm evaluated on MRI were allocated to chemoradiation. Preoperative conization was performed in the absence of a macroscopic tumor or when a biopsy showed ≤5 mm of invasion into the cervical stroma. Laparoscopy with conventional instruments was used in the first 7 patients, and the robotic platform was used for the remaining patients. MIRH was performed by five surgeons in the same manner as ARH. The training periods are included in the analyses. No uterine manipulators were routinely used. A vaginal probe was used to delineate the vaginal fornices. Colpotomy and vaginal closure were performed intracorporeally without any protective procedure in the MIRH group.

2.5. Statistical analysis

Time to recurrence (TTR) was calculated from the date of surgery to the date of first recurrence and defined according to Punt et al. [21]. Patients who died from treatment-related complications and causes/reasons other than CC were censored at the date of the event, while other patients without recurrence were censored on June 30, 2020. The cancer-specific survival (CSS) duration was calculated from the date of surgery to the date of death due to CC and censored at the date of death from other causes or June 30, 2020 (if the patient was still alive after this cutoff date). OS was calculated from the date of surgery to the date of death from any cause and censored on June 30, 2020 (if the patient was still alive after this cutoff date).

The demographics and clinical characteristics of the patients were compared between the ARH and MIRH groups using the Mann-Whitney *U* test for continuous variables and Fisher's exact test for categorical variables. Univariable analyses of differences in survival were performed with the log-rank test for categorical variables. Univariable analyses of continuous variables and all multivariable analyses were performed using the Cox proportional hazards model. All standard prognostic variables were included in the multivariable models (age, FIGO stage, histological type, pathological tumor measure, LVSI, stromal invasion into the outer third of the cervical stroma, parametrial invasion, uterine isthmus invasion, and reason for postoperative radiotherapy). Patients with at least one missing value were excluded from the multivariable analyses. In the competing risk analyses of recurrence and disease-specific death, death from causes other than CC was defined as a competing event. Two-sided *p*-values <0.05 were considered statistically significant. All statistical analyses were performed using Stata/SE 16.1.

3. Results

3.1. Study population

A total of 582 patients were included in the analyses (Fig. 1). Relevant clinicopathological patient characteristics are given in Table 1. Compared to the ARH group, patients in the MIRH group were significantly younger ($p = 0.019$), more often had tumors ≤2 cm versus >2 cm ($p = 0.0022$), had less stromal invasion into the outer third of the cervical stroma ($p = 0.0002$), had less LVSI ($p = 0.0009$) and had fewer lymph nodes removed and examined ($p < 0.0001$). In the MIRH group, preoperative conization was performed more often (64.2% versus 45.0%, $p < 0.0001$) than in the ARH group.

3.1.1. Adjuvant therapy

Postoperative chemoradiation was administered to 44 (12.5%) ARH patients and 14 (6.1%) MIRH patients ($p = 0.015$). The most common reason was lymph node metastasis in 24 ARH patients and 10 MIRH patients, followed by invasion into parametria, invasion into the isthmus of the uterine corpus, inadequate vaginal resection margin or tumors >2 cm in size with invasion into the outer third of the cervical stroma.

Table 1
Clinicopathologic characteristics of the study population stratified by procedure.

