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Possibility of less radical treatment for patients with early invasive uterine cervical cancer

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Abstract

Aim: Radical trachelectomy (RT) with lymphadenectomy has become a standard treatment modality for patients with early invasive uterine cervical cancer who hope to preserve fertility. However, pregnancy after RT has high risks of preterm birth. The possibility of more conservative RT and the application of RT for patients with higher clinical stages were studied.

Methods: The medical charts and specimens of 42 patients who underwent RT and 64 patients who underwent radical hysterectomy were retrospectively studied. Tumor size, distance between the margin of the cancer and the internal orifice of the uterus (os), parametrial invasion, lymph node metastasis and prognoses were investigated.

Results: The average distances between the inner margin of the cancer and the internal os were 37 mm, 29 mm, 18.7 mm and 14 mm for patients with stage 1 A2, 1B1 (≤ 2 cm), 1B1 (> 2 cm) and 1B2, respectively. When amputation was performed 10 mm below the internal os, all 10 patients with 1 A2, 57 with 1B1 (≤ 2 cm), 19 with 1B1 (> 2 cm), and one with 1B2 had a cancer-free margin > 10 mm. Patients with stage 1 A2 had a cancer-free margin > 10 mm even if we amputated the cervix 20 mm below the internal os. Parametrial invasion was detected in two patients with stage 1B1.

Conclusions: A simple trachelectomy 20 mm below the internal os with pelvic lymphadenectomy might be possible for stage 1 A2 patients. The present method is best for stage 1B1 patients (≤ 2 cm). RT for stage 1B1 (> 2 cm) or higher stages should be contraindicated.

Key words: conservative operation, radical trachelectomy, uterine cervical cancer.

Introduction

Since Dargent *et al.*'s 1990 report, radical trachelectomy (RT) with lymphadenectomy has become a standard treatment option for patients with early invasive uterine cervical cancer who would like to preserve their fertility.¹ No differences between RT and radical hysterectomy (RH) regarding the oncological prognosis of patients have been reported. In their recent review, Gizzo *et al.* reported a RT recurrence rate of $< 5\%$, and a mortality rate of $< 3\%$.²

We commenced vaginal RT at our institute in 2003 and have performed 42 vaginal RTs, with 12 subsequent pregnancies among these patients.³⁻⁶ However, pregnancy after RT is still a challenge for obstetricians because of the high risk of preterm premature rupture of membranes (pPROM) and the subsequent occurrence of preterm birth.³⁻⁶ Our follow-up modality for pregnant patients after RT and transabdominal cerclage for those who have trouble with cerclage of the residual cervix after RT seems to improve the obstetric prognosis of

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these patients, although pregnancy after RT requires strict bed rest under hospitalization for a long duration in order for the pregnancy to continue.^{3,4,7,8} From a standpoint of the quality of life of patients, and in view of medical economics, it is necessary to establish a more conservative and less invasive operation for RT. In our operative procedure, we usually amputate the cervix approximately 10 mm below the internal orifice of the uterus (os). For the removal of the parametrium, we cut at the level of a type II hysterectomy. Is it possible to perform a more conservative procedure without impairing oncological prognosis? Is it possible to perform RT in patients with stage 1B1 with a tumor size > 2 cm or a higher stage? Although several trials with limited numbers of patients have been conducted, the results are still controversial.^{9,10} In this study, we focused on the distance between the inner margin of the cancer and the internal os of the uterine cervix wall, as the existence of parametrial invasion, and studied the possibility of a more conservative operation and the application of RT for patients with higher clinical stages.

Methods

A total of 106 patients with uterine cervical cancer were enrolled in this study. They consisted of 42 patients with International Federation of Gynecologists and Obstetrics (FIGO) stage 1 A2-1B1 who underwent vaginal RT with pelvic lymphadenectomy between 2003 and 2014 at our university hospital, and 64 patients with FIGO stage 1 A2-1B2 who underwent RH with pelvic lymphadenectomy as the first treatment modality in the same period.

