# Total mesometrial resection for the treatment of cervical cancer – an exploratory study of feasibility, safety and oncological outcomes in developing countries

## Totální mezometriální resekce pro léčbu karcinomu děložního čípku – exploratorní studie proveditelnosti, bezpečnosti a onkologických výsledků v rozvojových zemích

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**Summary**

***Background:*** Total mesometrial resection (TMMR) has shown excellent locoregional control for treatment of cervical cancer without adjuvant radiation therapy in highly selected centers. However, this procedure was never evaluated in resource-limited setting. We hypothesized that the procedure can be reproduced outside the university centers without compromising results. ***Materials and methods:*** This is a retrospective, observational, multicenter cohort study of patients with IB1–IIB cervical cancer who underwent TMMR in developing countries and omitted adjuvant radiation therapy. ***Results:*** A total of 124 patients who met the inclusion criteria were identified between 2015 and 2024 in three centers. The median follow-up was 29 months. The relapse rate was 6.1% (2 out of 33) for IB1, 3% (1 out of 33) for IB2, 11.1% (2 out of 18) for IB3, 20% (1 out of 5) for IIA1, and 16% (6 out of 24) for node-positive patients. No relapses were detected among IIA2 and IIB stages (3 and 8 patients, respectively). There was no significant difference (P = 0.36) in the relapse rate between patients who met the Sedlis criteria (2.9%) and those who did not (8.8%). ***Conclusion:*** According to the study, TMMR outcomes can be reproduced without compromising oncologic outcomes. However, prospective evaluation, longer follow-up and a larger cohort are needed to confirm these preliminary data.

**Key words**

cancer of the uterine cervix – operative surgical procedure – intermediate-risk factors – adjuvant radiotherapy

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## Souhrn

***Východiska:*** Při totální resekci mezometria (total mesometrial resection – TMMR) byla prokázána vynikající lokoregionální kontrola při léčbě karcinomu děložního čípku bez adjuvantní radioterapie ve vysoce specializovaných centrech. Tento postup však nebyl nikdy hodnocen v podmínkách s omezenými zdroji. Předpokládali jsme, že tento postup lze reprodukovat i mimo univerzitní centra bez ohrožení výsledků. ***Materiál a metody:*** Jedná se o retrospektivní, observační, multicentrickou kohortovou studii pacientek s karcinomem děložního čípku ve stadiích IB1–IIB, které podstoupily TMMR v rozvojových zemích a u nichž byla vynechána adjuvantní radioterapie. ***Výsledky:*** Celkem 124 pacientek splňujících inkluzní kritéria bylo sledováno ve třech centrech v období let 2015–2024. Medián doby sledování byl 29 měsíců. Míra relapsu byla 6,1 % (2 z 33) u stadia IB1, 3 % (1 z 33) u stadia IB2, 11,1 % (2 z 18) u stadia IB3, 20 % (1 z 5) u stadia IIA1 a 16 % (6 z 24) u pacientek s postižením lymfatických uzlin. U stadií IIA2 a IIB (3 a 8 pacientek) nebyly zaznamenány žádné relapsy. Nebyl zjištěn významný rozdíl (p = 0,36) v míře relapsu mezi pacientkami, které splňovaly Sedlisova kritéria (2,9 %), a těmi, které je nesplňovaly (8,8 %). ***Závěr:*** Podle této studie lze výsledky TMMR reprodukovat bez ohrožení onkologických výsledků. Pro potvrzení těchto předběžných údajů je však nutné provést prospektivní hodnocení, delší sledování a zapojit větší kohortu pacientek.