Characteristic	All	ARH	MIRH	*p*-value[a]
	n = 582	*n* = 353	*n* = 229	
Follow-up time, years				
Median (IQR)	10.2 (5.9–15.4)	14.4 (9.9–17.3)	6.1 (4.1–8.9)	**<0.0001**
Age, years				
Median (IQR)	44 (38–53)	45 (38–55)	42 (38–50)	**0.019**
<35 years	80 (13.7%)	54 (15.3%)	26 (11.4%)	**0.0003**
35–44 years	231 (39.7%)	121 (34.3%)	110 (48.0%)	
45–54 years	151 (25.9%)	91 (25.8%)	60 (26.2%)	
55–69 years	101 (17.4%)	69 (19.5%)	32 (14.0%)	
≥70 years	19 (3.3%)	18 (5.1%)	1 (0.4%)	
FIGO stage (2009)				**0.0049**
IA1	42 (7.2%)	29 (8.2%)	13 (5.7%)	
IA2	54 (9.3%)	30 (8.5%)	24 (10.5%)	
IB1 ≤ 2 cm	356 (61.2%)	200 (56.7%)	156 (68.1%)	
IB1 > 2 cm	130 (22.3%)	94 (26.6%)	36 (15.7%)	
Histological type				0.92
Squamous	362 (62.2%)	221 (62.6%)	141 (61.6%)	
Adenocarcinoma	201 (34.5%)	120 (34.0%)	81 (35.4%)	
Adenosquamous	19 (3.3%)	12 (3.4%)	7 (3.1%)	
Grading of adenocarcinoma			0.35	
Well differentiated	110 (18.9%)	57 (16.1%)	53 (23.1%)	
Moderately differentiated	19 (3.3%)	10 (2.8%)	9 (3.9%)	
Poorly differentiated	17 (2.9%)	12 (3.4%)	5 (2.2%)	
Missing information	55 (9.5%)	41 (11.6%)	14 (6.1%)	
Not adenocarcinoma	381 (65.5%)	233 (66.0%)	148 (64.6%)	
Cone margins				**<0.0001**
Clean	109 (18.7%)	65 (18.4%)	44 (19.2%)	
Involved	197 (33.8%)	94 (26.6%)	103 (45.0%)	
No conization	276 (47.4%)	194 (55.0%)	82 (35.8%)	
LNs examined, number				
Median and IQR	23 (17–29)	25 (20−32)	20 (15–25)	**<0.0001**
LN metastasis	34 (5.8%)	24 (6.8%)	10 (4.4%)	0.28
LVSI	178 (30.6%)	126 (35.7%)	52 (22.7%)	**0.0009**
Missing information	7 (1.2%)	4 (1.1%)	3 (1.3%)	
Invasion into the cervical stroma				**0.0002**
Inner or middle	511 (87.8%)	296 (83.9%)	215 (93.9%)	
Outer	71 (12.2%)	57 (16.1%)	14 (6.1%)	
Parametrial invasion	8 (1.4%)	7 (2.0%)	1 (0.4%)	0.16
Uterine isthmus invasion	26 (4.5%)	20 (5.7%)	6 (2.6%)	0.10
Vaginal invasion	9 (1.5%)	8 (2.3%)	1 (0.4%)	0.096
Postoperative radiotherapy	58 (10.0%)	44 (12.5%)	14 (6.1%)	**0.015**

p-values less than 0.05 are in bold.
Abbreviations: ARH = abdominal radical hysterectomy; IQR = interquartile range; LN = lymph node; LVSI = lymphovascular space invasion; MIRH = minimally invasive radical hysterectomy.
[a] Fisher's exact (categorical variables) or Mann-Whitney *U* (continuous variables) test evaluated using only nonmissing values.

3.2. Follow-up and event incidences

The median follow-up time was much longer for the ARH group, with 14.4 years (total range 0.6–20.5, interquartile range (IQR) 9.9–17.3) compared to 6.1 years (total range 0.1–15.8, IQR 4.1–8.9) in the MIRH group ($p < 0.0001$). Among the patients who were alive at the end of follow-up, the median follow-up time in the ARH group was 15.0 years (total range 3.4–20.5, IQR 10.9–17.7) and that in the MIRH group was 6.2 years (total range 2.5–15.8, IQR 4.3–9.1) ($p < 0.0001$).

