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Intention-to-Treat Analysis of Radical Trachelectomy for Early-Stage Cervical Cancer With Special Reference to Oncologic Failures

Single-Institutional Experience in Hungary

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Objective: The aim of our study was to evaluate clinical and pathological data in order to draw eligibility criteria for oncologically sufficient radical trachelectomy (RT) in early-stage cervical cancer. Reviewing all cases of attempted RT performed at our unit, we focused attention on prognostic indicators of the need for additional oncologic treatment following RT. The analysis was extended by extensive literature review to include previously published cases of oncologic failures.

Methods: The authors retrospectively analyzed data of patients who underwent RT at the Department of Obstetrics and Gynecology, University of Debrecen. Electronic records and case notes of RT cases were reviewed to determine the incidence of abdominal and vaginal route, distribution of clinicopathologic data, and follow-up results of individual cases. Individual procedures were categorized as oncologically insufficient if additional oncologic treatment was necessary following RT. Theoretical eligibility criteria for RT in early-stage cervical cancer were determined retrospectively by selecting prognostic features that were associated with oncologic insufficiency from clinicopathologic indicators of the complete series.

Results: Twenty-four cases of RT were performed by the authors, 15 vaginal RTs with laparoscopic pelvic lymphadenectomy and 9 abdominal RTs with open pelvic lymphadenectomy. Fifteen of 24 cases proved oncologically sufficient. Three cases required immediate conversion to radical hysterectomy because of positive sentinel nodes and/or positive isthmic disc on frozen section. In further 5 cases, final pathology results indicated additional oncologic treatment, that is, radical hysterectomy (n = 2), chemoradiotherapy (n = 2), or chemotherapy (n = 1). One patient among immediately converted cases and another 3 among those who required additional oncologic treatment died of their disease later. There were no other cases of recurrences over a median follow-up of 34 months (range, 12–188 months). Factors that may predict oncologic insufficiency of RT were stage IB1 or greater, tumor size of greater than 2 cm in 1 dimension or greater than 15 mm in 3 dimensions, G3, nonsquamous/adeno histological type, stromal invasion of greater than 9 mm, and lymphovascular space involvement in the primary tumor.

Conclusions: Most cases of oncologically insufficient RTs have significant risk features that can be identified preoperatively. There is a need for more clinicopathologic data on oncologic failure of RT cases in order to improve patient selection.

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Cervical cancer is the third most common malignant disease among women. In the last few decades, the average age of women at first confinement has been increasing, while the mean age at diagnosis of cervical cancer patients has been decreasing. These facts lead to an increasing number of women requesting fertility-preserving treatment for cervical cancer. Radical hysterectomy is an effective treatment method of early-stage cervical cancer (stages IA1–IIA) with 73.4% to 97.5% 5-year overall survival, but this technique is not without complications. This operation carries a significant morbidity that is related to bleeding, vessel and nerve injury, and bladder and bowel dysfunction. Postoperatively, there is considerable risk of fistula formation, lymphedema, sexual dysfunction, and the ultimate loss of fertility. Therefore, it is not surprising that a growing intention for less invasive interventions in early-stage cervical cancer has arisen over the last few decades. Conization and simple hysterectomy seem an acceptable alternative treatment in microinvasive carcinoma. Although radical hysterectomy remained the recommended treatment method in early-stage (IA2–1B1) disease, in cases where fertility preservation is desired, radical trachelectomy (RT) can be an appropriate alternative method.[1,2] The aim during radical vaginal RT (VRT) is to excise the cervix together with the associated parametrium and upper vaginal cuff in addition to a pelvic lymphadenectomy (PLND) performed via laparoscopy (LSC PLND). Soon after the introduction of the Dargent technique of VRT in the early 1990s, Hungarian gynecologic oncologists contributed to the elaboration of the technique of abdominal RT (ART).[3,4] Generally, the abdominal route gives an opportunity for a wider parametrial dissection. Although RT can preserve fertility, the operation carries a considerable risk of perioperative morbidity that is mostly related to parametrectomy. In contrast, VRT requires a more experienced surgeon and is technically more challenging, but recovery time is shorter, the incidence of perioperative morbidity is lower, and LSC PLND is equivalent to open PLND. Nowadays, RT is performed in more and more departments via laparoscopy. The advantage of ART over VRT is that it provides an opportunity for a wider parametrial dissection and in special cases allows excision of tumors with a larger diameter.[5]