As we have reported previously, our operative procedure for vaginal RT is based on that of Dargent *et al.*¹ We usually amputate the cervix approximately 10 mm below the internal os of the uterus. For removal of the parametrium, we cut at the level of a type II hysterectomy and a nylon suture is placed around the residual cervix.

Our vaginal RT was performed in patients who: (i) strongly desired to preserve their fertility; (ii) had a lesion sized ≤ 2 cm; (iii) had FIGO stage 1 A1 with vascular space involvement, stage 1 A2 or 1B1 with squamous histology or adenocarcinoma; (iv) had no involvement of the upper endocervical canal, determined by colposcopy or magnetic resonance imaging (MRI); and (v) had no evidence of lymph node (LN) metastasis. These operative criteria are originally based on those proposed by Plante *et al.*¹¹ Although we conducted RT in patients with squamous cell carcinoma (SCC) and adenocarcinoma,

we excluded patients with carcinomas with high recurrence potential, such as very low grade adenocarcinoma and neuroendocrine carcinoma as candidates for RT.

The clinical characteristics of patients who underwent RT and RH are described in Table 1. Twelve patients with stage 1B1 (> 2 cm) received RT because of a strong desire for the preservation of fertility, with an understanding of the risk of unfavorable outcomes. Patients who underwent RT were significantly younger than patients who underwent RH and more frequently had adenocarcinoma histology and nulliparity than those who underwent RH.

Two patients underwent additional treatments after RT for a positive stump. One patient had recurrence after RT and underwent a total hysterectomy and was administered anti-cancer agents. Five other patients had recurrence after RH and received radiation therapy or chemotherapy.

Tumor size, the tumor position in the uterus, the distance between the margin of the cancer cells and the internal os of the uterus, the existence of parametrial invasion, lymphovascular space involvement of tumor cells (LVI), LN metastasis and their obstetrical and oncological prognoses were studied using hematoxylin and eosin (H&E) stained specimens after surgery and medical charts. The distance between the cancer cell margin and the internal os was determined using at least three specimens under appropriate magnification, and the shortest distance was selected as the representative length. The experiments were repeated three times. We also calculated the reduction ratio after fixation of the specimens from the change of the length of a specific location in the uterus before and after surgery.

A nonparametric Mann–Whitney U test was employed for group comparison. A chi-square test was also used to analyze the difference in various parameters between the RT and RH groups. $P < 0.05$ was considered significant.

Results

There is no consensus regarding the definition of a safe cancer-free margin for uterine cervical cancer. Of course, the width of the cancer-free margin is not the sole factor affecting recurrence. However, an appropriate cancer-free margin clinically has the same meaning as complete resection of the tumor. In this study, we regarded a distance of 10 mm between the inner margin of the cancer and the inner edge of the removed tissue as a safe margin (Fig. 1). Distance was measured considering the reduction ratios of specimens, 8%, after formalin fixation.

Table 1 Clinical characteristics of patients who underwent RT and RH

Operation	RT			RH		P value *
Clinical stage	1 A2 & 1B1	1 A2	1B1 (≤ 2 cm)	1B1 (> 2 cm)	1B2	
Number of patients	1 A2 5 1B1 37	5	33	21	5	
Age (\pm SD) †	33.2 \pm 4.7	47.2	44.3 \pm 13.0	49.14 \pm 12.1	42.4 \pm 2.5	$P < 0.05$ for RT and RH *
Parity 0	38	2	7	5	1	$P < 0.05$ for RT and RH
1	4	2	14	9	2	
2	0	1	11	7	2	
Histology SCC	31	5	30	19	5	$P < 0.05$ for RT and RH
Adenocarcinoma	7	0	3	2	0	
Other‡	4	0	0	0	0	
Recurrence	1	0	2	3	0	ns for RT and RH [§]
LVI	7	1	5	12	3	ns for RT and RH
LN metastasis	0	0	0	3	1	ns for RT and RH
Parametrial invasion	1 (1B1)	0	1	0	0	ns for RT and RH

*Mann–Whitney U and Chi-square tests were employed for comparison of the various parameters between radical trachelectomy (RT) and radical hysterectomy (RH) groups. $P < 0.05$ was significant. †Age of each group is expressed as average \pm standard deviation (SD). ‡Other includes adenosquamous carcinoma, glassy cell carcinoma, and verrucous carcinoma. LN, lymph node; LVI, lymphovascular space involvement of tumor cells; NS, not significant; SCC, squamous cell carcinoma.