A total of 60 (10.3%) patients experienced disease recurrence, including 30 (8.5%) patients in the ARH group and 30 (13.1%) patients in the MIRH group ($p = 0.093$). Intraperitoneal combined recurrences accounted for 12 of 30 (40.0%) recurrences in the MIRH group but were not identified after ARH ($p = 0.0001$). A total of 27 patients died of CC (Table 2). Out of the 96 patients with stage IA tumors, three (3.1%) had recurrence, with two after ARH and one after MIRH. Five (5.2%) patients with stage IA tumors died, of whom one (1.0%) died of CC. According to the competing risk analysis, the 5-year cumulative incidence of recurrence in patients with stage IB1 tumors ≤2 cm was 6.0% (95% CI: 3.3%–9.9%) in the ARH group and 12.0% (95% CI: 7.4%–17.8%) in the MIRH group. For those with tumors >2 cm, the 5-year cumulative incidence of recurrence was 10.6% (95% CI: 5.4%–17.8%) in the ARH group and 25.6% (95% CI: 12.7%–40.7%) in the MIRH group.

With regard to stage IB1 disease, intraperitoneal carcinomatosis occurred in 12 of the 192 (6.3%) patients in the MIRH group compared to none of the 294 in the ARH group ($p < 0.0001$). Carcinomatosis was not seen in stage IA disease nor in patients who underwent conization with clean margins. As specified in Table 3, patients with intraperitoneal carcinomatosis had simultaneous metastases at other sites. Interestingly, one port-site metastasis occurred 90 days after robotic ureter reimplantation in the ARH group. In patients with IB1 disease, central recurrences accounted for 11 of the 28 (39.3%) recurrences in the ARH group and 9 of the 29 (31.0%) recurrences in the MIRH group, and 2 patients in the latter group had concomitant peritoneal carcinomatosis. Locoregional recurrences with or without peritoneal carcinomatosis accounted for 19 of the 28 (67.6%) recurrences in the ARH group and 17 of the 29 (58.6%) recurrences in the MIRH group (Table 3).

3.3. Survival outcomes

The risk of recurrence was nearly three times as high in the MIRH group as in the ARH group according to the multivariable analyses adjusted for the standard prognostic variables (HR 2.69, 95% CI: 1.56–4.66; $p = 0.0004$) (Table 4). Additionally, the risk of death due to CC (HR 2.78, 95% CI: 1.20–6.45; $p = 0.018$) and the overall risk of death (HR 2.14, 95% CI: 1.13–4.05; $p = 0.020$) were in disfavor of the MIRH procedure. Five-year survival rates are shown in Table 2.

3.3.1. Stage IB1

In multivariable analyses of patients with stage IB1 tumors, the risk of recurrence was significantly higher in the MIRH group than in the ARH group (HR 2.73, 95% CI: 1.56–4.80; $p = 0.0005$), as were the risk of death due to CC (HR 3.04, 95% CI: 1.28–7.20; $p = 0.012$) and the overall risk of death (HR 2.35, 95% CI: 1.21–4.59; $p = 0.038$). The Kaplan-Meier curves related to tumor size are shown in Fig. 2.

3.3.2. Stage IB1 tumors and relation to preoperative conization

For patients with stage IB1 tumors ≤2 cm, the risk of recurrence was approximately three times higher in the MIRH group than in the ARH group (HR 3.17, 95% CI: 1.55–6.48; $p = 0.0016$) in multivariable analysis. Similar relative differences were observed for CSS (HR 3.55, 95% CI: 1.22–10.26; $p = 0.02$) and OS (HR 2.27, 95% CI: 1.05–4.91; $p = 0.038$) in multivariable analysis.

Among the 200 patients treated with ARH, 36 (18.0%) had clean margins after conization, 59 (29.5%) had involved cone margins, and

Table 2
Oncological outcomes in the ARH and MIRH groups.

