Safety evaluation of abdominal trachelectomy in patients with cervical tumors ≥2 cm: a single-institution, retrospective analysis

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Original Article

Safety evaluation of abdominal trachelectomy in patients with cervical tumors ≥2 cm: a single-institution, retrospective analysis

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ABSTRACT

Objective: For oncologic safety, vaginal radical trachelectomy is generally performed only in patients with cervical cancers smaller than 2 cm. However, because inclusion criteria for abdominal trachelectomy are controversial, we evaluated the safety of abdominal trachelectomy for cervical cancers ≥2 cm.
Methods: We began performing abdominal trachelectomies at our institution in 2005, primarily for squamous cell carcinoma ≤3 cm or adenocarcinoma/adenosquamous carcinoma ≤2 cm. If a positive sentinel lymph node or cervical margin was diagnosed intraoperatively by frozen section, the trachelectomy was converted to a hysterectomy. Medical records of these patients were reviewed retrospectively. Patients who had undergone simple abdominal trachelectomy were excluded from this study.
Results: We attempted trachelectomy in 212 patients. Among the 135 patients with tumors <2 cm, trachelectomy was successful in 120, one of whom developed recurrence and none of whom died of their disease. Among 77 patients with tumors ≥2 cm, trachelectomy was successful in 62, 2 of whom developed recurrence and 1 of whom died of her disease. The overall relapse rate after trachelectomy was 1.6% (0.8% in <2 cm group and 3.2% in ≥2 cm group), and the mortality rate was 0.5% (0% in <2 cm group and 1.6% in ≥2 cm group). Recurrence-free survival (p=0.303) and overall survival (p=0.193) did not differ significantly between the <2 cm and ≥2 cm groups.
Conclusions: Abdominal trachelectomy with intraoperative frozen sections of sentinel lymph nodes and cervical margins is oncologically safe, even in patients with tumors ≥2 cm.

Keywords: Trachelectomy; Uterine Cervical Neoplasms; Treatment Outcome

INTRODUCTION

Cervical cancer (CC) is the second most common cancer among women of childbearing age [1]. Conventional treatment for women with early-stage CC has been hysterectomy or radiotherapy; however, these treatments prevent future childbearing.

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Trachelectomy, surgical removal of the uterine cervix and surrounding tissue with preservation of the uterine body, was designed as a fertility-preserving technique for young patients with early-stage CC who wish to preserve their fertility. The first report of trachelectomy to treat early-stage CC described a procedure involving vaginal radical trachelectomy (VRT) with laparoscopic pelvic lymph node dissection [2,3]; later, the first patient to undergo abdominal radical trachelectomy (ART) was reported [4]. In 2005, we began a clinical trial of abdominal trachelectomy. So far, we have published reports of oncologic and obstetric outcomes, diagnoses, and complications of trachelectomy [5-9]. Currently, VRT, ART, laparoscopic radical trachelectomy (LRT), and robotic radical trachelectomy (RRT) are all widely performed [10].

Because Plante et al. [11] reported that lesions >2 cm are associated with greater risk of recurrence in patients who undergo VRT, tumor size ≥2 cm has been commonly considered to be a risk factor for cancer recurrence after this treatment; thus VRT has mainly been performed for tumors <2 cm in size. The National Comprehensive Cancer Network (NCCN) guideline (version 1.2019, CC) states that radical trachelectomy is a fertility-sparing treatment for patients with stage IB1 cancer [12]. On the basis of the above-mentioned findings, the guideline also states that fertility-sparing surgery for stage IB1 is most strongly validated for tumors ≤2 cm [12].

ART is a modification of abdominal radical hysterectomy and enables more radical resection of the parametrium and upper vagina than VRT. ART is often performed on patients with tumors larger than 2 cm [13-15], that is, larger than those targeted by VRT. However, there is no unequivocal evidence that ART is safe for patients with tumors ≥2 cm and inclusion criteria for abdominal trachelectomies are controversial.

Although several reports on the safety of ART in patients with CC and tumors ≥2 cm have been published [16-19], they include only small cohorts, reflect single-institution experiences with ART limited to tumors ≥2 cm, or are literature reviews of ART for tumors ≥2 cm. Although a report from a single institution is meaningful from the viewpoint that the surgical technique is consistent and not biased, no large single institution studies that focus on tumor size and compare detailed outcomes of abdominal trachelectomy for tumors <2 cm and ≥2 cm have yet been published.