## Klíčová slova

karcinom děložního čípku – chirurgický zákrok – středně rizikové faktory – adjuvantní radioterapie


## Introduction

Despite vaccination and screening programs, cervical cancer still remains a significant healthcare problem in almost all countries, particularly in developing ones [1]. Early-stage disease (IA–IB2 according to International Federation of Gynecology and Obstetrics (FIGO) 2018) can be treated with surgery or radiation therapy [2]. To uphold the curative intention of the surgical treatment, pathological risk factors were defined according to which adjuvant therapy (radiation or chemoradiation) was indicated [3,4]. Adjuvant radiation was applied in every third patient even in presumed low-risk population undergoing radical hysterectomy [5]. Primary locally advanced disease (IB3-IVA) is treated with definitive chemoradiation therapy; however, surgery may be an option for selected patients who are not amenable to or who reject radiation [6].

Adjuvant radiation therapy is mainly given to patients who have intermediate-risk factors, also known as the Sedlis criteria. This treatment option was based on a single randomized controlled trial (RCT) initiated in 1989, even though the difference in overall survival (OS) did not reach statistical significance between the adjuvant radiation therapy and observation groups [7]. Recent data have shown excellent local control without adjuvant radiation due to modifications in surgical techniques [8].

There is only one RCT comparing adjuvant chemotherapy, adjuvant radiation, and observation only in high-risk cervical cancer patients [9]. In that trial, adjuvant treatment did not improve OS compared to the observation arm. Consequently, current standards based on the GOG 109 trial compare adjuvant radiation therapy and concurrent chemoradiotherapy, but not observation alone [4].

Due to increasing treatment toxicity and short-term complications, the combination of surgery and radiation therapy should be avoided [6,20]. While the main consequence of radical hysterectomy is short-term (except for lymphedema), radiation therapy significantly deteriorates quality of life in almost all aspects for a long time [10–12].

In parallel, Höckel et al. have spent efforts in recent decades to understand the locoregional dissemination of cervical cancer, based on the embryological development of the female genital system. According to a cancer field model, tumor spread is restricted by the Müllerian compartment for a long period during malignant progression. Total mesometrial resection (TMMR) was designed to remove all tissues potentially harboring tumor cells [13–16]. Recently published mature data have shown superior oncologic results for TMMR without adjuvant radiation therapy, compared to the standard of care (surgery and adjuvant radiation therapy based on risk factors) for IB1-IIA2 cervical cancer [17].

Until recently, long-term outcomes were only available from a single-center study [18]. Thus, the main criticism against the spread of the procedure without radiation therapy was based on the reproducibility of the data. In 2022, Buderath et al. published data from a multicentric registry showing results comparable to Höckel's [19]. Nevertheless, inclusion criteria restrict the popularization of the procedure, because the surgical technique in every participating center must be evaluated on-site by Höckel, which again limits the spread of the procedure.

The prevalence of cervical cancer is a significant social and medical problem in developing countries. In contrast to developed ones, healthcare resources and access to modern radiation therapy equipment may be limited in developing countries. Moreover, TMMR has never been evaluated without the omission of the intraoperative frozen section for specimens and lymph nodes, nor without the supervision of an experienced person. In this study, we present the preliminary results of a cohort of patients from three different centers undergoing TMMR and therapeutic lymphadenectomy (tLND) for cervical cancer FIGO IB–IIB stages without adjuvant radiation therapy in developing countries.

## Materials and methods

We conducted a retrospective, observational, cohort multi-institutional study to evaluate long-term outcomes after TMMR and tLND in developing countries. The study was approved by the local ethics committee of the Moscow City Oncology Hospital 62. The selected

centers were identified through a search of articles and videos on YouTube. We also sought recommendations for a proposed surgeon from Höckel. Four centers performing TMMR in developing countries were identified; however, one center was excluded due to a low number of accrued patients. The list of the centers is provided in Tab. 1.

All surgeons in the study participated in the Leipzig School of Radical Pelvic Surgery with at least one TMMR course. All cases were operated on by these surgeons or under their supervision.