Characteristic	ARH	MIRH	*p*-value[a]
	n = 353	*n* = 229	
Recurrence, total	30 (8.5%)	30 (13.1%)	0.093
With intraperitoneal component	0 (0.0%)	12 (5.2%)	**<0.0001**
Deaths	47 (13.3%)	17 (7.4%)	**0.030**
Died due to cervical cancer	15 (4.2%)	12 (5.2%)	0.69
Died due to other causes	32 (9.1%)	5 (2.2%)	**0.0007**
5-year TTR rate	93.4 (90.3–95.6)	87.1 (81.8–90.9)	
5-year CSS rate	97.4 (95.1–98.6)	95.5 (91.4–97.6)	
5-year OS rate	94.6 (91.7–96.5)	93.2 (88.7–95.9)	
Stage IA			
N	59 (16.7%)	37 (16.2%)	
5-year TTR rate	98.3 (88.6–99.8)	96.6 (77.9–99.5)	
5-year CSS rate	98.3 (88.4–99.8)	100	
5-year OS rate	94.9 (85.1–98.3)	97.3 (82.3–99.6)	
Stage IB1			
N	294 (83.3%)	192 (83.8%)	
5-year TTR rate	92.4 (88.7–95.0)	85.3 (79.3–89.7)	
5-year CSS rate	97.2 (94.6–98.6)	94.6 (89.8–97.2)	
5-year OS rate	94.5 (91.2–96.6)	92.3 (87.1–95.5)	
Stage IB1 tumors ≤2 cm		12.0 (7.7–17.8)	
N	200 (56.7%)	156 (68.1%)	
5-year TTR rate	93.9 (89.5–96.5)	87.9 (81.4–92.2)	
5-year CSS rate	97.4 (94.0–98.9)	93.4 (88.1–96.9)	
5-year OS rate	94.5 (90.2–96.9)	91.1 (84.8–94.9)	
Stage IB1 tumors >2 cm			
N	94 (26.6%)	36 (15.7%)	
5-year TTR rate	89.3 (81.1–94.1)	74.4 (56.4–85.8)	
5-year CSS rate	96.8 (90.4–99.0)	97.2 (81.9–99.6)	
5-year OS rate	94.7 (87.7–97.7)	97.2 (81.9–99.6)	

TTR, CSS and OS rates are presented as percentages (95% confidence intervals). *p*-values < 0.05 are in bold.
Abbreviations: ARH = abdominal radical hysterectomy; CSS = cancer-specific survival; MIRH = minimally invasive radical hysterectomy; OS = overall survival; TTR = time to recurrence.
[a] Fisher's exact test evaluated using only nonmissing values.

Table 3
Adjudicated sites of recurrence in FIGO stage IB1 tumors stratified by surgical approach.

Site of recurrence	No (%)	
	ARH	MIRH
Locoregional	19 (67.9)	11 (37.9)
Locoregional+IPM	0 (0.0)	6 (20.7)
Distant only	6 (21.4)	2 (6.9)
Locoregional+distant	3 (10.7)	4 (13.8)
Locoregional+distant+IPM	0 (0.0)	6 (20.7)
Total	28 (100.0)	29 (100.0)

Abbreviations: ARH = abdominal radical hysterectomy; MIRH = minimally invasive radical hysterectomy; IPM = intraperitoneal metastasis.

105 (52.5%) did not undergo conization. Among the 156 patients treated with MIRH, 21 (13.5%) had clean margins after conization, 73 (46.8%) had involved cone margins, and 62 (39.7%) did not undergo conization. Kaplan-Meier survival curves in relation to preoperative conization suggested that there was no substantial difference in TTR between those with clean and involved cone margins in either of the surgery groups but that there was an increased risk of recurrence among patients who did not undergo preoperative conization, at least in the MIRH group (Supplementary Fig. 2). The 5-year cumulative risk of recurrence in patients with stage IB1 tumors ≤2 cm with clean margins after conization was 2.8% (95% CI: 0.2%–12.4%) in the ARH group and 10.1% (95% CI: 1.7%–27.4%) in the MIRH group. For those with tumors ≤2 cm with involved margins, these figures were 3.5% (95% CI: 0.6%–10.6%) in the ARH group and 5.6% (95% CI: 1.8%–12.7%) in the MIRH group, respectively. No significant prognostic difference between the ARH and MIRH groups was observed for patients with stage IB1 tumors ≤2 cm with conization in multivariable analyses of TTR (HR 1.85, 95% CI: 0.47–7.35; $p = 0.38$), CSS (HR 2.32, 95% CI: 0.08–66.21; $p = 0.62$), and OS (HR 0.92, 95% CI: 0.18–4.76; $p = 0.92$), but the numbers of events were low (11 experienced recurrences and 10 died, 3 of whom died due to CC). For patients with stage IB1 tumors ≤2 cm who did not undergo conization, the HRs in multivariable analyses were 4.00 (95% CI: 1.67–9.57; $p = 0.0019$) for TTR, 3.71 (95% CI: 1.19–11.58; $p = 0.024$) for CCS, and 3.02 (95% CI: 1.24–7.34; $p = 0.015$) for OS, all in disfavor of the MIRH approach.

