Radical vaginal trachelectomy (RVT) combined with laparoscopic pelvic lymphadenectomy: Prospective multicenter study of 100 patients with early cervical cancer

Hermann Hertela, Christhardt Köhlerb, Dorothee Grundb, Peter Hillemannsa, Marc Possoverc, Wolfgang Micheld, Achim Schneiderb,*

for the German Association of Gynecologic Oncologists (AGO)

a Department of Gynecology, Medical School Hanover, Germany
b Department of Gynecology, Charité Campus Benjamin Franklin, Hindenburgdamm 30, D-12200 Berlin, Germany
c Department of Gynecology, St. Elisabeth Hospital Hohenlind, Cologne, Germany
d Department of Gynecology, Friedrich-Schiller-University Jena, Germany

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Abstract

Objective. The aim of this prospective clinical multicenter study “Uterus 6” of the German Association of Gynecologic Oncologists (AGO) was to prove the recurrence rate of patients treated with pelvic lymphadenectomy and radical vaginal trachelectomy (RVT). We also wanted to prove the surgical safety of RVT.

Methods. Between March 1995 and November 2005, we intend to treat 108 patients with cervical cancer (TNM stage 1A1, L1 n = 18, 1A2 n = 21, 1B1 n = 69) by RVT. Eight patients were excluded since the study criteria were not met after RVT (tumor size >2 cm, neuroendocrine tumor type, tumor-involved resection margins, or positive pelvic lymph nodes). Thus, 100 patients were treated by RVT according to protocol. With 4 recurrences in a sample size of 100 patients, an upper limit of the 95% confidence interval (including continuity correction) of 10.5% was calculated. Recruitment had to be stopped if five or more recurrences occurred.

Results. The median follow-up time was 29 (1–128) months. Three (3%) recurrences occurred in 100 patients treated with RVT according to protocol. Thus, the upper confidence limit was 9.2%. The projected 5-year recurrence-free and overall survival rates were 97% and 98%. The average duration of surgery was 253 (115–402) min. Perioperative complications were: postoperative bleeding, embolism of the external iliac artery, retroperitoneal lymphocele, or paralytic ileus in one patient, respectively.

Conclusions. RVT combined with laparoscopic pelvic and parametric lymphadenectomy for treatment of patients with early stage cervical cancer ≤2 cm results in a recurrence-free survival of more than 90.8%.

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Introduction

The prognosis of women with lymph node negative, early stage cancer of the cervix is excellent, with a 5-year survival rate of greater than 90% [1–3]. RVT in combination with pelvic lymph node dissection has emerged as an alternative to the standard treatment, i.e. radical hysterectomy or chemoradiation, for patients who desire preservation of fertility [4–6].

Recently, published data [7–10] suggest that RVT may have a low risk of recurrence and is, thus, a reasonable therapeutic curative approach for low-risk cervical cancer patients. However, only limited data or metaanalyses are available, and no clear hypothesis was formulated in these case series for expected oncologic safety for all patients treated with RVT. Thus, it still remains open if this approach is as effective as...
standard radical hysterectomy in terms of recurrence. Therefore, we initiated a prospective clinical evaluation to prove the oncological safety for all patients with early cervical cancer treated with RVT (study "Uterus 6" of the German Association of Gynecologic Oncologists). In addition, the characteristics and complications of the surgical procedure were studied.

Patients and methods

Between March 1995 and November 2005, all women fulfilling the following criteria were offered participation in the study at the Departments of Gynecology, University of Cologne, Charité Berlin and Jena, Germany: age ≥ 18 years, performance status ≤ 2 (WHO), signed informed consent of the patient (preoperative), patient with histopathologically confirmed cervical cancer (squamous, adenosquamous, or adenocarcinoma, stage IA1, I1, or IA2 or IB1 with ≤ 2 cm diameter) by punch or cone biopsy. In addition, all patients still wanted to become pregnant or preserve their childbearing potential. Exclusion criteria were: pregnancy, serious concomitant disease, preoperative diagnosis of nodal metastasis, previous pelvic lymphadenectomy, estimated tumor diameter of more than 2 cm, and neuroendocrine tumor type.

After we showed that the combination of vascular space and lymphatic space involvement (L1 + V1) was proved as an independent risk factor for recurrence in cervical cancer patients [11], the study protocol was amended by the study board, and no further patients with this criterion were included in the study.

Permission to study RVT for treatment of patients with early cervical cancer to preserve fertility was given by the Ethical Committee of the Friedrich-Schiller-University of Jena, Germany.