We compared outcomes of abdominal trachelectomy for tumors <2 cm and ≥2 cm in a single institution and evaluated the safety of this procedure for CC ≥2 cm.

MATERIALS AND METHODS

We began a clinical trial of abdominal trachelectomy, including ART, abdominal modified radical trachelectomy (AmRT), and abdominal simple trachelectomy (AST), at our institution in 2005. Because vaginal surgery had not been performed for invasive cervical carcinoma in our institution, we chose to assess abdominal rather than vaginal trachelectomy. Our Institutional Review Board approved this clinical study in March 2005 (authorization number: 247). Informed consent to participate and for publication of their clinical data was obtained in writing from each patient.

Eligibility criteria, indications for each surgical procedure and detailed surgical technique are described in our previous reports [5,9]. Briefly, the preoperative criteria for CC consisted

primarily of 1) stage IB1 or less advanced squamous cell carcinoma (SCC) ≤3 cm (including stage IIA1 with slight vaginal involvement); or 2) adenocarcinoma/adenosquamous carcinoma (ASC) ≤2 cm. Patients with CC that slightly exceeded these size criteria were also included after determining that the patient strongly desired fertility-sparing treatment and sufficient discussion. One cm or more cancer-free space between the tumor's edge and the internal os was confirmed by preoperative magnetic resonance imaging (MRI). Patients whose CCs were of histological types associated with poor prognoses (e.g., small cell carcinoma) or whose imaging findings suggested extrauterine spread were also excluded from this study. Some patients whose tumor diameters were near the upper limits of the preoperative criteria received neoadjuvant chemotherapy (NAC) with paclitaxel and carboplatin. Patients whose removed tumors were found postoperatively to exceed the size criteria were still included in this study. Intraoperative eligibility criteria consisted of the absence of lymph node metastasis and a ≥5-mm cancer-free margin in the extirpated cervix. If a positive sentinel lymph node (SLN) or cervical margin was diagnosed intraoperatively by frozen section, trachelectomy was converted to hysterectomy. Lymph node metastasis was evaluated by intraoperative serial frozen sections of bilateral SLNs. The SLN sampling technique, and its feasibility and accuracy, have been described in detail in our previous report [20,21]. High-risk patients received postoperative adjuvant therapy, such as chemotherapy with taxane and carboplatin, radiotherapy or hysterectomy.

Patients were staged according to the International Federation of Gynaecology and Obstetrics (FIGO) 2008 staging system. Medical records and clinical information about patients in whom trachelectomy was attempted were reviewed retrospectively. Tumor diameter was comprehensively determined by preoperative vaginal speculum examination, preoperative MRI, or pathological examination of a conization or trachelectomy specimen. Patients were allocated to two groups (tumors <2 cm and ≥2 cm). When a tumor that had been measured as <2 cm preoperatively was found postoperatively to be ≥2 cm, the patient was allocated to the ≥2 cm group. Because AST targets much smaller tumors than does AmRT or ART, we excluded patients who had undergone AST from this analysis.

Age differences were analyzed using Student's t-test and categorical variables with the χ^2 test or Fisher's exact test. The Kaplan-Meier method was used for survival analysis and statistical significance was assessed with the log rank test. The $p<0.05$ was considered to denote significance. All statistical analyses were conducted using JMP 14 (SAS Institute, Cary, NC, USA).

RESULTS

From June 2005 to December 2018, abdominal trachelectomy was planned for 212 patients attending our institution. The patients' characteristics are summarized in **Table 1**. One hundred and thirty-five patients had tumors <2 cm (defined as <2 cm group) and 77 had tumors ≥2 cm (defined as ≥2 cm group). The 2 groups did not differ significantly in age. Adenocarcinoma and ASC accounted for 37% (50/135) of the <2 cm group and 16% (12/77) of the ≥2 cm group. Lymphovascular space invasion (LVSI) was more common in the ≥2 cm group (45%) than the <2 cm group (40%); however, this difference was not significant (p=0.419). Eleven patients in the ≥2 cm group received 2–3 courses of NAC comprising paclitaxel and carboplatin (TC), one of whom also received two courses of bevacizumab. Positive SLNs were found in 10 patients and positive margins in 5 of the 135 patients in the <2 cm group; consequently, the fertility of those 15 patients was not preserved (conversion