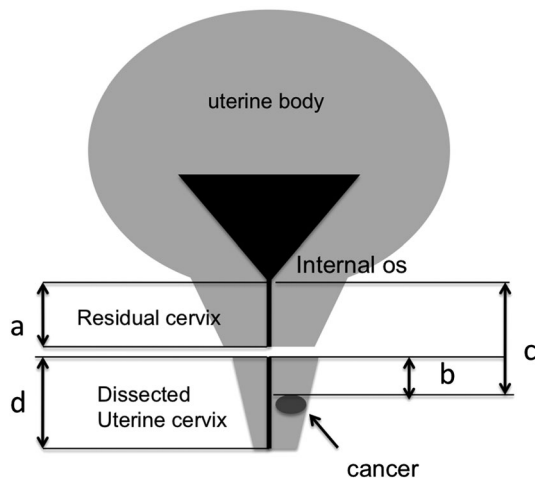


Figure 1 Definitions of various distances of the specimens after radical trachelectomy (RT) or radical hysterectomy (RH): a, length of the residual cervix, usually 10 mm; b, cancer-free margin of the dissected specimen; c, the distance between the inner margin of the cancer cells and the internal orifice of the uterus (os); d, trachelectomy height. In cases of RT, c was regarded as a (10 mm) + b. In cases of RH, c was directly measured. If no cancer was detected in the trachelectomy specimens, a + d was regarded as the distance between the edge of the cancer and the internal os.

Resection of the uterine cervix

Stage 1 A2

There were 10 patients with stage 1 A2: five underwent RT and five RH. None has experienced recurrence. Figure 2

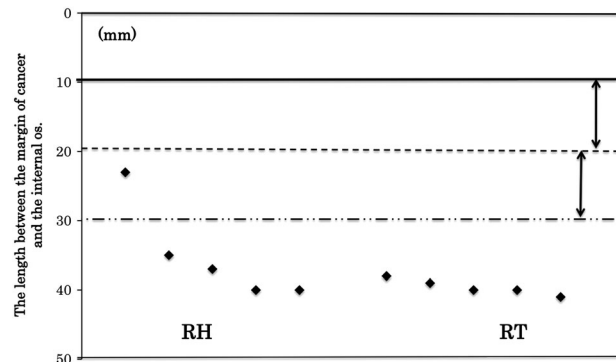


Figure 2 Distance between the inner margin of the cancer and the uterine internal orifice of the uterus (os) in stage 1 A2 cancer. ◆: cases of radical trachelectomy (RT) and radical hysterectomy (RH)— indicates 10 mm from the internal os, which assumes resection 10 mm below the internal os.— — indicates 20 mm from the internal os, which assumes resection 20 mm. below the internal os.— — — indicates 30 mm from the internal os. Arrows indicate cancer-free margin in cases of 10 mm and 20 mm resection below the internal os.

shows the distance between the inner edge of the cancer and the internal os of the uterus in each patient. In RT patients, as it is impossible to measure the correct length, the length between the inner margin of the cancer cells (if they exist) or the edge of ectocervical side of the cervix (if cancer cells do not exist after conization), the amputated endocervical side of the cervix + 10 mm (the length of the estimated residual cervix) was regarded as the distance between the cancer and the internal os (Fig. 1).

The average distance between the margin of cancer and the internal os was 37.8 ± 7.60 mm for 10 cases. We could obtain a cancer-free margin wider than 10 mm for all patients when we performed RT or, assuming that amputation was performed, 10 mm below the internal os in RH cases. Furthermore, as shown in Figure 2, nine of 10 cases had a cancer-free margin wider than 10 mm, even if we amputated the cervix 20 mm below the internal os.