All consecutive patients eligible were treated by RVT and had to consent for participation in the study before surgery.

The procedure started with a complete laparoscopic pelvic and parametric lymph node dissection. From December 1998, the sentinel lymph node concept [12] was used as part of the study "Uterus 3" of the AGO but all patients had complete lymphadenectomy. The lymph nodes were sent for frozen section. Meanwhile, the suprarectal septum was transected and tumor involvement of the bladder wall was excluded. The paravesical space was opened. If lymph nodes were confirmed to be histopathologically negative for tumor, the vaginal part of the procedure was performed.

RVT entailed resection of a 1.5-cm-long vaginal cuff, opening of the paravesical and pararectal spaces, identification of the ureter in the uterosacral ligament, and resection of the infrarectal bladder pillar, the medial half of the cardinal ligament, and of the rectal pillar. Thus, only the vaginal branch of the uterine artery was transected and ligated. The cervix was transected approximately 1 cm distally from the internal cervical os. Resection margins are shown in Fig. 1. A permanent cerclage was performed (in case of later pregnancy, caesarean section was performed). The vagina was sutured to the cervical stump (lower uterine segment) and an 8 Charrière catheter was placed and fixed in the endocervical canal. This catheter was removed on postoperative day 5.

If permanent section confirmed tumor-involved resection margins or endocervical tumor-free margin less than 5 mm or a tumor diameter of more than 20 mm (taking also into account the volume of tumor removed by prior conization), radical hysterectomy had to be performed. Lymphovascular space involvement was analyzed by HE staining and by immunohistochemical staining using immunohistochemistry (CD 34/factor VIII marker). Blood vessels were diagnosed when the lumen of the vessel contained erythrocytes.

Patients were followed up for a minimum of 5 years with clinical examinations four times per year.

The primary objective of this study was to prove the recurrence rate for all patients treated by RVT in a sample of 100 patients. We estimated more than 50% of patients with tumor stage IB1 in the study cohort which yields a recurrence rate of about 10% [13–15]. With not more than 4 recurrences in the observed sample size of 100 patients, we verify that for all RVT patients fulfilling our entry criteria not more than 10.5% recurrences will occur (including continuity correction [16,17]). Recruitment had to be stopped if five or more recurrences occurred since the upper confidence limit of the 95% confidence interval would be 12% or more.

All patients' data were collected anonymously, entered into a database, and evaluated using the statistical program SPSS. The Kaplan–Meier method was used to calculate recurrence-free and overall survival. The Exact Fisher test was used to compare the recurrence rate of tumors of diameter ≤ 2 cm with >2 cm.

Results

In the cohort of 108 patients treated primarily by RVT, the median age was 32 (21–41) years and the median weight 63 (45–98) kg with a median Quetelet index of 22 (16–34). 92 patients were nulligravidae. Invasive cancer was diagnosed by cone biopsy in 100 (92%) and by punch biopsy in 8 (8%) patients. In 11/39 (28%) patients with stage 1A1, L1, or 1A2 and 33/59 (56%) patients with stage 1B1, tumor-involved margins of cone biopsy specimen were found. The stage of disease (TNM) was distributed after trachelectomy as follows: stage 1A1, L1 n = 18, 1A2 n = 21, and IB1 n = 69. Squamous cancer was diagnosed in 75 (69%) and adenocarcinoma in 33 (31%) patients. Lymphovascular space involvement was found in 38 (35%), angiovascular space involvement in 9 (8%), and the combination of angiovascular and lymphovascular space involvement in 5 (5%) patients.

The average duration of surgery was 253 (115–402) min. Paraortic lymphadenectomy was performed in the first eight (8%) patients and on average six (1–19) lymph nodes were removed. Pelvic lymphadenectomy was performed in all 108 patients, and on average 20 (5–52) lymph nodes were removed. Sentinel lymph node detection was performed in 68 (63%) patients, and on average four (1–16) sentinel lymph nodes were detected.

Major intraoperative injuries did not occur. Perioperative complications such as postoperative vaginal bleeding (four units of blood were transfused), embolism of the external iliac artery (immediate embolotomy was done), retroperitoneal lymphocele (managed laparoscopically), or small bowel obstruction (managed laparoscopically) was seen in one patient, respectively. Bladder function was restored after a mean of eight (1–50) postoperative days. Patients were discharged after a mean of eight (3–23) days. Postoperative complaints occurred as lymphedema in one (1%) patient, femorocutaneous nerve irritation in four (4%) patients, and dysmenorrhea due to
cervical stenosis in eight patients. One patient with cervical stenosis is pregnant and conceived spontaneously.