Within the literature of RT, most articles are retrospective, present a small number of cases, and contain levels II and III recommendations. More importantly, most reports do not give specific details regarding the oncologically insufficient cases, that is, those cases of RTs that were either aborted or required additional oncologic treatment such as radical hysterectomy, chemoradiation, or chemotherapy. Intention-to-treat (ITT) analysis was introduced in medical research methodology in the 1990s. As compared with per-protocol analysis, ITT admits noncompliance, protocol deviations, and dropouts and provides greater accountability for all patients enrolled into the study. Intention-to-treat analysis gives more realistic idea about generalizability of the results. The majority of reports on RTs analyze data of trachelectomies that were actually performed, and less attention is paid to cases where failures and protocol deviation occurred or follow-up data are missing. Ultimately, an aborted trachelectomy or additional oncologic interventions can be considered as a failed attempt to treat cervical cancer with RT alone. Probably due to the relatively short follow-up intervals, most reports do not have much data about recurrences and do not present details of patients who died of their disease. In this study, we summarize our experiences and present details of not only successful cases, but also the failed ones. Avoiding publication bias by an ITT analysis is of crucial importance in helping accurate patient selection in the future, and it is likely to help avoiding oncologically insufficient interventions in the future.

METHODS

A retrospective study was conducted on patients in whom an RT was attempted between 2002 and 2015 at the Unit of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Debrecen. The aim of our study was to evaluate clinical and pathological data in order to draw eligibility criteria for oncologically sufficient RT in early-stage cervical cancer. In our view, the need for additional oncologic treatment means that RT alone was oncologically insufficient; therefore, oncologic insufficiency was defined as a case requiring additional oncotherapy beyond RT. Early and late outcome data, as well as primary histology, intraoperative frozen-section histology, and final pathology data, were subjected to prognostic evaluation in relation to oncologic sufficiency of RTs. The results were also compared with internationally published data and recommendations.

Preoperative magnetic resonance imaging (MRI) or computed tomography (CT) and chest radiography were performed in all cases of RT. Magnetic resonance imaging was the default abdominopelvic imaging technique in the preoperative workup; however, in 2 referred cases in which CT scans had already been performed, pelvic ultrasound findings considered a subsequent MRI scanning unnecessary.

Patients were eligible for inclusion into the study if RT was attempted. Patients were considered prospectively eligible for RT if the extent of the histologically confirmed cervical cancer was confined to the cervix on preoperative physical

examination, no extracervical spread was detected on imaging studies, and there was a desire to retain fertility. According to the ITT principle, we did not exclude any cases with attempted RT.

Initially, in patients with early-stage cervical cancer due for fertility-preserving surgery, we used the technique described by Dargent et al.[1] In ART, we used the technique described by Palfalvi et al.[3,4] A cerclage is routinely used to partially close the internal cervical orifice of the uterus. An intrauterine catheter was occasionally inserted and left in situ for a couple of weeks to keep the uterine orifice open and to prevent stricture. Sentinel nodes were identified with blue-dye technique and were submitted to frozen-section histology together with a 3- to 5-mm-thick isthmic disc. Positive result in the dissected isthmic disc or in the sentinel lymph node was an indication for conversion to radical hysterectomy. In cases, where intraoperative histology was negative, but the final histological result was positive, a consideration of a second operation or adjuvant therapy was made by the institutional multidisciplinary tumor board.

