A less radical treatment option to the fertility-sparing radical trachelectomy in patients with stage I cervical cancer☆

Lukas Rob a,⁎, Marek Pluta a, Pavel Strnad a, Martin Hrehorcak a, Roman Chmela a, Petr Skapa b, Helena Robova a

a Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Charles University Prague, 2nd Medical Faculty, Prague, Czech Republic
b Department of Pathological Anatomy and Molecular Medicine, Charles University Prague, 2nd Medical Faculty, Prague, Czech Republic

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Abstract

The purpose of the two pilot studies was to determine the feasibility and safety of using less-radical fertility-preserving surgery: laparoscopic lymphadenectomy with sentinel lymph node identification (SLNI) followed by a large cone or simple trachelectomy (LAP-I protocol) and the LAP-III protocol, which includes neoadjuvant chemotherapy (NAC).

LAP-I: Forty women underwent laparoscopic SLNI, frozen-section analysis, and a complete pelvic lymphadenectomy as the first step of treatment. Seven days after final histopathological processing of dissected nodes, a large cone or simple vaginal trachelectomy was performed in patients with negative nodes. Nine women had a tumor larger than 20 mm, prompting the administration of three cycles of NAC before surgery.

LAP-I: Six frozen sections were positive (15%). In these cases, a type III Wertheim was immediately performed. There were no false-negative SLNs. There was one central recurrence, but after chemoradiation therapy, there was no evidence of the disease 62 months post-treatment. Twenty-four of 32 women whose reproductive ability had been maintained tried to conceive. Of these 24 women, 17 became pregnant (71% pregnancy rate). Eleven mothers gave birth to 12 children (1 at 24 weeks, 1 at 34 weeks, 1 at 36 weeks, and 9 between 37 and 39 weeks).

LAP-III: Nine patients were included. In 7 of these 9 women, reproductive ability was maintained, with 3 women becoming pregnant (1 full term and 2 ongoing).

SLNI improves safety in fertility-sparing surgery. Large cone or simple trachelectomy combined with laparoscopic pelvic lymphadenectomy can be a feasible method that yields a high, successful pregnancy rate. NAC followed by fertility-sparing surgery is an experimental alternative treatment for larger tumors.

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Introduction

Due to the effective use of screening, an increasing number of women are being diagnosed with cervical cancer at a younger age. Many of these women are of childbearing age and wish to preserve their fertility. Meanwhile, the mean age of primiparous women and women planning pregnancy has increased. This postponement of childbearing coupled with the comparatively young age at which many women are diagnosed with cervical cancer has led to the innovation of various fertility-sparing procedures. The most common of these procedures is the radical vaginal trachelectomy. Alternative procedures include a less radical simple vaginal trachelectomy or a more radical procedure, such as the radical abdominal trachelectomy or total radical laparoscopic trachelectomy [1–12].

Oncology outcomes are usually very good if the tumor does not exceed 2 cm in diameter at its largest point or if it does not infiltrate more than half of the stroma. The 5-year survival rate is greater than 95% in these cases [1,3,4,7–11]. Pregnancy outcome is excellent in women treated with a radical vaginal trachelectomy or simple trachelectomy despite the significantly
increased number of premature deliveries; however, pregnancy outcome is not as good in women treated with a radical abdominal or total radical laparoscopic trachelectomy [3,7,9–11,13–15].

Our experience with sentinel lymph node mapping (SLNM) enabled us to employ this method in the management of conservative surgeries in cases of early cervical carcinoma and to reduce the radicality of the medial part of the lateral parametria [16,17]. We performed a large cone (stage IA2) or simple trachelectomy (IB1) in women with negative sentinel nodes (based on frozen-section analysis and ultramicrostaging) and other negative pelvic nodes [7]. In this article, we present our two-step, less-radical treatment option to the radical trachelectomy, as well as oncological results and reproductive outcomes. We also present a second, new experimental protocol, which highlights the use of high-dose density neoadjuvant chemotherapy (NAC) followed by less-radical surgery.