Table 1. Characteristics of patients for whom trachelectomy was planned

Characteristics	Tumor size		p-value
	<2 cm (n=135)	≥2 cm (n=77)	
Median age (range)	33 (21–44)	33 (23–42)	0.977
Stage			<0.001
IA1	4	0	
IA2	23	0	
IB1	107	70	
IIA1	1	7	
Histology			0.001
SCC	85	65	
Adeno	42	7	
ASC	8	5	
LVSI			0.419
Positive	50	35	
Negative	76	42	
Unknown	9	0	
NAC			<0.001
No	135	66	
Yes	0	11	
Conversion to hysterectomy			0.093
No	120	62	
Yes	15	15	
Positive SLN	10	6	
Positive margin	5	9	

Adeno, adenocarcinoma; ASC, adenosquamous carcinoma; LVSI, lymphovascular space invasion; NAC, neoadjuvant chemotherapy; SCC, squamous cell carcinoma; SLN, sentinel lymph node.

rate: 11%); however, trachelectomy was successfully completed in the remaining 120. Positive SLNs were found in six patients (including one who received NAC) and positive margins in nine patients (including one who received NAC) in the ≥2 cm group (n=77). Thus, the fertility of 15 of these patients was not preserved (conversion rate: 19%); trachelectomy was successfully completed in the remaining 62. The conversion rate was higher in the ≥2 cm than the <2 cm group; however, this difference was not significant (p=0.093).

Oncologic characteristics of patients whose fertility was preserved and of those who required conversion to hysterectomy are summarized in **Tables 2** and **3**, respectively. In all, 182 trachelectomies were performed (53 ART and 67 AmRT in the <2 cm and 61 ART and one AmRT in the ≥2 cm group) with a median follow-up of 72 months (range, 2–165). Three patients with stage IA1 tumors (2 with SCC with LVSI and 1 with adenocarcinoma) underwent AmRT. LVSI was identified in 36% (63/174; LVSI status of eight patients unknown) of patients who underwent trachelectomy and 76% (22/29; LVSI status of one patient unknown) of patients who required conversion to hysterectomy. LVSI was identified significantly more often in patients who required conversion to hysterectomy than in those who underwent trachelectomy (p<0.001). Among patients who required conversion to hysterectomy, 60% (9/15) had LVSI in the ≥2 cm group, compared with 93% (13/14) in the <2 cm group. Twenty-two patients in the <2 cm group and 14 in the ≥2 cm group developed cervical stenosis after trachelectomy and were treated by surgical cervical dilatation (data not shown). Twenty-four patients (13%) received adjuvant therapy after trachelectomy (six chemotherapy and one hysterectomy in the <2 cm group and 16 chemotherapy and one external irradiation in the ≥2 cm group) because they were considered at high risk on the basis of postoperative pathological findings. In the <2 cm group, these high-risk patients consisted of 2 with deep stromal invasion >2/3 with LVSI, two with LVSI in the cardinal ligament, two with diffuse cervical invasion, and one with a skip lesion in the vagina. In the ≥2 cm group, these high-risk patients

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Table 2. Characteristics of patients who underwent trachelectomies

Characteristics	Tumor size		p-value
	<2 cm (n=120)	≥2 cm (n=62)	
Median age (range)	33 (21–44)	33 (23–42)	0.668
Stage			<0.001
IA1	3	0	
IA2	23	0	
IB1	94	58	
IIA1	0	4	
Histology			<0.001
SCC	72	53	
Adeno	41	5	
ASC	7	4	
LVSI			0.242
Positive	37	26	
Negative	75	36	
Unknown	8	0	
NAC			<0.001
No	120	53	
Yes	0	9	
Type of trachelectomy			<0.001
ART	53	61	
AmRT	67	1	
Adjuvant therapy			<0.001
None	113	45	
Chemotherapy	6	16	
Radiation	0	1	
Hysterectomy	1	0	
Recurrence	1	2	0.230

Adeno, adenocarcinoma; AmRT, abdominal modified radical trachelectomy; ART, abdominal radical trachelectomy; ASC, adenosquamous carcinoma; LVSI, lymphovascular space invasion; NAC, neoadjuvant chemotherapy; SCC, squamous cell carcinoma.