The route for RT was primarily determined on the basis of preoperative prognostic indicators together with the surgeon's and the patients' preferences. Because local practice, as well as international practice, has gone through a dynamic evolution over the years, our protocol for choosing between vaginal and abdominal approach among the presented cases has changed significantly over the past years. Because of a traditionally strong experience in vaginal surgery at our institute, the first 7 cases of our RTs were performed via the vaginal route. Then, according to encouraging published results of ARTs, we started gaining experience with this approach in cases where vaginal exposure of the paracervical region was deemed unsatisfactory by the surgeon. With a considerable experience in both techniques, roughly in the second half of the presented cases, more stringent criteria were used to choose between the vaginal and abdominal route. Generally, in stages IB1 and IB2 cases ART was performed, whereas in stages IA1 and IA2 cases VRT was performed. Among the stage IB2 cases, there was 1 exception from this approach. In that case, complete radiological response was achieved following platinum-based neoadjuvant chemotherapy (NACT), and colposcopic and physical examination revealed full disappearance of the lesion; therefore, VRT was performed. Among stages IA1 and IA2 cases, there was 1 exception from the vaginal route because of positive sentinel node on frozen section. Laparoscopic PLND was performed transperitoneally in all VRT cases. Blue-dye technique was used to identify sentinel nodes bilaterally, and sentinel nodes were sent for intraoperative frozen-section histology together with the isthmic disc.

Patients were followed up 3-monthly for 2 years then at every 6 months. Follow-up assessment included physical examinations, cytology, and abdominal and pelvic ultrasound examination. Magnetic resonance imaging studies were performed on a yearly basis or any time out of schedule when disease progression was suspected by symptoms or findings of routine follow-up assessment.

RESULTS

Between 2002 and 2015, 24 patients were scheduled for ART or VRT in our institution. Vaginal RT was done in 15 patients, and ART in 9 patients. Preoperative MRI was performed before the referral, with the exception of 2 cases in whom contrast-enhanced 64-slice CT was performed. The

TABLE 1. Patients' characteristics

Characteristics	
Patients	24
Follow-up, median (range), mo	34 (12–188)
Age, median (range), y	32 (26–49)
Parity, n (%)	
0	15 (62.5)
1	5 (21)
2	4 (16.5)
Stage, n (%)	
IA1	6 (25)
IA2	4 (17)
IB1	9 (37.5)
IB2	3 (12.5)
IIA1	2 (8)
Histology, n (%)	
Squamous*	16 (67)
Adenocarcinoma†	8 (33)
Grade, n (%)	
1	14 (58)
2	3 (13)
3	7 (29)
LVSI, n (%)	
Positive	5 (21)
Negative	19 (79)
Stromal invasion, n (%)	
<5 mm	15 (62.5)
5–10 mm	5 (20.5)
>10 mm	4 (17)
Tumor size, n (%)	
<1 cm	11 (46)
1–2 cm	8 (33)
2–4 cm	4 (17)
>4 cm	1 (4)
Residual cancer on final pathology, n (%)	
Yes	20 (83)
No	4 (17)
Lymph nodes removed, median (range)	15 (10–27)
No. of positive nodes, n (%)	
0	20 (83)
1	3 (11)
2	1 (4)

*One case with neuroendocrine elements.
†One case with clear cell elements.

findings of CT scans together with expert transvaginal ultrasound assessment were considered as sufficient to waive MRI scanning. Chest radiography was performed in all cases. Imaging studies showed no sign of extracervical spread of the tumor. Characteristics of all cases undergoing RT are shown in Table 1. No intraoperative complication occurred and no greater than grade I postoperative complication occurred according to the Clavien-Dindo classification.

Among 9 ART cases, preoperative histology confirmed 4 squamous, 3 adenocarcinoma, 1 neuroendocrine, and 1 clear cell tumors. The latter 2 cases were initially diagnosed as squamous type and adenocarcinoma, respectively. The mean of the largest diameter of the primary tumor and the mean depth of stromal invasion were 17.5 mm and 7 mm, respectively. Three (33%) of the 9 ART cases had lesion of more than 2 cm. Lymphovascular space involvement (LVSI) was found in 4 cases. Intraoperative frozen-section histology was positive in 2 cases; therefore, RT was considered as oncologically insufficient, and the operation was converted to radical hysterectomy (Table 2, patients 5 and 7). With regard to obstetric outcome, no pregnancy has occurred so far among our ART cases.