All TMMR cases performed for cervical cancer with curative intent were collected from local databases. Pseudonymized data were added to a Microsoft Excel template and sent to the first author. We included patients with histologically confirmed cervical cancer, preoperatively staged IB1-IIB (FIGO 2009). Stage IIB included only cases without bladder involvement and were selected at the discretion of the operating surgeon. There were no age limits. Preoperative imaging included at least pelvic MRI or expert ultrasonography. Abdominal and chest CT or PET/CT was performed at the discretion of the surgeon or tumor board to exclude distant metastases. Examination under general anesthesia was not performed before surgery; however, a pelvic examination by the operating surgeon before the operation was obligatory.

After obtaining the primary data, we excluded the following cases:

- neuroendocrine and endometrioid subtypes;
- neoadjuvant chemotherapy;
- minimally invasive surgery;
- patients treated with adjuvant radiation therapy;
- less than 6 months since the surgery date.

**Tab. 1. Baseline characteristics**

| Characteristic | Value |
|---|---|
| age (median, IQR) | 45 (38.5–54.5) |
| age (mean, min–max, SD) | 46.5 (22–85, 12.1) |
| ASA physical status classification system | |
| ASA 1 | 88 (71%) |
| ASA2 | 36 (29%) |
| BMI (median, IQR) | 26 (24–29.3) |
| histological type | |
| squamous cell carcinoma | 87 (70.2%) |
| adenocarcinoma | 30 (24.2%) |
| adenosquamous carcinoma | 7 (5.6%) |
| FIGO stage (2018) at diagnosis | |
| IB1 | 35 (28.2%) |
| IB2 | 46 (37.1%) |
| IB3 | 27 (21.8%) |
| IIA1 | 5 (4%) |
| IIA2 | 5 (4%) |
| IIB | 6 (4.8%) |
| node-positive | 8 (6.5%) |
| preoperative tumor size, mm (median, IQR) | 29.5 (18–40) |
| preoperative tumor size, mm (mean, SD) | 29.9 (14.7) |
| type of lymph node dissection | |
| first line | 26 (21%) |
| first + second lines | 66 (53.2%) |
| first + second + third + fourth lines | 32 (25.8%) |
| skin-to-skin time, min (mean, SD) | 246 (66.4) |
| estimated blood loss, ml (mean, SD) | 161 (109) |
| length of hospital stay (mean, SD) | 5.2 (3.4) |
| Clavien-Dindo grade III complications | 6 (4.8%) |
| Clavien-Dindo grade IV–V complications | 0 |
| center name | |
| Armenia | 45 (36%) |
| Brazil | 50 (40%) |
| Russia | 29 (23%) |

ASA – American Society of Anesthesiologists, FIGO – International Federation of Gynecology and Obstetrics, IQR – interquartile range, SD – standard deviation

## Surgical procedure

TMMR was performed according to the description by Höckel [17]. The procedure began with therapeutic lymph node dissection. Despite Höckel's protocol for TMMR requiring a frozen section for all removed lymph nodes, none of the included centers had the feasibility for it. Instead, only enlarged lymph nodes were assessed during surgery. In cases of metastases, paraaortic lymph node dissection was performed without aborting the hysterectomy. If no enlarged nodes were found during tLND, at least second-line lymph nodes (common iliac and presacral) should be removed for tumors larger than 2 cm. For tumors smaller than 2 cm, only first-line tLND (external iliac, obturator, presciatic)

**Tab. 2. Histopathological characteristics.**

| Characteristic | Value |
|---|---|
| tumor size, mean (SD), mm | 32 (16.4) |
| tumor size, median (IQR), mm | 30 (20–43.8) |
| FIGO stage (2018): | |
| IB1 | 33 (26%) |
| IB2 | 33 (26%) |
| IB3 | 18 (14.5%) |
| IIA1 | 5 (4%) |
| IIA2 | 3 (2.4%) |
| IIB | 8 (6.5%) |
| IIIC | 24 (19.4%) |
| depth of cervical stroma invasion | |
| 1/3 | 35 (28.2%) |
| 2/3 | 34 (27.4%) |
| 3/3 | 55 (44,4%) |
| LVSI-positive | 56 (45.2%) |
| Sedlis criteria positive | 34 (27.4%) |
| high-risk factors | 33 (26.6%) |
| ontogenetic stage | |
| oT1 | 97 (78.2%) |
| oT2 | 27 (21.8%) |
| number of lymph nodes, median (IQR) | 37 (29–50) |
| number of positive lymph nodes, median (IQR) | 2 (1–3) |
| R1 resection | 1 (<1%) |
| uterine corpus involvement | 15 (12.1%) |