**Materials and methods**

From January 1999 to December 2006, 40 women (mean age, 28.3 years) underwent laparoscopic sentinel lymph node identification (SLNI) as the first step for conservative fertility-sparing surgery (LAP-I protocol) at our institution. All 40 patients strongly desired fertility preservation. The inclusion criteria included a tumor size less than 20 mm in largest diameter or infiltration of less than half of the cervical stroma based on magnetic resonance imaging (MRI) and ultrasonography (US) volumetry [7]. The ethical committee of our institution approved the study.

Having sent the sentinel nodes for frozen-section analysis, we perform a complete laparoscopic pelvic lymph node dissection and parametrial node dissection as the first step of our management. If the frozen section is positive, laparoscopy is abandoned and we continue with a laparotomic radical hysterectomy (Wertheim type III) and lower para-aortic lymphadenectomy. During the second step of our LAP-I protocol, patients with negative pelvic nodes and stage IA2 disease are treated with a large cone trachelectomy, and patients with negative pelvic nodes and stage IB1 disease are treated with a simple trachelectomy 7 days after the final histopathological processing of the dissected nodes (Fig. 1). In January 2005, our institutional ethical committee approved a new study, which features the use of high-dose density NAC (cisplatin [75 mg/m²] + ifosfamide [2 g/m²] for squamous disease or cisplatin [75 mg/m²] + adriamycin [35 mg/m²] for adenocarcinoma) followed by fertility-sparing surgery for early-stage cervical cancer patients (LAP-III–NAC protocol). Nine women under the age of 40 who desired fertility preservation and who had cervical cancer involving more than half of the stroma but not more than two thirds or a tumor larger than 2 cm were included in the study.

![Fig. 1. NAC-SLNM and conservative surgery (NAC, neoadjuvant chemotherapy; SLNM, sentinel lymph node mapping; SLN, sentinel lymph node; LN, lymph node; MRI, magnetic resonance imagings; US, ultrasonography; IHC, immunohistochemistry).](image)
Results

In the LAP-I protocol, there were 3 stage IA1 patients (100% with lymph-vascular space invasion [LVSI]), 10 IA2 patients (40% with LVSI), and 27 IB1 patients (38.5% with LVSI). Of the total 40 cases, 80% (32 cases) were of squamous cell histology, 17.5% (7 cases) were adenocarcinomas, and 2.5% (1 case) were adenosquamous. The preoperative diagnosis was established by a loop electrosurgical excision procedure (LEEP) or conization in 26 patients (65%) and by cervical biopsy in 14 patients (35%).

Operative details and surgical outcomes

We detected sentinel lymph nodes in all of the women (detection rate per patient [DR], 100%; specific side detection rate [SSDR], 95%). The average number of sentinel nodes per side was 1.50 (range, 1–4). Six (15%) frozen sections were positive; in these cases, a Wertheim radical hysterectomy (type III) with low para-aortic lymphadenectomy was performed. In cases of negative frozen section after SLNI, laparoscopic pelvic lymphadenectomy was continued. The average total gain of lymphatic nodes was 24.8 (range, 12–48). As for the second step of our LAP-I protocol, patients with negative pelvic nodes and stage IA2 disease were treated with a large cone trachelectomy in 10 women), and patients with negative pelvic nodes and stage IB1 disease were treated with a simple trachelectomy (24 women) 7 days after the final histopathological processing of the dissected nodes. In this study, all of the positive nodes were detected by frozen-section analysis.

The median follow-up was 47 months (range, 12–102 months). One central recurrence occurred (in the isthmic part of the uterus) 14 months after surgery. This patient was treated with radical chemoradiation therapy, and there was no evidence of disease 60 months later. During the follow-up, an abnormal cytological finding showing a high-grade lesion and positivity of high-risk papillomavirus were detected in 1 patient; in this patient, a total abdominal hysterectomy was performed.