Among 15 VRT cases, there were 11 squamous and 4 adenocarcinoma histological types. The mean of the largest diameter of the primary tumor and the mean depth of stromal invasion were 12.5 mm and 3 mm, respectively. Three (20%) of the 15 VRT cases had lesion of more than 2 cm. Lymphovascular space involvement was found in 1 case. Intraoperative frozen section was positive in 2 cases. In the first case, lymph node mapping was performed, and only 1 proximal lymph node contained a 1-mm-diameter subcapsular metastasis (Table 3, patient 3). In view of the small-volume disease and no LVSI on primary histology, a decision was made not to convert the procedure into radical abdominal hysterectomy. Final pathology confirmed microscopic residual disease in the cervix with wide clear margins of more than 1 cm and no further lymph node involvement. The patient is well with no evidence of disease at 36 months after the procedure. The other case with positive intraoperative histology had positive margin of the isthmic disc; therefore, the procedure was converted to radical abdominal hysterectomy (Table 2, patient 4). At 87 months of follow-up, she has no evidence of disease. The mean follow-up time of VRT patients was 58 months (range, 21–188 months). One patient among our VRT cases had radical abdominal hysterectomy based on the final pathology findings (Table 2, patient 1). Having received postoperative chemoradiotherapy, she was diagnosed as having pulmonary metastasis at 58 months. Platinum-taxane combination chemotherapy resulted in temporary remission, and she died of her disease 121 months after VRT (Table 4, patient 4). With regard to obstetric outcome, 4 VRT patients have achieved pregnancy so far. One of these pregnancies ended in a second-trimester abortion, and the other 3 resulted in live birth by elective cesarean delivery at term.

Radical trachelectomy in our series was oncologically sufficient in 16 of 24 cases (Table 3). In this group of patients, the final pathology showed 9 × 8 × 6-mm average tumor diameter in 3 dimensions; the largest dissected specimen was 40 × 35 × 30 mm. Histologically 11 of 15 were squamous cell, and 4 of 15 were adenocarcinoma. None of these cases showed LVSI, and intraoperative frozen-section pathology showed lymph node metastasis in only 1 of them. The single subcapsular lymph node metastasis measured 1 mm; no other mapped lymph nodes showed involvement; therefore, the RT procedure was not aborted. The moderately differentiated squamous primary tumor of this case measured 10 × 10 × 12 mm and showed 9-mm depth of stromal invasion with wide clear margins and no LVSI. The final pathology did not reveal further lymphatic involvement, and the patient's follow-up showed no evidence of disease at 36 months after surgery.

Eight cases of RT required additional oncotherapy; hence, these cases were considered as oncologically insufficient ones (Table 2). Four of them had abdominal, and another 4 had VRT. The mean tumor diameter in 3 dimensions was 23 × 19 × 16 mm; the largest one was 60 × 50 × 30 mm. There were 6 cases with squamous, 1 squamous with neuroendocrine elements, and 1 adenocarcinoma with clear cell elements. The average stromal invasion was 5.75 mm; the deepest one was 15 mm. In

TABLE 2. Oncologically insufficient trachelectomies

Patient	Tumor Size, mm	Type	Grade	Stromal Invasion, mm or thirds	LVSI	Nodal Status (Positives/Total)	Stage
1	40 × 40 × 40	Squamous	3	3/3	1	1/16*	IIA
2	10 × 10 × 10	Squamous	3	7	0	0/16	IIA
3	7 × 3 × 2	Squamous	1	3	0	0/17	IB1
4	3 × 2 × 2	Squamous	1	2	0	0/12	1A1
5	20 × 15 × 10	Adeno	3	3/3	1 + V1	1/21	1B1
6	30 × 20 × 20	Squamous with neuroendocrine elements	3	10	1 + V1	0/12	1B2
7	60 × 50 × 30	Squamous	2	15	1	2/21	1B2
8	14 × 12 × 10	Adeno with clear cell elements	3	10	0	0/19	1B1

*Positive node and positive margin revealed by final pathology.

Radical trachelectomy was oncologically insufficient in cases with stage IB1<, grade 3 tumor, deep stromal invasion, positive lymph node, or LVSI in the primary tumor.