Eight of 108 patients were excluded since the study criteria were not met after RVT.

In four patients, frozen section of sentinel lymph nodes was negative and RVT was performed. However, permanent section proved one positive pelvic sentinel lymph node in each patient. Localization of lymph node metastasis and tumor stage is demonstrated in Fig. 1 and Table 2. All 4 patients did not consent to adjuvant chemoradiation or radiotherapy since them which to preserve fertility. Therefore, adjuvant chemotherapy with carboplatin/ifosfamide or cisplatin was performed in all patients with lymph node metastases (N1) and they are alive with no evidence of disease.

After a median follow-up of 29 (1–128) months, overall recurrence-free survival was ≥24 months in 54% of patients and ≥60 months in 12% of all patients. Four (4%) recurrences occurred in all patients primarily treated by RVT. Three (75%, \( P = 0.087 \)) of the 4 recurrences were observed in patients with adenocarcinoma (Table 1). Site of recurrence varied (Table 1). Two (2%) patients died of recurrence. Three (3%) recurrences occurred in the 100 patients treated according to protocol. Thus, the confidence interval has his upper limit at 9.2%. The primary aim of the study was achieved, and we can be very sure that the expected recurrence-free

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**Table 1**

<table>
<thead>
<tr>
<th>Recurrence (n)</th>
<th>Time (months)</th>
<th>Stage</th>
<th>Site</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 &lt;sup&gt;a&lt;/sup&gt;</td>
<td>34</td>
<td>Adeno. pT1b1 pN0 M0 L1 V0 G2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Cervix</td>
<td>Radical hysterectomy, type III</td>
</tr>
<tr>
<td>2 &lt;sup&gt;a&lt;/sup&gt;</td>
<td>7</td>
<td>Squam. pT1b1 pN0 Mx L0 V0 G3</td>
<td>Uterus</td>
<td>Radiochemotherapy (death 26 months postoperatively)</td>
</tr>
<tr>
<td>3 &lt;sup&gt;a&lt;/sup&gt;</td>
<td>11</td>
<td>Adeno. pT1b1 pN0 M0 L0 V0 G2</td>
<td>Pelvic side wall</td>
<td>LARVH&lt;sup&gt;c&lt;/sup&gt;, radiochemotherapy (death 19 months postoperatively)</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>Adeno. pT1b1 pN0 M0 L0 V0 G2&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Corpus</td>
<td>LARVH&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

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<sup>a</sup> RVT according to protocol.
<sup>b</sup> Adenocarcinoma in situ after 24 months, cone biopsy, R0 (hysterectomy was not accepted by the patient at this time).
<sup>c</sup> Laparoscopic-assisted radical vaginal hysterectomy (LARVH).
<sup>d</sup> Primary tumor size 7 × 21 mm, recurrence in the corpus uteri versus persistent tumor after RVT (R1).
survival rate is more than 90.8% for all early cervical cancer patients treated by RVT and fulfilling the entry criteria of the study. The projected 5-year recurrence-free survival rates for RVT were 97% for the patients treated according to protocol and 96% for 108 patients with the intention to treat by RVT (Fig. 2). The projected 5-year overall survival is 98% for both groups (Fig. 3). The number of patients trying to become pregnant is not known. Twelve babies were delivered by caesarian section between the 26th–40th weeks of pregnancy. Three pregnancies are ongoing, one patient experienced a missed abortion in the 13th week and two pregnancies were terminated on patients’ request.

Discussion

Parametric lymph nodes and/or lymph vessels may contain tumor cells in up to 8% of patients with negative pelvic lymph nodes [18]. Patients with stage 1A1 or 1A2 may develop pelvic recurrence in up to 3% when treated by simple hysterectomy [19]. In the majority of these recurrent patients, vessel infiltration was found retrospectively in the primary tumor. When radical hysterectomy is performed in patients with stage 1A2, in 3%, single metastasis is found in the parametrium [19]. Thus, the risk for tumor involvement of lymphatic vessels or lymph nodes in the parametrium has to be appreciated. RVT, pelvic, and parametric lymphadenectomy was recommended to all patients with cervical cancer stage 1A1 and lympho-vascular space involvement and all patients with stage 1A2 since our study committee felt that safety was a priority for our patients.