Stage 1B1 (≤ 2 cm)

There were 58 patients with stage 1B1 (≤ 2 cm): 25 underwent RT and 33 underwent RH. There was recurrence in one of the RT and two of the RH cases. Figure 3 shows the distance between the margin of the cancer and the internal os in each patient after RT and RH, respectively.

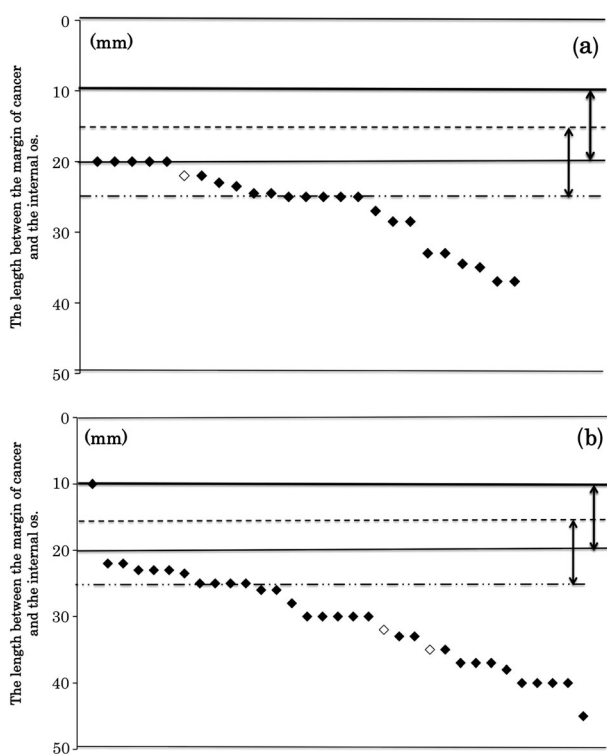


Figure 3 Distance between the inner margin of the cancer and the uterine internal orifice of the uterus (os) in stage 1B1 cancer (≤ 2 cm): a, cases of radical trachelectomy (RT); b, radical hysterectomy (RH). \blacklozenge non-recurrent cases \diamond recurrent cases — indicates 10 mm from the internal os, which assumes resection 10 mm below the internal os. - - indicates 15 mm from the internal os, which assumes resection 15 mm below the internal os. - · - · indicates 25 mm from the internal os. Arrows indicate cancer-free margin in cases of the — resection 10 mm and 15 mm below the internal os.

After RT, the distance was determined using the same method as for patients with stage 1A2 after RT. The average distance between the edge of the cancer and the internal os in this stage was 29.5 ± 7.3 mm for the 58 patients. As shown in Figure 3a, all of the patients who underwent RT had a cancer-free margin wider than 10 mm when we amputated the cervix 10 mm below the internal os. Figure 3b shows the results of the RH cases. If we amputated the cervix 10 mm below the internal os, a cancer-free margin wider than 10 mm would have been obtained for 32 of the 33 patients. The remaining patient had a positive margin.

As shown in Figure 3, had we amputated with a 5 mm shorter distance, that is, 15 mm below the internal os (line - -), 18 of the 58 patients (31%) would have had a cancer-free margin of less than 10 mm or been margin positive.

Stage 1B1 (> 2 cm)

Stage 1B1 cervical cancer (> 2 cm) is generally contraindicated for RT in our hospital; however, some patients with this stage underwent RT as a result of a strong desire to preserve fertility, with an understanding of the risk of unfavorable outcomes. There were 33 patients with stage 1B1 (> 2 cm): 12 underwent RT and 21 underwent RH. None of those who underwent RT had recurrence, but three of those with RH did. Figure 4 shows the distance between the edge of the cancer and the internal os in each patient after RT and RH, respectively. The average distance between the edge of the cancer and the internal os in this stage was 18.7 ± 8.1 mm for 33 patients.

As shown in Figure 4a, of the 12 patients who underwent RT, nine (75%) had a cancer-free margin wider than 10 mm when we amputated the cervix 10 mm below the internal os. In one patient, the margin without cancer cells was less than 10 mm, and two patients had positive margins. Figure 4b shows the results of the RH cases. A cancer-free margin wider than 10 mm was obtained in only 10 of the 21 patients (47%) when we amputated the cervix 10 mm below the internal os. In six patients, the margin was less than 10 mm, and five patients had positive margins. Although the distance between the edge of the cancer and the internal os did not directly affect recurrence, positive margins and insufficient cancer-free margins increased compared with 1B1 (≤ 2 cm) cases.