In stage IB1 ≤ 2 cm disease, intraperitoneal metastasis occurred in 12 of the 156 (6.4%) patients in the MIRH group compared to none of the 200 patients in the ARH group ($p = 0.0002$). Two of the 12 patients had cancer in the cervical resection margin after preoperative conization, and the other 10 did not undergo conization. Intraperitoneal carcinomatosis did not occur in any patient with clean margins after conization. Among the 156 MIRH patients with stage IB1 tumors ≤2 cm, 21 (13.5%) had clean margins after conization, 73 (46.8%) had involved cone margins, and 62 (39.7%) did not undergo conization.

In patients with stage IB1 tumors >2 cm, 64 (68.1%) patients in the ARH group underwent conization, of whom only 4 had clean margins. In the MIRH group, 21 (58.3%) underwent conization, of whom none had clean margins. Among patients with stage IB1 tumors >2 cm, the HRs in the MIRH group compared with the ARH group were greater than two in the multivariable analyses of TTR, CSS and OS, which were similar to the HRs for the total group with stage IB1 disease. For the group of patients with stage IB1 tumors >2 cm who underwent conization, the HR was 5.26 (95% CI: 0.49–56.93; $p = 0.17$) in the multivariable analysis of TTR, and in the corresponding group without preoperative conization, this HR was 2.08 (95% CI: 0.35–12.28; $p = 0.42$). Due to the small numbers, the confidence limits are very wide, and the HRs approach infinity in multivariable analysis of CSS and OS for the group of patients with stage IB1 tumors >2 cm who underwent preoperative conization.

4. Discussion

4.1. Main findings

In this large, single-institution, retrospective database study including 582 early-stage CC patients with a median follow-up time of 14.4 years in the ARH group and 6.1 years in the MIRH group and no patients lost to follow-up, the MIRH approach was significantly associated with a worse prognosis than the ARH approach in terms of TTR, CSS and OS in multivariable analyses adjusted for standard prognostic variables. The risk of recurrence was low in patients with FIGO stage IA (only 3.1%), with no significant difference between the ARH and MIRH groups. In patients with stage IB1 tumors, multivariable analyses of TTR, CSS and OS showed significantly increased risk associated with MIRH. Even in patients with stage IB1 tumors ≤2 cm, the risk of TTR and CSS was more than threefold higher and OS was doubled in the MIRH compared with the ARH group.

Multivariable analysis showed no significant differences in TTR, CSS and OS between ARH and MIRH in patients with stage IB1 tumors ≤2 cm who underwent conization. On the other hand, among the stage IB1 patients with tumors ≤2 cm who did not undergo conization, those in the MIRH group had a considerably worse prognosis than those in the ARH

Table 4
Analysis of time to recurrence associated with surgery type and standard prognostic variables.