Pregnancy details and results

Twenty-four of 32 women whose reproductive ability had been maintained tried to conceive (by January 2008). Altogether, we recorded 23 pregnancies in 17 women. In 4 of these 17 women, assisted reproduction methods were applied (twice by intrauterine insemination [IUI] and twice by in vitro fertilization [IVF]). Eleven women gave birth to 12 children; in only one of these cases premature delivery occurred in the 24th week of pregnancy. The child, with a birth weight of 650 g, is

Table 1
Neoadjuvant chemotherapy and fertility-sparing surgery — patient characteristics

<table>
<thead>
<tr>
<th>Patient age</th>
<th>Diagnosis</th>
<th>Histopathology</th>
<th>MRI</th>
<th>Chemotherapy</th>
<th>Toxicity</th>
<th>Surgery</th>
<th>Histopathology</th>
<th>Parity</th>
<th>Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1, 25 years</td>
<td>Punch biopsy</td>
<td>Squamous cell Grade 2</td>
<td>20 x 20 x 10 mm</td>
<td>DDP 75 mg/m²</td>
<td>Grade 2</td>
<td>SLNI, PLN</td>
<td>16 LN negative</td>
<td>Nulliparous</td>
<td></td>
</tr>
<tr>
<td>#2, 26 years</td>
<td>Conization</td>
<td>Adeno Grade 3</td>
<td>44 x 36 x 19 mm</td>
<td>DDP 75 mg/m²</td>
<td>0</td>
<td>Simple trachelectomy</td>
<td>No residual disease</td>
<td>Nulliparous</td>
<td></td>
</tr>
<tr>
<td>#3, 30 years</td>
<td>Biopsy 20 x 15 mm</td>
<td>Adeno Grade 1</td>
<td>17 x 11 x 5 mm</td>
<td>DDP 75 mg/m²</td>
<td>0</td>
<td>Simple trachelectomy</td>
<td>No residual disease</td>
<td>Nulliparous</td>
<td></td>
</tr>
<tr>
<td>#4, 24 years</td>
<td>Punch biopsy</td>
<td>Squamous cell Grade 3</td>
<td>23 x 10 x 30 mm</td>
<td>DDP 75 mg/m²</td>
<td>Grade 2</td>
<td>SLNI, PLN</td>
<td>15 LN negative</td>
<td>Nulliparous</td>
<td></td>
</tr>
<tr>
<td>#5, 32 years</td>
<td>Biopsy 8 x 8 mm</td>
<td>Squamous cell Grade 3</td>
<td>15 x 17 x 24 mm</td>
<td>DDP 75 mg/m²</td>
<td>0</td>
<td>Simple trachelectomy</td>
<td>No residual disease</td>
<td>Nulliparous</td>
<td>Pregnancy 20th week</td>
</tr>
<tr>
<td>#6, 31 years</td>
<td>Punch biopsy</td>
<td>Squamous cell Grade 1</td>
<td>27 x 17 x 26 mm</td>
<td>DDP 75 mg/m²</td>
<td>0</td>
<td>Simple trachelectomy</td>
<td>1 x 1 mm</td>
<td>Nulliparous</td>
<td>Pregnancy 34th week</td>
</tr>
<tr>
<td>#7, 33 years</td>
<td>Biopsy 18 x 8 mm</td>
<td>Squamous cell Grade 3</td>
<td>17 x 13 x 28 mm</td>
<td>DDP 75 mg/m²</td>
<td>Grade 1</td>
<td>SLNI, PLN</td>
<td>21 LN negative</td>
<td>Nulliparous</td>
<td></td>
</tr>
<tr>
<td>#8, 31 years</td>
<td>Conization 20 x 15 mm</td>
<td>Squamous cell Grade 3</td>
<td>17 x 22 x 17 mm</td>
<td>DDP 75 mg/m²</td>
<td>0</td>
<td>Simple trachelectomy</td>
<td>No residual disease</td>
<td>Nulliparous</td>
<td></td>
</tr>
<tr>
<td>#9, 32 years</td>
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<td>Squamous cell Grade 3</td>
<td>18 x 27 x 29 mm</td>
<td>DDP 75 mg/m²</td>
<td>0</td>
<td>Simple trachelectomy</td>
<td>16 LN negative</td>
<td>Nulliparous</td>
<td></td>
</tr>
</tbody>
</table>