Table 3. Characteristics of patients who required conversion to hysterectomy

Characteristics	Tumor size		p-value
	<2 cm (n=15)	≥2 cm (n=15)	
Median age (range)	35 (25–41)	31 (23–39)	0.425
Stage			0.598
IA1	1	0	
IA2	0	0	
IB1	13	12	
IIA1	1	3	
Histology			0.830
SCC	13	12	
Adeno	1	2	
ASC	1	1	
LVSI			0.039
Positive	13	9	
Negative	1	6	
Unknown	1	0	
NAC			0.143
No	15	13	
Yes	0	2	

Adeno, adenocarcinoma; ASC, adenosquamous carcinoma; LVSI, lymphovascular space invasion; NAC, neoadjuvant chemotherapy; SCC, squamous cell carcinoma.

consisted of 10 with deep stromal invasion >2/3 with LVSI, 4 with SLN metastasis detected postoperatively, 1 with parametrial invasion, 1 with parametrial node metastasis, and 1 with diffuse cervical invasion. Among all patients who had undergone trachelectomy, 1 in the <2 cm and 2 in the ≥2 cm group developed recurrences. The overall relapse rate after trachelectomy

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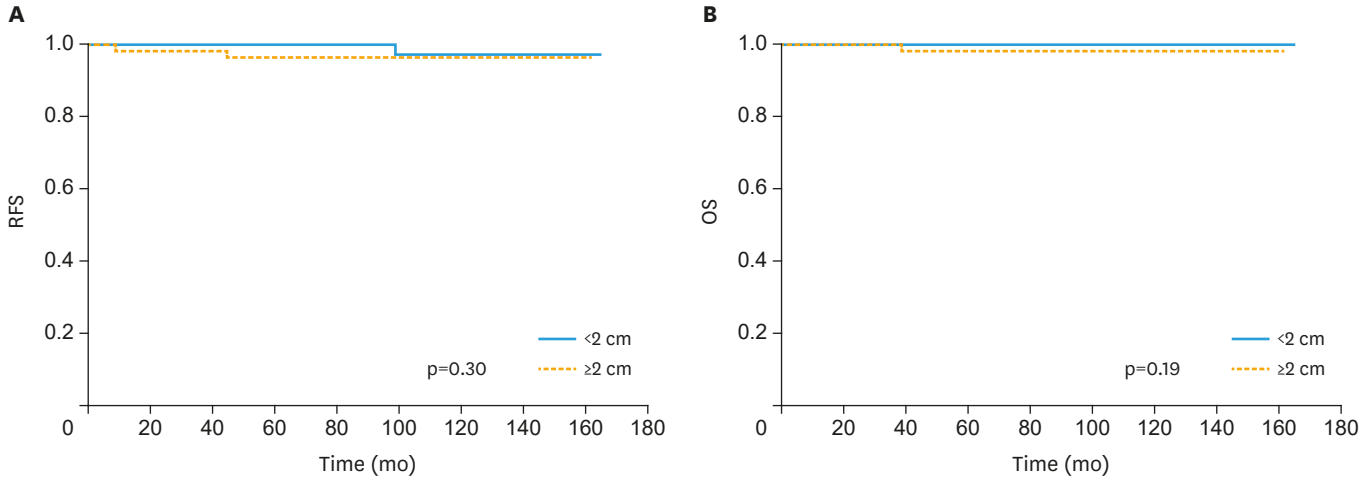

Fig. 1. Kaplan–Meier curves for patients who had undergone trachelectomy. RFS (A) and OS (B). Log-rank test for p-values.
OS, overall survival; RFS, recurrence-free survival.

was 1.6% (0.8% in the <2 cm and 3.2% in the ≥2 cm group). Recurrence-free survival (RFS) did not differ significantly between the <2 cm and ≥2 cm groups (p=0.303) (**Fig. 1A**).

Characteristics of these three patients with recurrences are listed in chronological order of recurrence in **Table 4**. Patient No. 1 had a 3.5-cm stage IB1 SCC tumor with parametrial node metastasis and LVSI. Despite receiving six courses of post-trachelectomy adjuvant TC chemotherapy, she developed a recurrence in the preserved uterine cervix 5 months after the last chemotherapy. She received multimodality treatment but died of tumor progression 38 months after trachelectomy. Patient No. 2 had a 3-cm stage IB1 ASC with LVSI. She developed a recurrence in her right lung 44 months after trachelectomy, for which she underwent right lobectomy and received TC plus bevacizumab postoperatively. She is currently alive without disease. Patient No. 3 had a small stage IB1 SCC and underwent AmRT after conization. She developed recurrence in her left internal iliac lymph node 99 months after trachelectomy, for which she underwent lymphadenectomy and received concurrent chemoradiotherapy postoperatively. She is also currently alive without disease. The overall mortality rate after trachelectomy was 0.5% (0% in the <2 cm and 1.6% in the ≥2 cm group). Overall survival (OS) did not differ significantly between the <2 cm and ≥2 cm groups (p=0.193) (**Fig. 1B**).