FIGO – International Federation of Gynecology and Obstetrics, IQR – interquartile range, LVSI – lymph-vascular space invasion, SD – standard deviation

was performed. After tLND, TMMR was proceeded. During that, fallopian tubes, uterine corpus, uterine cervix, vascular and ligamentous mesometria and at least upper third of vagina were removed. A frozen section for the TMMR specimen was omitted in most cases, except in cases of doubt about vaginal resection margins involvement. Ovarian preservation was considered in premenopausal women.

## Adjuvant treatment

Adjuvant chemotherapy without irradiation was recommended for node-positive patients. However, in the case of a single node metastasis, adjuvant therapy might be omitted. In cases of parametrial involvement, observation or adjuvant (chemo)radiation therapy was discussed with the patient. In the case of positive vaginal margins, close surveillance, re-excision (if possible), or adjuvant (chemo)radiotherapy was discussed. For other situations, no additional treatment was recommended.

## Follow-up

Patients underwent follow-up according to local guidelines or at the surgeon's discretion. Follow-up was performed every 3 months for the first two years and included examination by a gynecological oncologist and pelvic MRI or pelvic and renal ultrasonography. For cases with potentially higher recurrence probability, a CT scan was carried out during follow-up. From years two to five, semi-annual pelvic examinations and pelvic and renal ultrasonography were performed. After five years, patients were followed up annually or on a volunteer basis.

To define patient status, we retrieved data from the local health information system or contacted the patient directly if data were unavailable at the host institution. We classified tumor relapses as local (including any pelvic tissues), distant, or both. The primary outcome is disease-free survival (DFS), defined as the time from the surgery date to the relapse date. Secondary endpoints include histopathological characteristics, relapse pattern, and OS.

The Sedlis criteria were defined as positive if at least two of the following parameters were met: lymphovascular space invasion (LVSI), more than one-third of cervical stroma invasion, and tumor size greater than 4 cm. Patients were considered high-risk if at least one of the following factors was present: parametrial involvement, positive resection margins, or lymph node metastases.

Statistical analysis was performed using Microsoft Excel and IBM SPSS 26. Medians with interquartile range (IQR) and means with standard deviation (SD) are given for quantitative data. For survival analysis, Kaplan-Meier curves were drawn using SPSS. For comparison of survival data, a log-rank test was used.

## Results

A total of 179 patients who underwent TMMR for cervical cancer were identified in three institutions between February 2015 and June 2024 (Armenia – since 2015, Brazil – since 2020, Russia – since 2022). According to the exclusion criteria, we excluded 15 patients who received neoadjuvant chemotherapy, 11 patients who were operated on laparoscopically, 10 patients who received adjuvant radiation therapy, and 1 patient who had a neuroendocrine tumor. A total of 18 patients were operated on