TABLE 3. Oncologically sufficient trachelectomies

Patient	Tumor Size, mm	Type	Grade	Stromal Invasion, mm	LVSI	Nodal Status (Positive/Total)	Stage
1	15 × 15 × 10	Adeno	1	3	0	0/12	1A2
2	2 × 1 × 1	Squamous	1	1	0	0/14	1A1
3	10 × 10 × 12	Squamous	2	9	0	1/10	1B1
4	2 × 2 × 2	Adeno	1	2	0	0/14	1A1
5	10 × 5 × 3	Adeno	1	3	0	0/11	1B1
6	40 × 35 × 30	Squamous	1	7	0	0/14	1B2
7	2 × 2 × 1	Squamous	1	1	0	0/13	1A1
8	3 × 2 × 2	Squamous	1	2	0	0/16	1A1
9	5 × 5 × 4	Squamous	1	4	0	0/12	1A2
10	4 × 5 × 3	Squamous	1	3	0	0/12	1B1
11	7 × 6 × 3	Adeno	1	3	0	0/12	1B1
12	6 × 4 × 2	Squamous	1	2	0	0/15	1A1
13	10 × 10 × 10	Adeno	3	7	0	0/18	1B1
14	11 × 7 × 3	Squamous	2	3	0	0/27	1A2
15	4 × 2 × 2	Squamous	1	1	0	0/13	1A1
16	5 × 5 × 3	Squamous	1	3	0	0/19	1A2

In 1 case with stage IB2 and in another case with lymph node micrometastasis, no additional treatment was considered as necessary.

4 cases, LVSI could be identified in the primary tumor, and in 2 of these cases, positive lymph nodes were also present. Radical trachelectomy was followed by radical hysterectomy in all oncologically insufficient cases. Despite additional oncotherapy, 4 of these 8 patients had died of their disease (Table 4).

The 33% rate of additional oncologic treatment in our series appears to be largely related to risk factors that had been identified before RT. These factors include bulky lesion, G3 tumor, deep stromal invasion, LVSI, and the presence of aggressive histological component. There were only 2 cases in which no preoperative high-risk feature could be identified (Table 2, patients 3 and 4). The first of these 2 cases had microscopic residual disease on the trachelectomy specimen and opted for hysterectomy after RT, which revealed moderate cervical dysplasia in the stump. In patient 4, positive isthmic disc indicated conversion to radical hysterectomy during the course of RT. There were 2 cases (Table 2, patients 5 and 7) in which the intraoperative finding of positive nodes led us to convert to radical hysterectomy.

DISCUSSION

The management of fertility-sparing surgery must include a thorough selection of patients and complete information about this technique. Besides the possibility of early and late complications and obstetric outcomes, patients have to be informed about the potential need for additional surgery, as well as adjuvant oncologic treatment.[6]

Current National Comprehensive Cancer Network guidelines suggest fertility-preserving surgery in only stage IB tumors with less than 2-cm diameter, and it is not recommended in cases with gastric-type adenocarcinoma, adenoma malignum, and neuroendocrine malignancy.[7] Radical trachelectomy is also recommended as an alternative intervention (level IIB evidence) in stages IA1 and IA2 lesions with positive excision margin or less than 3-mm intact border with LVSI. One of our cases with neuroendocrine tumor and another one with clear cell tumor can be seen as inappropriate inclusions. Indeed, according to current guidelines, they should not have been offered fertility preservation on the basis of the final histology. At the time of the procedure, in 2004, an initial histology showed squamous histology with scattered foci of neuroendocrine elements. A documented response to NACT and the patient's request led to the decision to proceed with fertility-preserving surgery. National Comprehensive Cancer Network guidelines were updated, with neuroendocrine tumors and rare-type adenocarcinomas being considered as inappropriate for RT only at a later date.

According to Pareja and colleagues'[8] analysis, the risk of relapse is increasing with the diameter of tumor. Radical trachelectomy in a patient with a lesion of more than 2 cm in largest diameter is therefore not recommended. In their opinion, good prognostic factors include less than 2-cm diameter, limited depth of invasion, absent LVSI, and no positive lymph nodes. In the presence of these conditions, the risk of parametrial spread is less than 1%. Plante et al[9] formulated bad prognostic factors in their study to include high-grade tumor, the presence of LVSI, and greater than 2-cm tumor diameter. Sixty-nine percent of their cases had IB1 disease; therefore, lesions of greater than 4 cm may not be represented in this conclusion. In Dargent's original series, the most important risk factor of relapse was tumor diameter. For this reason, he did not recommend performing RT tumors with a diameter of greater than 2 cm.[1] Despite these recommendations, a lot of studies have tried to expand the eligibility criteria of RT. This is possible especially in ART because wider resection zone can