Stage 1B2

There were only five patients with stage 1B2. All underwent RH, and there has been no recurrence. The

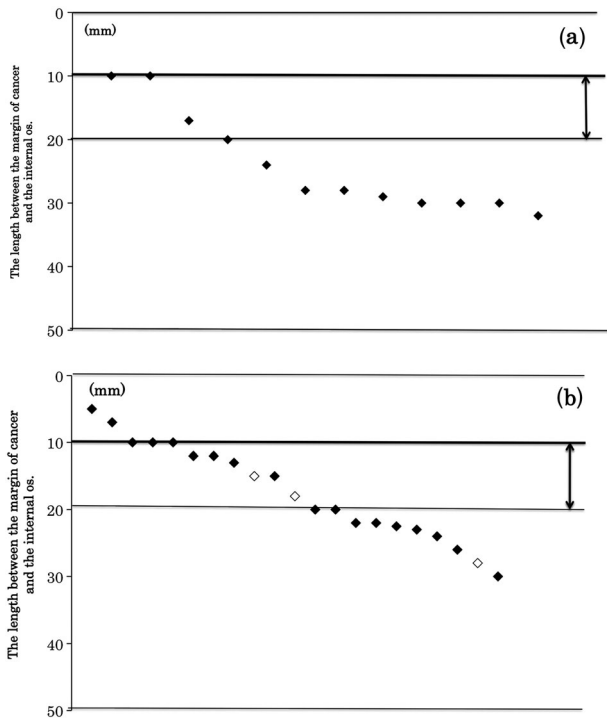


Figure 4 Distance between the inner margin of the cancer and the uterine internal orifice of the uterus (os) in stage 1B1 cancer (> 2 cm): a, cases of radical trachelectomy (RT); b, cases of radical hysterectomy (RH).◆ non-recurrent cases ◇ recurrent cases. Thick line indicates 10 mm from the internal os, which assumes resection 10 mm below the internal os. Thin line indicates 10 mm from the resection line. Arrow indicates the length of cancer-free margin.

average distance between the margin of the cancer and the internal os in this stage was 14 ± 7.2 mm. As shown in Figure 5, two patients (40%) would have been margin positive and another two (40%) would have had cancer-free margins of less than 10 mm if the cervix had been amputated 10 mm below the internal os, which indicates that RT for patients with this stage should be contraindicated.

Parametrial invasion

As shown in Table 1, there were only two cases of parametrial invasion among the patients studied, one with stage 1B1 with a ≤ 2 cm tumor and one with stage 1B1 with a > 2 cm tumor. None of the patients with stage 1A2 had parametrial invasion. However, in both cases it was proximal invasion, and no positive margin of the parametrium was detected. LVI and LN metastasis also tended to increase with clinical stage. However, there was no relation to recurrence.

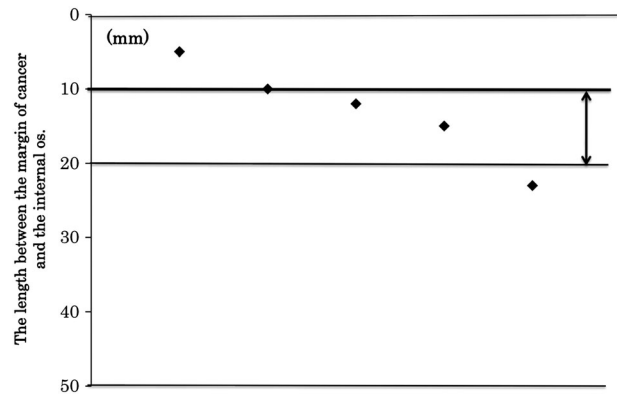


Figure 5 Distance between the inner margin of the cancer and the uterine internal orifice of the uterus (os) in stage 1B2 cancer.◆: cases of radical hysterectomy (RH).Thick line indicates 10 mm from the internal os, which assumes resection 10 mm below the internal os. Thin line indicates 10 mm from the resection line. Arrow indicates the length of cancer-free margin.