Variable	Variable treatment	Univariable analysis		Multivariable analysis	
		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Surgery type	MIRH versus ARH	1.91 (1.14–3.19)	**0.012**	2.69 (1.56–4.66)	**0.0004**
Age	10-year increment	1.16 (0.94–1.44)	0.16	1.24 (0.98–1.56)	0.070
Stage with tumor size			**0.0116**		0.091
	IA	ref.		ref.	
	IB1 tumor ≤2 cm	3.57 (1.10–11.58)	**0.0340**	2.83 (0.83–9.68)	0.097
	IB1 tumor >2 cm	5.32 (1.58–17.90)	**0.0069**	4.18 (1.12–15.62)	**0.033**
LVSI	Yes versus No	1.99 (1.20–3.31)	**0.0067**	1.66 (0.96–2.89)	0.071
Stromal invasion in thirds of the cervical stroma	Outer versus Inner/Middle	1.22 (0.60–2.48)	0.58	0.84 (0.36–1.98)	0.70
Parametrial invasion	Yes versus No	0.00 (0.00-∞)	0.33	0.00 (0.00-∞)	1.0
Uterine isthmus invasion	Yes versus No	0.74 (0.18–3.05)	0.68	0.49 (0.11–2.16)	0.35
Vaginal invasion	Yes versus No	2.56 (0.63–10.50)	0.17	2.10 (0.43–10.25)	0.36
Histological type	Squamous versus Nonsquamous	1.22 (0.71–2.08)	0.47	1.10 (0.63–1.92)	0.73
Reason for postoperative radiotherapy			**0.0183**		0.22
	No postoperative radiotherapy	ref.		ref.	
	LN metastasis	2.76 (1.31–5.83)	**0.0076**	1.97 (0.87–4.50)	0.11
	Other reasons	0.82 (0.20–3.37)	0.7823	0.74 (0.14–3.83)	0.72

p-values < 0.05 are in bold.
Abbreviations: ARH = abdominal radical hysterectomy; CI = confidence interval; HR = hazard ratio; LN = lymph node; LVSI = lymphovascular space invasion; MIRH = minimally invasive radical hysterectomy.