**Tab. 3. Survival and relapse pattern.**

| FIGO stage | Number of patients, N (%) | Relapses, N (%) | Median follow-up, months | Relapse details |
|---|---|---|---|---|
| IB1 | 33 (26.6%) | 2 (6.1%) | 35 | 1 – adenosquamous carcinoma, pelvic relapse in 27 months after surgery, treated with surgery and EBRT, patient died in 9 months after relapse.<br>2 – squamous cell carcinoma, pelvic relapse in 5 months, treated with EBRT, patient died in 29 months after relapse. Both Sedlis-negative. |
| IB2 | 33 (26.6%) | 1 (3%) | 26 | 1 – endocervical adenocarcinoma, mesorectal lymph nodes and lung metastases in 9 months after surgery. Patient died in 10 months after relapse. Treatment with chemotherapy. Sedlis-negative. |
| IB3 | 18 (14.5%) | 2 (11.1%) | 28.5 | 1 – squamous cell carcinoma, 85 mm in diameter, pelvic relapse in 12 months after surgery, treated by chemoradiation therapy. Patient still alive without evidence of disease (3 years after relapse). Sedlis-negative.<br>2 – squamous cell carcinoma, 56 mm in diameter, mesorectal and retroperitoneal lymph nodes and liver metastases in 7 months after surgery. Patient died 8 months after relapse. Sedlis positive. |
| IIA1 | 5 (4%) | 1 (20%) | 36 | 1 – squamous carcinoma, mesorectum lymph nodes relapse in 14 months after surgery, treatment with chemoradiation therapy. Patient is still alive without evidence of disease (28 months after relapse). Sedlis negative. |
| IIA2 | 3 (2,4%) | 0 | 36 | – |
| IIB | 8 (6.5%) | 0 | 28 | – |
| IIIC | 24 (19.4%) | 4 (16%) | 31.5 | 1 – pelvic relapse in 19 months after surgery, treated by EBRT. Patient is alive without evidence of disease 8 months after relapse.<br>2 – distant metastases in 8 months after surgery. Patient is alive for 16 months after relapse, ongoing treatment (chemotherapy).<br>3 – pelvic relapse (probably, lymph nodes) in 7 months after surgery. Treated by chemoradiation therapy, without evidence of disease in 30 months after relapse.<br>4 – vaginal stump relapse in 2 months after surgery, treated by chemoradiation therapy. Patient died due to radiation therapy complications. |

EBRT – external beam radiation therapy, FIGO – International Federation of Gynecology and Obstetrics

in the last 6 months and were excluded. Therefore, 124 patients met the inclusion criteria and were included in the final analysis. The median follow-up was 29 months. Preoperative characteristics are listed in Tab. 1. According to FIGO 2018, 28.2% of patients had stage IB1, 37.1% had stage IB2, 21.8% had stage IB3, 4% had stage IIA1, 4% had stage IIA2, and 4.8% had stage IIB. Among them, 8 patients (6.5%) had enlarged lymph nodes considered metastatic. The median preoperative tumor size was 29.5 mm.

## Perioperative details

The mean operative time was 246 minutes (SD 66.4 minutes). The mean blood loss was 161 ml. Only the first line of lymph nodes was removed in 21% of cases; the first and second lines in 53.2%, and the first to fourth lines in 25.8% of cases. The median number of removed lymph nodes was 37. The mean length of hospital stay was 5.2 days. Postoperative complications of Clavien-Dindo grade III occurred in 5 cases (4%). Among them were 2 cases of ureteral injury that required stenting, 2 cases of wound dehiscence, and 1 case of bladder injury during self-catheterization. No Clavien-Dindo IV-V complications occurred in our cohort. Twenty-two patients (17.7%) received adjuvant chemotherapy.