Discussion

It has been almost 10 years since we reported the first case of pregnancy after RT.³ Now this operative method is widely performed in Japan, and the number of pregnancies after RT will likely reach more than 100 throughout Japan in 2015. However, the management of patients after RT is very difficult, not only for obstetricians, but also for reproductive specialists and oncologists. Various complications after RT, such as infertility resulting from stenosis of the cervical canal, sexual dysfunction and increased preterm delivery, are reported.^{3-7,12-14} For obstetricians, preterm delivery is the greatest concern because of the lack of mechanical support of the residual cervix and chorioamnionitis caused by disruption of the endocervical glands and reduced secretion of mucus.⁵⁻⁷ Large resection of both the uterine cervix and the parametrium is required for RT. We usually amputate the uterine cervix 10 mm below the internal os of the uterus, and cut the parametrium at the level of a type II (vaginal RT)~III (abdominal RT) hysterectomy. However, excessive resection of the uterine cervix and the parametrium will impair the integrity of the residual cervix and weaken mechanical support of the cervix. Berretta *et al.* reported that resection of 1.5 cm or more of the cervix in conization resulted in an increased risk of preterm birth.¹⁵ For an improvement of obstetric prognosis, a more conservative and less invasive procedure might be the best policy, as long as it does not impair oncological prognosis. Of course, a clear cancer-free margin can be a prognostic factor, and insufficient resection can

result in an unfavorable prognosis. However, there is no consensus regarding a safe cancer-free margin, and although we chose 10 mm it does not always guarantee that there will be no recurrence. Various factors, such as tumor grade, existence of LVI and sensitivity to radiation and chemotherapy, determine recurrence.^{16,17} However, if we obtain a sufficient cancer-free margin, the possibility of recurrence after RH and RT is the same.

How much can we minimize the reduction in size? We have to consider this from both the parametrial and cervical sides. The effects of parametrial resection on early cervical cancer are controversial. We cut the parametrium at the level of a type II hysterectomy, although surgeons who adopt abdominal RT usually cut at the level of a type III hysterectomy. Resection of the parametrium at the level of a type II hysterectomy preserves the parametrium to some extent. If cancer invasion to the parametrium exists, residual cancer can exist. On the other hand, resection of the parametrium at the level of a type III hysterectomy can be a cause of permanent complications, such as a loss of urinary sensation.¹⁸ Furthermore, overresection of the parametrium can cause deterioration of the uterine cervical environment as a result of impaired blood flow around the cervix.¹⁹ Neither the cases of RT nor the cases of RH with stage 1 A2 in our hospital showed invasion to the parametrium. Therefore, we believe we can omit resection of the parametrium for cases of stage 1 A2, although our results were from only 10 cases.

One case of stage 1B1 with a ≤ 2 cm tumor (1.7%) had parametrial invasion, as did one with a > 2 cm tumor (3.0%). None had deep parametrial invasion. Our results were consistent with Schmeler *et al.*, who reported that parametrial invasion occurred in less than 1% of patients with stage 1 A2-1B1 with a < 2 cm tumor with no lymphovascular invasion.²⁰ Are these percentages high or low? Considering the complications resulting from resection of the parametrium at the level of a type III hysterectomy, resection of the parametrium at the level of a type II hysterectomy seems the best choice.

Considering our results, it might be possible to perform more conservative resection of the uterine cervix for patients with stage 1 A2, although we usually amputate the cervix approximately 10 mm below the internal os. As shown in Figure 2, if we assume 10 mm to be a safe cancer-free margin, resection 20 mm below the internal os might be possible, although our results were derived from only 10 cases. However, for patients with stage 1B1 and a ≤ 2 cm tumor, the distance between the internal os and the inner margin of the cancer tends to be shorter than for those with stage 1 A2. In patients with stage 1B1 (≤ 2 cm), amputation of the uterine cervix

at of 10 mm below the internal os seemed to be appropriate for the resection position. Shortening of the resection by more than 5 mm might be possible for some cases with a cancer-free margin of 10 mm. Uterine cervical extension of 5 mm can be of significant benefit to pregnant patients; however, it is impossible to anticipate deep infiltration or skip invasion with RT. Considering these results, more conservative resection of the cervix has a risk of remaining lesions or recurrence of the cancer in some cases.