Plante and co-workers published a metaanalysis of 346 patients with early cervical cancer treated by RVT with a median follow-up time of 44 months (1–176) and report a recurrence rate of 4.1% (0–7.3) [10]. A study comparing patients after RVT and radical hysterectomy showed similar oncologic efficacy [23]. Thus, it was concluded that RVT is an oncologically safe procedure in well-selected patients.

Tumor size is an important factor for recurrence in patients following RVT [8–10]. Tumor size may be assessed preoperatively usually by colposcopy or when cone biopsy was performed or by measurement of the formalin-fixed histopathologic specimen.

In our study, only patients with an estimated tumor diameter \(\leq 2\) cm were primarily included. Of the four recurrences in our study, only one patient had a tumor size >2 cm.

Analyzing published data on patients following RVT, 30 out of 366 patients (8.2%) had tumor size >2 cm, with a recurrence rate of 23.3%. Thus, patients with tumors >2 cm are not good candidates for RVT. In 336 patients with tumor size \(\leq 2\) cm, the recurrence rate is only 1.2% ($P < 0.01$) (Table 2). Combining our data with other case series of patients with tumor size \(\leq 2\) cm, three of four (75%, $P > 0.05$) recurrences occurred in patients with adenocarcinoma (Table 3). In patients with cervical adenocarcinoma, further recurrences after RVT have been reported [20–22]. Which tumor biological factors of

<table>
<thead>
<tr>
<th>Patient</th>
<th>Stage</th>
<th>Site of sentinel lymph node</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Squam. pT1b1 pN1 M0 L0 V0 G3</td>
<td>Right com. iliac artery</td>
</tr>
<tr>
<td>2</td>
<td>Squam. pT1b1 pN1 M0 L1 V0 G3</td>
<td>Left com. iliac artery</td>
</tr>
<tr>
<td>3</td>
<td>Squam. pT1b1 pN1 M0 L1 V0 G3</td>
<td>Right int. iliac artery</td>
</tr>
<tr>
<td>4</td>
<td>Squam. pT1b1 pN1 M0 L1 V0 G2</td>
<td>Left parametric lymph node of 2 mm size in trachelectomy specimen</td>
</tr>
</tbody>
</table>

Fig. 3. Overall survival after a median follow-up time of 29 (1–128) months for 108 patients with intention to treat by RVT and 100 patients treated according to protocol.
adenocarcinoma are responsible for recurrence in early stage cervical cancer is unknown.

RVT is described as a safe surgical procedure to preserve fertility in patients with early cervical cancer. In our study, no injuries of the urinary tract, bowel, or blood vessels occurred during surgery. The rate of major postoperative complications was 4%, and there was no single operation which had to be converted to laparotomy. In the published RVT case series [8–10,23,24], injury rates and major perioperative problems vary between 2.1% and 25%. In these series, the majority of intraoperative injuries of urinary tract or bowel were managed during primary surgery without negative sequelae for the patient. In the literature, the rates of conversions to open surgery or secondary surgeries for parametrical bleeding, blood vessel injury, lymphocele, suprapubic or vulvar hematoma range between 0 and 1% [7–10]. However, during the study period, the surgeons in our study performed more than 300 laparoscopic-assisted radical vaginal hysterectomies (LARVH) which include steps identical to RVT, and no major injuries occurred. Thus, the incidence of complications associated with RVT is still considerable but will probably decrease with increasing experience of the surgeons, which is what we have observed for LARVH, previously [11].

Our study is the first prospective evaluation with a clear hypothesis regarding the oncologic safety. In a cohort of 100 patients treated with RVT, the fifth recurrence during recruitment was defined as stop criterion. The upper confidence limit of the 5th event is 12% for all patients treated with RVT, the fifth recurrence during recruitment was defined as stop criterion. The upper confidence limit of the 5th event is 12% for all patients treated with RVT.

During the 10-year period of recruitment, three recurrences occurred in 100 patients treated according to protocol. One further recurrence occurred in the group of eight additional patients which had to be excluded from the study after following RVT. The projected 5-year recurrence-free survival for 100 patients treated according to protocol was 97% and 96% for the patients with intention to be treated by RVT (Fig. 2). These results are comparable with the recurrence-free survival rate in the study cohort of Plante [10].

RVT combined with laparoscopic pelvic and parametric lymphadenectomy is an oncologically appropriate approach for treatment of selected patients with early stage cervical cancer ≤2 cm who wish to preserve fertility.

Acknowledgments

Dedicated to Daniel Dargent MD, who established this surgical technique which allows women with cervical cancer to fulfill their family life. We thank Mitchel Hofmann, MD for critical review of the manuscript.

References