TABLE 4. Cases who died of their disease following initial RT

Patient	Age, y	Stage	Therapy	Tumor Size, mm	Histology	Grade	Stromal Invasion, mm	LVSI	Nodes +/ Total	Follow-up, mo
1	26	IB1	ART + PLDN, local and distant recurrence at 1 y	14 × 12 × 10	Adeno with clear cell elements	3	10	0	0/19	28
2	30	IB2	3 BIP NACT, ART + PLDN, CDDP + VEP for pelvic wall and distant recurrence at 3/12	30 × 20 × 20	Squamous with neuroendocrine elements	3	10	1 + V1	0/12	16
3	34	IB1	ART, conversion to WM, chemoradiotherapy, pelvic side wall recurrence at 7 mo	25 × 20 × 15	Squamous	3	3/3	1 + V1	1/14	29
4	39	IIA1	VRT + LSC PLDN, brachytherapy, WM, chemoradiotherapy, pulmonary recurrence at 58 mo, 6 TC	40 × 40 × 40	Squamous	3	3/3	1	1/16	121

Most cases of oncologically insufficient trachelectomies including those with fatal-outcome RT were converted to radical abdominal hysterectomy during the primary intervention. After these operations, additional treatment modalities were also required. Poor prognostic factors could be identified in all cases.

BIP, bleomycin-ifosphamide-cisplatin; CDDP, cisplatin; VEP, vepesid; WM, radical abdominal hysterectomy; TC, taxol-cisplatin.

be achieved compared with VRT.[5] Cibula et al[10] proposed that the patient selection for fertility-sparing procedure should be based on the cranial extent of the tumor rather than on horizontal size or tumor volume. In their opinion, it is a free margin of at least 1-cm length along the endocervical canal toward the internal os that should define eligibility for fertility-preserving surgery. Indeed, expanding the inclusion criteria to lesions larger than 2 cm, fertility-sparing surgery may become available for women with locally advanced disease. Nonetheless, among these patients, the rate of oncologically insufficient cases is higher; therefore, the need for conversion and for additional adjuvant chemo/chemoirradiation therapy is more likely to arise.[11]

In our view, the need for additional oncologic treatment means that RT alone is oncologically insufficient. According to our data in relation to tumor size, trachelectomy was oncologically not sufficient in stages greater than IB1, in cases with more than 2-cm primary tumor, and in cases where the lesion measured more than 15 mm in all 3 dimensions. It is important to note that these criteria could be overwritten by NACT, when optimal down-staging had been achieved. Furthermore, trachelectomy was oncologically insufficient in cases with a stromal invasion depth of more than 9 mm and in grade 3 cancers. We also conclude that the procedure should not be recommended in rare histological types such as neuroendocrine or clear cell tumors because of their aggressive nature, even if these elements are not the predominant features of the initial histology. The presence of LVSI or vascular space involvement was also and indicator of the need for additional oncologic treatment. Positive lymph nodes were used as indication for conversion to radical hysterectomy except in 1 case, in which the exemption was based on favorable associated prognostic features.

Plante et al[9] are one of the most experienced teams in performing VRT. Of 140 planned VRTs 125 were actually performed. Twenty-one percent of their cases had stage IA2 disease, and 69% had stage IB1. Histological grade was G1 in 41% of cases. Histological type was squamous in 56% and adenocarcinoma in 37% of their cases. In 29%, LVSI was present, and the largest tumor diameter was less than 2 cm in 88.5% of cases. The median follow-up time was 93 months (range, 2–225 months). Relapse rate was 4.8%, and 1.6% of cases died of their disease.[9] In our series, 4 of 15 VRTs proved to be oncologically insufficient, and only one of them developed a late distant recurrence, which eventually led to the patient's death. The 7% relapse rate in our series is comparable to that in the literature, but the 27% rate of cases requiring additional oncologic treatment is concerning. One explanation could be the higher rate of lesions of more than 2 cm in our series (33% vs 14%); however, our case numbers might be considered as too small for such a comparison. Nevertheless, our cases seem to corroborate Plante and colleagues'[9] findings that among cases with lesion of more than 2 cm there is a 3 times' higher risk of abandoning VRT than among cases with lesion of less than 2 cm (33% vs 11%). In a recent review of 117 cases with VRT, Zusterzeel et al[12] found high-grade and nonsquamous histology to be associated with a significantly higher risk of recurrence. Data of our cases support these findings; however, the histological type of