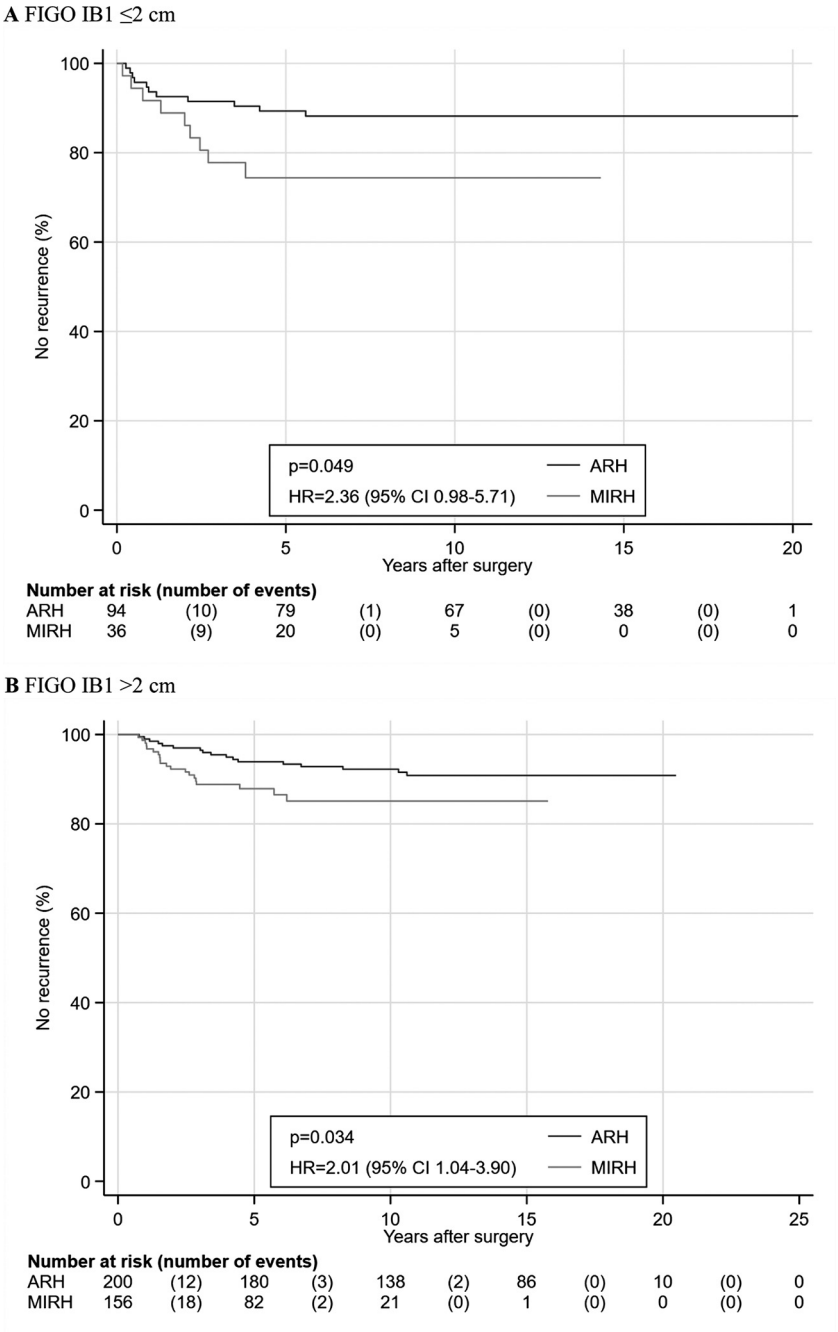

Fig. 2. Kaplan-Meier curves of FIGO 2009 stage IB1 patients stratified by surgical approach for the analysis of time to recurrence. A: Tumors ≤2 cm. B: Tumors >2 cm. ARH = abdominal radical hysterectomy; MIRH = minimally invasive radical hysterectomy.

group for all analyzed endpoints, i.e., TTR, CSS and OS. In stage IB1 patients with tumors >2 cm, the risk associated with MIRH was more than twice compared to ARH, irrespective of preoperative conization. However, when dividing this subgroup of patients by whether or not they underwent conization, the statistical power became low and no statistically significant difference was observed between MIRH and ARH group. Overall, our results indicate similar survival outcome for MIRH and ARH in stage IA patients and stage IB1 patients with tumor ≤2 cm undergoing conization, and worse survival outcome for MIRH than ARH group in other stage IB patients.

An important finding in our study was the observed high rate of intraperitoneal carcinomatosis which accounted for 40.0% of all recurrences in the MIRH group. These patients had simultaneous metastasis at other locations. Among the stage IB1 patients with tumors ≤2 cm in size intraperitoneal metastasis were not observed in any patients with clean margins after conization.

Additional studies are needed to confirm whether patients with stage IA and stage IB1 tumors ≤2 cm who undergo conization and have clean margins are subgroups in which the MIRH approach is not contraindicated.

4.2. Comparisons with previous studies

Our overall findings are in line with those of the LACC trial [15], indicating that MIRH is associated with higher rates of recurrence and death than ARH. Several other studies have reported the same results [9–14], including a recent meta-analysis of 15 studies [22]. In contrast, a Danish study [23], a Swedish study [24] and a study by Brandt et al. [17] found

no significant difference in oncological outcomes between the ARH and MIRH groups. The lower recurrence rate in these three studies may be the results of the shorter follow-up times and high frequencies of postoperative radiotherapy. Notably, the Danish [23] and Swedish studies [24] did not cover training periods for robotic surgery, which were included in our study and in many other studies [9–14,22]. It is also noteworthy that the LACC trial reported that there were no differences in quality of life [25] and the incidence of adverse events [26] between the ARH and MIRH groups supporting that the MIRH approach should not be used in patients where this approach confers an increased risk of recurrence.