Post-trachelectomy obstetric outcomes are summarized in **Table 5**. In total, 36 pregnancies were achieved in 26 women and 20 infants were delivered by cesarean section. In the <2 cm group, 28 pregnancies were achieved in 21 women and the pregnancy rate was 18%; whereas

Table 4. Characteristics of the three patients who developed recurrence after trachelectomy

No.	Age at surgery	Stage	Histology	Tumor size	LVSI	Procedure	Adjuvant therapy	Time to recurrence (mo)	Recurrence site	Therapy after recurrence	Present status
1	28	IB1 pT1b1N1M0	SCC	3.5 cm	+	ART	6 cycles of TC	5*	Uterine cervix	Hysterectomy, radiotherapy, CCRT, tumor resection	Died of disease
2	29	IB1 pT1b1N0M0	ASC	3 cm	+	ART	-	44	Lung	Lobectomy TC+bevacizumab	No evidence of disease
3	29	IB1 pT1b1N0M0	SCC	<2 cm (after conization)	–	AmRT	-	99	Left internal iliac lymph node	Lymphadenectomy CCRT	No evidence of disease

AmRT, abdominal modified radical trachelectomy; ART, abdominal radical trachelectomy; ASC, adenosquamous carcinoma; CCRT, concurrent chemoradiotherapy; LVSI, lymphovascular space invasion; SCC, squamous cell carcinoma; TC, paclitaxel+carboplatin.
*Time since last chemotherapy.

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JOURNAL OF GYNECOLOGIC ONCOLOGY

Table 5. Obstetric outcomes after trachelectomy

Obstetric outcomes	Tumor size		p-value
	<2 cm (n=120)	≥2 cm (n=62)	
Pregnant patient (n=26)	21	5	0.085
Total pregnancy cases (n=36)	28	8	
Outcome			
Spontaneous abortion	11	2	
Stillbirth	1	0	
Premature delivery	9	3	
Delivery at term	5	3	
On-going	2	0	

in the ≥2 cm group eight pregnancies were achieved in five women for a pregnancy rate of 8.1%. Although the pregnancy rate was higher in the <2 cm group, pregnancy rates did not differ significantly between the 2 groups (p=0.085). In total, the premature delivery rate was 60%, preterm premature rupture of the membranes (pPROM) having occurred in nine cases. There were no neonatal deaths.

DISCUSSION

Since 2005, we have been performing abdominal trachelectomy with intraoperative frozen sections of SLNs and cervical margins at our institution. Although vaginal radical trachelectomy is generally limited to patients with CC tumors <2 cm, inclusion criteria for abdominal trachelectomy, which enables removal of wider parametrium and paracervical tissue than VRT, remain controversial. Although it is generally considered that ART can target larger tumors than can VRT, no large study from a single institution investigating whether ART is safe for patients with tumors ≥2 cm has been published. We thought that a large study from a single institution (i.e., in which surgical technique was stable and not biased) would be beneficial. Therefore, to evaluate the safety of abdominal trachelectomy for CC ≥2 cm, we investigated patients in whom abdominal trachelectomy was attempted at our institution, allocated them to two groups (tumors <2 cm and ≥2 cm), and compared their outcomes. In this study, we excluded patients who had undergone AST from the analysis, because AST targets much smaller tumors than does AmRT or ART.

In our study, conversion rates were 11% and 19% in the <2 cm and ≥2 cm groups, respectively. Positive SLNs were the commonest reason for conversion (67%; 10/15 of patients requiring conversion) in the <2 cm group, whereas positive margins were the most common cause in the ≥2 cm group (60%; 9/15). Because large tumors often spread toward the cervical canal, positive margins seem more likely than positive SLN in the ≥2 cm group. Pareja et al. reviewed outcomes of ART in patients with cervical tumors >2 cm and reported that 82.7% of patients successfully underwent fertility-preserving procedures [18], which is in accordance with the conversion rate in the ≥2 cm group in our study. As our data suggests, the larger-tumor group tended to have a higher conversion rate than did the smaller tumor group. However, when the preoperative exclusion criteria eliminate patients with tumors ≥2 cm, all patients with such tumors undergo hysterectomies. Therefore, conversion because of positive margins in the ≥2 cm group is not a disadvantage in treating CC. We also found that patients with LVSI were more likely to require conversion to hysterectomy. In the present study, 93% of patients who required conversion to hysterectomies in the <2 cm group had LVSI. Therefore, we have to know beforehand that the possibility of conversion increases when LVSI is present, even with smaller tumors. Twenty-four of the study patients were found to be at high-risk on the basis of

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postoperative pathological findings and considered to require postoperative adjuvant therapy. One of these patients underwent external irradiation and one underwent hysterectomy; the remaining 22 received adjuvant chemotherapy and consequently preserved their fertility.