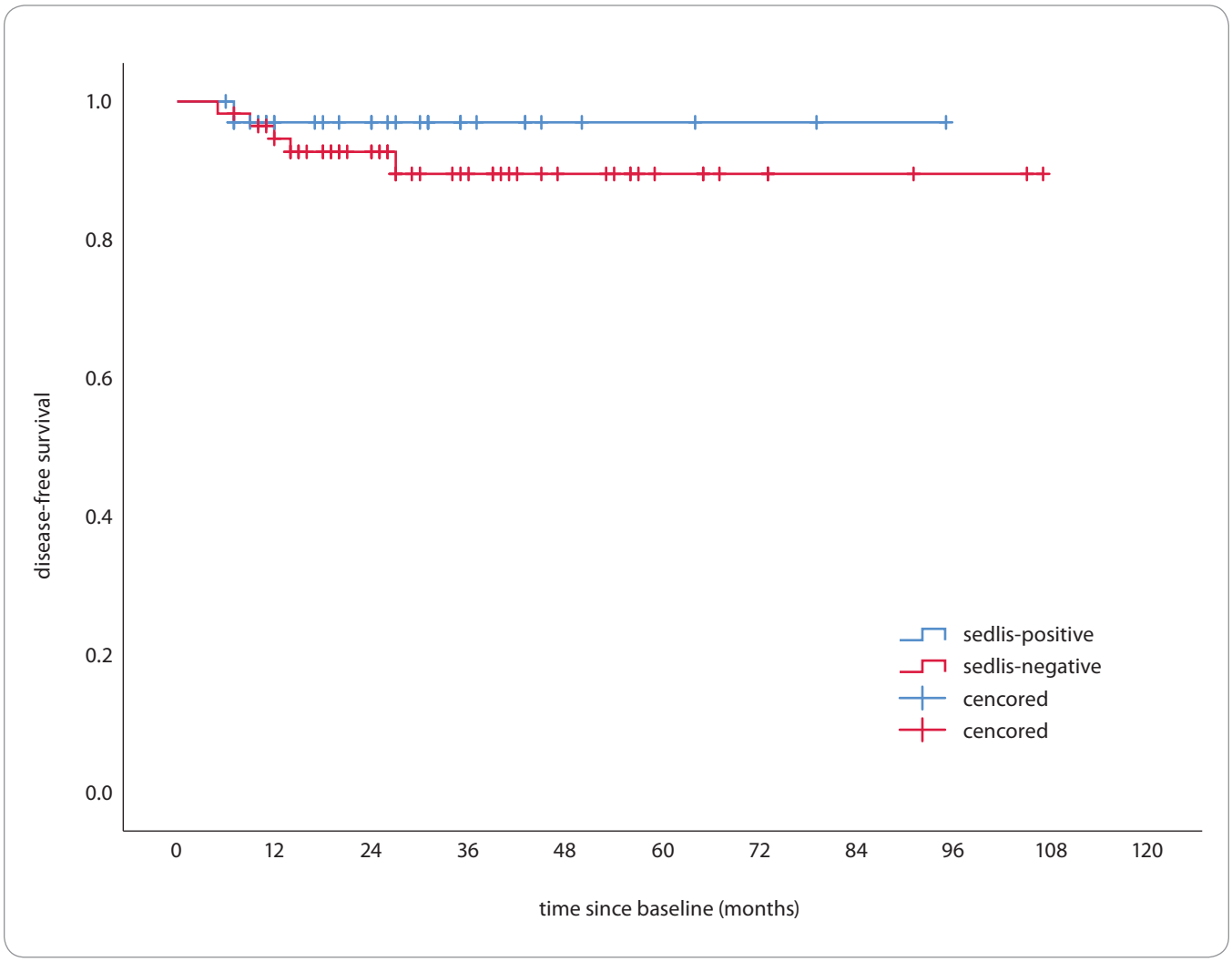
## Postoperative histopathological characteristics

The mean postoperative tumor size was 32 mm. Among the patients, 26% were staged as IB1, 26% as IB2, 14.5% as IB3, 4% as IIA1, 2.4% as IIA2, 6.5% as IIB, and 19.4% as IIIC. A total of 27.4% of patients met the Sedlis criteria, and 26.6% of patients were considered as a high-risk group. The median number of positive lymph nodes was 2.

## Oncologic outcomes

Overall, 10 relapses were observed (8.1%). The relapse rate was 6.1% (2 out of 33) for IB1, 3% (1 out of 33) for IB2, 11.1% (2 out of 18) for IB3, 20% (1 out of 5) for IIA1, and 16% (4 out of 24) for node-positive patients. No relapses were detected among IIA2 and IIB stages (3 and 8 patients, respectively). Detailed relapse specifications are listed in Tab. 3

Among 34 patients who met the Sedlis criteria with a median follow-up of 26 months, 1 patient experienced a re-