The combination of CO_2 intraabdominal pressure and airborne exfoliated cancer cells from tumor spillage during abdominal colpotomy leads to a favorable environment for the peritoneal implantation of cancer cells with the MIRH approach [27]. In our study, intraperitoneal carcinomatosis did not occur in patients who underwent preoperative conization with clean margins, indicating the importance of avoiding intraabdominal spillage during surgery. Koehler et al. [28] described a surgical technique with closure of the vaginal top before the performance of a laparoscopic radical hysterectomy. Their 4.5- and 10-year DFS rates of 95.8% and 93.1%, respectively, are promising, and further investigation of this surgical technique is warranted. Moreover, an international European observational cohort study (SUCCOR) reported that when intrauterine manipulators were avoided and maneuvers to avoid tumor spread at the time of colpotomy were used, MIRH had oncological outcomes similar to those of ARH [29]. However, Uppal et al. [10] pointed out they did not find any differences in recurrence rate with intrauterine manipulators compared to a vaginal blunt probe. Our study highlights the importance of avoiding tumor spread at the time of colpotomy. Intrauterine manipulators were not a confounding factor in our study, as we did not use them.

We did not observe any significant prognostic difference between ARH and MIRH in multivariable analysis of stage IB1 tumors ≤2 cm with preoperative conization, while we noted a considerably worse TTR, CSS and OS associated with MIRH than with ARH in patients with stage IB1 tumors ≤2 cm without conization and in all patients with stage IB1 tumors >2 cm. This is logical, as preoperative conization is usually performed in patients with smaller tumors in whom a biopsy has indicated superficial tumor growth or the absence of a macroscopically visible tumor. It is also likely that a conization in stage IB1 tumors ≤2 cm reduced the risk of contamination by colpotomy even in cases with microscopically positive margins.

An important difference between this study and most other studies is our frequency of postoperative adjuvant treatment, which was 12.5% in the ARH group and 6.1% in the MIRH group. The low incidence of postoperative radiotherapy in our study is likely obtained by the uniform preoperative evaluation based on an algorithm including MRI, which allowed omission of surgery in cases most likely to be candidates for postoperative radiotherapy and avoidance of unintended "upstaging" to stage IB2 (FIGO 2009) in our institution. In contrast, up to approximately 50% of patients in other studies received postoperative adjuvant treatment. For instance, 58.7% of the ARH patients and 47.1% of the MIRH patients received postoperative adjuvant therapy in the SUCCOR study [29]. The combination of surgery and radiotherapy increases morbidity, especially from lymphoedema [30], and should therefore be avoided when possible.

4.3. Clinical implications

The MIRH approach confers a considerable risk of the intraperitoneal implantation of cancer cells in patients with residual cancer on the ectocervix and should not be performed in this group of patients until protective measures have been shown to be effective in randomized trials. This may not be true for conization evaluated lesions ≤2 cm, especially in cases with clean margins, however prospective validation is needed.

4.4. Strengths and limitations

Compared to the previously discussed studies comparing ARH and MIRH, a strength of our study is the large, single-center cohort from an institution that treats approximately two-thirds of all CC patients in Norway. Another strength is the uniform preoperatively evaluation including MRI, which may detect invasion into outer third of the cervical stroma and occult stage IB2 lesions. Other strengths include centralized pathology, a consistent scheme for adjuvant therapy, the performance of all surgeries by experienced gynecologic oncologists, and the availability of high-quality data that were contemporaneously registered into an institutional database for quality assurance and control. No patient was lost to follow-up.

The limitations of our study include the retrospective design and the differences between the two surgical groups in terms of important prognostic factors such as tumor size and preoperative conization.

5. Conclusions

We observed inferior oncological outcomes in the MIRH patients with stage IB1 disease, even in those with tumors ≤2 cm. Intraperitoneal combined recurrences accounted for 40.0% of all recurrences in the MIRH group but were not identified after ARH. Preoperative conization with clean margins appeared to be a protective factor against intraperitoneal carcinomatosis in the MIRH group. Prospective, randomized clinical trials are needed to identify safer measures to avoid the dissemination of cancer cells into the abdominal cavity.

Funding

No funding was received for this research.

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.

Acknowledgments

We are thankful to Stein Aaserud for statistical comments and Karin A. Skogsfjord for her excellent help with data collection.

Previous presentation: Parts of this study were presented at a Scientific Plenary Session of the *Annual Global Meeting of the International Gynecologic Cancer Society (IGCS),* Rio de Janeiro, Brazil, September 2019.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2021.05.028.

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