In principle, we performed RT for patients with a ≤ 2 cm lesion, according to criteria used by Plante *et al.*¹¹ For patients with a tumor larger than 2 cm, the risk of an insufficient margin and the existence of metastatic lesions could result in recurrence, although Wethinton *et al.* recently reported the possibility of RT for patients with stage 1B1 (> 2 cm).²¹

Although not considered in this study, there are two types of cervical cancer growth: exophytic and endophytic. We believe exophytic cervical cancers might have better prognosis than endophytic, especially in SCC histology. Therefore, patients with exophytic carcinomas larger than 2 cm and SCC histology might be reasonable candidates for RT. Detailed comparative study of pathological and clinical characteristics of the both tumor types needs to be performed.

Our results suggest that simple trachelectomy approximately 20 mm below the internal os with pelvic lymphadenectomy or LN sampling might be possible for patients with stage 1 A2. For patients with stage 1B1 (≤ 2 cm), it is desirable to perform RT according to the present standard for the resection of the uterine cervix, although resection of the parametrium at the level of a type II hysterectomy is sufficient.

Thus, more conservative treatment is not easy for patients with stage 1B1 with a > 2 cm tumor or in higher stages. Recently, neoadjuvant chemotherapy (NAC) and concurrent chemoradiotherapy (CCRT) have been performed in patients with larger tumors, and these treatments have improved the prognosis of some patients in advanced stages.^{22,23} NAC + conservative surgery might be possible for patients who do not meet RT criteria.²⁴ However, considering the uncertainty of the effects of anti-cancer drugs and the damage to the ovaries by anti-cancer agents, administration of a combination of NAC or CCRT with RT should be carefully considered. Although Robova *et al.* recently reported the effects of fertility-sparing surgery followed by high dose NAC, their results were unfavorable.²⁵

This study demonstrated the possibility of more conservative surgery for early invasive uterine cervical

cancer. The number of patients included in this study is limited. However, as surgeons in a single institute performed the operations in this study, operative procedure technical bias is relatively low.

More conservative and less invasive operations for young patients with invasive uterine cervical cancer are in great demand all over the world. Accurate preoperative diagnosis of the cancer is important in order to select appropriate candidates for more conservative operations. We need correct interpretation of MRI and/or computed tomography scans, correct biopsies and diagnostic conization and detailed pathological examinations performed by skilled specialists. Cooperation among gynecologic oncologists, radiologists, pathologists, obstetricians and reproduction specialists will be essential to develop such procedures.

Disclosure

The authors have no conflicts of interest to declare.

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論文題名	Possibility of less radical treatment for patients with early invasive uterine cervical cancer (初期浸潤子宮頸癌患者に対しての妊孕性温存・周産期予後改善を目指した低侵襲治療の可能性)
結果の要旨	<p>これまで、初期進行子宮頸がんに対しては根治術として子宮摘出が余儀なくされていたが、罹患年齢の若年化に伴い妊孕性温存術式が必須となってきている。本研究では子宮頸癌に対する妊孕性温存手術後の妊娠分娩予後改善を目指した、より保存的な妊孕性温存手術の可能性の検討を行った。円錐切除ではより保存的な coin 型切除への変更は有用な術式であること、初期浸潤癌に対するトラケレクトミーでは 1A2 期に対しては更なる縮小手術の可能性、1B1 期 (<2cm)に関する現行術式の妥当性と更なる 5mm の温存の可能性、1B1 期 (≥2cm)以上に関するトラケレクトミーの非妥当性が示された。本研究は、初期浸潤子宮頸がんに対して術後妊娠予後改善を目指すうえで有用な研究であり、医学博士授与に値するとの評価を審査委員全員から頂いた。</p>