In this study, relapse and mortality rates of all patients who had undergone trachelectomy were 1.6% and 0.5%, respectively (<2 cm group: 0.8% and 0%, respectively; ≥2 cm group: 3.2% and 1.6%, respectively). Survival analysis revealed no statistically significant differences in RFS (p=0.303) or OS (p=0.193) between the <2 cm and ≥2 cm groups. In other studies, the recurrence and mortality rates for patients with tumors of all sizes who underwent ART were reportedly 3.8%–4.7% and 0.4%–1.4%, respectively [22,23]; which are similar to the abdominal trachelectomy outcomes in our study's ≥2 cm group. Generally, the incidence of lymph node metastasis increases in parallel with increasing tumor size [24] and tumors tend to spread to the uterine corpus. However, performing intraoperative frozen sections of SLNs and cervical margins enables safely performing abdominal trachelectomy even in patients with tumors ≥2 cm. Deng et al. have reported that ART with SLN biopsy is feasible in patients with tumors ≥2 cm [19]. However, Pareja et al. reported recurrence and mortality rates in patients with tumors ≥2 cm who underwent VRT of 17.1% and 4%, respectively; thus, VRT in patients with tumors ≥2 cm is considered risky [18].

Pregnancy rates were 18% and 8.1% in the <2 cm and ≥2 cm groups, respectively, in this study. A review by Pareja et al. [22] reported a pregnancy rate of 16.2% after ART, which is comparable to the pregnancy rate in our <2 cm group. The pregnancy rate was clearly lower in the ≥2 cm than in the <2 cm group. We performed 53 ART (44%) and 67 AmRT (56%) in the <2 cm group and 61 ART (98%) and one AmRT (2%) in the ≥2 cm group. More parametrium and paracervical tissue is removed during ART than during AmRT; thus, it is possible that the low pregnancy rate in the ≥2 cm group is attributable to the high rate of ART in that group (98%). The premature delivery rate was 60% in our study. This high premature delivery rate is thought to be attributable to a markedly shortened cervix and pPROM caused by reduced cervical mucus, as described in our previous paper [5].

As far as we know, this is the largest series focusing on tumor size and comparing detailed outcomes between patients with tumors <2 cm and ≥2 cm who had undergone abdominal trachelectomy at single institution. We have reported that abdominal trachelectomy with intraoperative frozen SLN and cervical margin sections is oncologically safe, even in patients with tumors ≥2 cm. However, because in most institutions' patients with tumors >4 cm are considered to be ineligible for ART, sufficient data concerning ART in patients with tumors >4 cm have not yet been accumulated. Furthermore, significantly lower rates of disease-free survival and OS were recently reported for minimally invasive radical hysterectomy (laparoscopic or robot-assisted radical hysterectomy) than for an abdominal approach [25]. The post-LRT recurrence rate in patients with tumors of 2–4 cm is reportedly high (17%–20%) [18,23]; however, there is as yet insufficient information about the results of RRT for tumors of 2–4 cm. Therefore, eligibility for trachelectomy should be limited to tumors ≤4 cm, and stage IB1 CC ≥2 cm should be treated by ART using intraoperative frozen sections at this time. As for growth pattern, tumors with mainly superficial or exophytic growth are more appropriate for trachelectomy.

Yamagami et al. [26] reported that 78.8% of patients with CC in Japan aged 39 years or younger were diagnosed with Stage I disease in 2014. Moreover, trachelectomy is reportedly increasingly being performed for Stage IB1 cervical tumors >2 cm in the USA [27]. These

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reports indicate that the demand for trachelectomy for young patients with stage IB1 CC >2 cm will further increase; thus, determining the safety, feasibility, and risk of abdominal trachelectomy for CC according to size will become increasingly important.

In conclusion, abdominal trachelectomy with intraoperative frozen sections of SLNs and cervical margins for patients with tumors ≥2cm appears to be oncologically safe. However, to improve trachelectomy outcomes, accumulation of more data about trachelectomy according to tumor size is needed worldwide.

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