adenocarcinoma alone did not seem to confer any negative prognostic relevance in our series.

Cibula et al[10] published 24 cases of ART in 2009. Preservation of fertility could not be achieved in 7 patients (29%) as RT was oncologically insufficient to control disease. In 4 cases, the excision margins were inadequate, or the sentinel node was positive; therefore, immediate conversion to radical hysterectomy followed. In 1 more case, definitive histology showed inadequate margins, and radical hysterectomy was performed as a separate procedure. Additional adjuvant chemotherapy was instituted in cases with lymph node micrometastasis or relapse. The median follow-up was 20 months. They reported only 1 case with relapse in which LVSI was not present, and the lymph nodes were negative (0/28).[10] Among our own cases, 8 patients (33%) required additional oncologic treatment after RT. Three of them had intraoperative conversion to radical hysterectomy, and another 5 patients required additional operation in the second-line therapy or chemoradiotherapy according to the results of final pathology. The total number of ARTs in our series might be considered too small for comparison, but it is of note that one third of them had lesion of more than 2 cm. In Li and colleagues'[13] series of 62 ART cases, 12 patients required additional oncologic treatment (immediate conversion, n = 2; chemotherapy, n = 7; chemoradiation, n = 3), which can be translated by our terms as oncologically insufficient cases (19%). In comparison to these results, our rate of 4 of 9 oncologic insufficiency among ART cases might be considered as too high. Again, the difference might be explained in part by the higher rate of tumors of more than 2 cm in our series (33% vs 22%). It is of note that half of the patients in Li and colleagues'[13] report had less than 23 months' follow-up.

Pareja et al[8] reviewed 485 cases based on published reports. Seventy-one percent of all patients had stage IB1 disease. Relapse rate was similar in the ART group (3.8%) to that in the VRT group (4.2%). Death rates were 0.4% in the ART group and 2.9% in the VRT group. The differences were statistically not significant between the groups in either relapse rate ($P = 0.47$) or in 5-year progression-free survival ($P = 0.69$) or in overall survival. Despite their statistical results, they concluded that ART is oncologically safer than VRT. It is of note that 113 (38%) of the 485 patients have attempted conceiving after the procedure, and 67 of them (58%) were successful. Of these 67 patients, 47 gave birth to a healthy newborn, and 18 had a miscarriage. Pregnancy rate after trachelectomy was similar in both groups.[8] In contrast, Wan et al. published pregnancy rates after ART ranging between 6.7% and 33.3%, which was lower than those after VRT (16.7%–100%).[6]