SLNI, sentinel lymph node identification; PLN, pelvic lymphadenectomy; DDP, cisplatin, ADM, doxorubicin; Ifo, Ifosfamide; LN, lymph node; MRI, magnetic resonance imaging; Hyst III, radical hysterectomy type III.
alive and in good health at the time of this writing. Two infants were born in the 34th and 35th weeks (2240 g and 2650 g), while the other 9 deliveries occurred between the 37th and 39th weeks of pregnancy. All children are reported to be in good health. For personal reasons, 2 women decided on elective abortion; one of these women was diagnosed with extrauterine pregnancy. One woman miscarried twice in the first trimester. In addition, there were 3 spontaneous abortions in the second trimester. At the time of the evaluation (January 2008), there were 3 pregnancies in progress.

Neoadjuvant chemotherapy and fertility-sparing surgery

Table 1 presents treatment details of the LAP-III–NAC protocol. From January 2005 to December 2007, 9 women fulfilled the inclusion criteria. In 7 of these 9 women, reproductive ability had been maintained, with 1 full-term pregnancy and 2 pregnancies in progress. During the very short follow-up, there has been no recurrence.

Discussion

Colposcopy, with MRI and US volumetry, can determine the exact amount of tumor infiltration of the cervix. This is the most important step in the decision process. Oncology outcomes are very good in all kinds of fertility-sparing procedures, assuming the tumor does not exceed 2 cm in diameter at its largest point or if it does not infiltrate beyond half of the stroma. The 5-year survival is greater than 95% in these cases. The extension of the parametrectomy is different in various fertility-sparing procedures. The fundamental question is: How many women after radical trachelectomy with negative sentinel lymph nodes and pelvic nodes had positive findings in the parametrium? Only abdominal radical trachelectomy or total radical laparoscopic trachelectomy fulfill “classical” criteria regarding oncological radicality. Preservation of the uterine artery in a radical vaginal trachelectomy is a withdrawal from radicality. The lymphatic channels are often close to the uterine artery in the parametrium and thus cannot be removed by a radical vaginal trachelectomy. When performing the laparoscopic sentinel lymph node procedure, we remove blue afferent lymphatic channels or nodes from the parametrium. These specimens are then sent separately to the histology laboratory to be investigated [7]. The importance of the radical medial part of parametrium removal in clinical stage IA2 and small IB1 tumors with negative sentinel nodes and negative other pelvic nodes still remains controversial [16–19]. In our opinion, the subgroup of patients with negative nodes could be candidates for less excessive parametrial tissue removal, with less related morbidity, than for a radical abdominal, laparoscopic surgery or radical vaginal trachelectomy. Two-step management facilitated by ultramicrostaging of sentinel nodes increases the safety of conservative procedures.

The obstetrical outcomes after vaginal simple or radical trachelectomy are very good. The crucial factor in second-trimester abortion or premature labor is the amount of remaining stromal tissue. However, the safe margins have to be the same in abdominal as in vaginal procedures [2,4,7–11]. Vaginal surgery provides for a more precise and friendly removal of the essential part of the cervical stroma. The newly created and shortened cervix represents an easier entry point for ascendant infections, and we agree with other centers that this exemplifies the problem of greatest concern following all types of trachelectomy [2–4,7–11]. The abdominal radical trachelectomy or full laparoscopic radical trachelectomy does not have good pregnancy outcome [9–11]. Poor pregnancy results are probably due to the complete discontinuation of the important nerves from the pelvic plexus for tubal motility during an abdominal or full laparoscopic radical trachelectomy.

NAC followed by SLNM and laparoscopic lymphadenectomy and trachelectomy in node-negative patients is a new, experimental modality for women who do not fulfill the criteria for primary surgical treatment (tumor more than 2 cm in largest diameter or infiltration of more than half but less than two thirds of the cervical stroma). The tumor volume reduction after NAC permits the less-radical removal of the cervical stroma, which, in turn, improves the chances for successful pregnancy [20,21].

At the present time, all kinds of fertility-sparing surgery procedures are experimental; we therefore need more data regarding oncological and obstetrical outcomes. The best options for minimizing recurrences are careful patient selection and treatment by skilled surgeons.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

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