Neoadjuvant chemotherapy can overwrite the earlier established selection criteria, but the applicability of this presumption demands further investigations.[5,14] Robova et al[15] investigated the role of NACT. In their publication, 28 cases with deep stromal invasion and lesions of more than 2-cm diameter were examined. They used cisplatin-ifosfamide combination for the treatment of planocellular carcinomas, while adenocarcinomas were treated with cisplatin-adriamycin protocols. On completion of chemotherapy, laparoscopic sentinel lymph node biopsy was performed. In case of negative frozen-section result (7%, 2 cases), LSC PLND was completed. Having received the negative results of final pathology, simple trachelectomy was performed as a second-line surgery. In case of positive sentinel node or intact margin of less than 8 mm of the trachelectomy specimen (22%, 6 cases), they performed type C2 radical hysterectomy. In the remaining 20 cases, the relapse rate was 20%. Two of them have died (10%). The median follow-up period was 42 months (range, 5–103 months). In 1 case of our own series, VRT with laparoscopic lymphadenectomy was performed after 3 cycles of NACT by BIP (bleomycin-ifosphamide-cisplatin) protocol in a young patient with stage IB2 disease. Histopathologic review of the operative specimens proved pathologically complete remission. Her follow-up period is continuing (97 months) with an uneventful pregnancy and childbirth before completion of the manuscript. Our experience with NACT is encouraging because we have witnessed a stage IB2 case with complete pathological response confirmed on VRT + LSC PLDN specimens, a term delivery 7 years later, and no evidence of disease at 97-month follow-up. It is of note that another case of NACT in our series achieved partial pathological remission. Final pathology proved clear margins and negative nodes. Unfortunately, unlike the initial histology, this final pathology was dominated by neuroendocrine elements. In retrospect, we assume that the initially predominant squamous elements responded well to chemotherapy and masked the chemoresistant progression of the neuroendocrine component. Local and distant recurrence developed at 3 months postoperatively, and the disease could not be brought into remission by further chemotherapy. In a recent review, Plante[16] underlined the caution that is needed in the management of bulky early-stage cases with suboptimal response to NACT for the notion that partial chemoresistance seems to be a surrogate indicator of a more aggressive disease.

Within the literature of RT, most reports do not give details of oncologically insufficient cases, that is, those cases of RTs that were either aborted or required additional oncologic treatment such as radical hysterectomy, chemoradiation, or chemotherapy. In Wethington and colleagues'[14] series of stage IB1 lesions of more than 2 cm, 9 patients (31%) required no further oncologic treatment in addition to RT. The other 20 cases required postoperative chemoradiation, hysterectomy, hysterectomy, and chemoradiation or definitive chemoradiation. In our series, only 1 patient among the oncologically sufficient cases had lesion of more than 2 cm, but she underwent NACT before the procedure. Eventually, RT provided pathologically complete remission, and following a successful confinement, she continues to be in complete remission at 97 months of follow-up. Among our oncologically insufficient cases, there were 4 patients with lesion of more than 2 cm. Despite definitive chemotherapy and conversion to radical hysterectomy followed by chemoradiotherapy or additional hysterectomy with chemoradiotherapy, 3 patients died of their disease at 16, 29, and 58 months of follow-up, respectively. All together we had 5 stage IB1 cases with tumor of more than 2 cm, and 3 of them had G3 lesion, 4 of them had deep stromal invasion and LVSI, and 2 of them had positive nodes. The only 1 case of ours with stage IB1 lesion of more than 2 cm who did not require additional oncologic treatment following RT was the one who received NACT prior to fertility-sparing surgery. Our data do not support the expansion of indications for RT to stage IB1

tumors greater than 2 cm, unless effective NACT preceded surgery. In a recent meta-analysis, Plante[16] showed that up-front RT for bulky early-stage lesions carries a 26% rate of additional oncologic treatment and 69% rate of fertility preservation, while RT following NACT carries that of 17.6% and 80%, respectively.

The 36% rate of additional oncologic treatment in our series is largely related to risk factors that had been identified before RT such as bulky lesion, G3 tumor, deep stromal invasion, LVSI, or the presence of aggressive histological component, and there were only 2 cases in which no preoperative high-risk feature could be identified (Table 2, patients 3 and 4). The first of these 2 cases had microscopic residual disease on the RT specimen and opted for hysterectomy 2 years after RT, which revealed moderate cervical dysplasia in the stump. In patient 4, positive isthmic disc indicated conversion to hysterectomy during the course of RT. There were 2 cases (Table 2, patients 5 and 7) in which the intraoperative finding of positive nodes led to the decision to immediate conversion to radical hysterectomy.

In conclusion, our results suggest that in tumors of more than 2 cm and in those with deep stromal invasion RT is not the appropriate intervention. Intermediate risk factors such as poorly differentiated tumor, nonsquamous/adeno histological type, and presence of LVSI are also poor prognostic indicators of the need for oncologic treatment in addition to RT. Reported meta-analysis of relapse rate and survival after fertility-sparing surgery proves that many cases of oncologic failures are not reported in full details. Gynecologic oncologists are encouraged to publish more clinicopathologic and follow-up data on trachelectomy cases in order to improve patient outcome by the definition of more accurate eligibility criteria.

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