**Graph 1. Disease-free survival of high-risk negative patients with or without Sedlis criteria.**

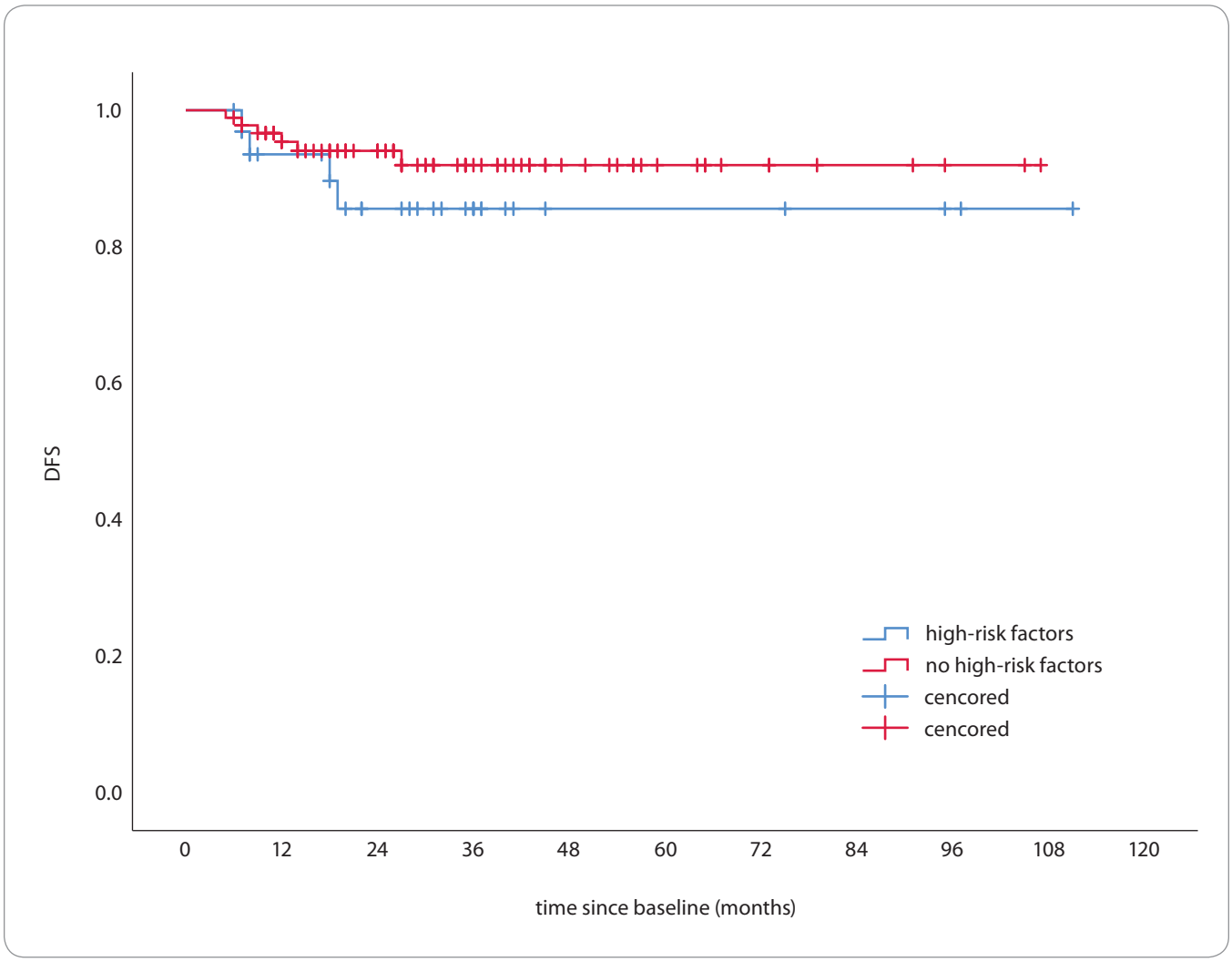
lapse (2.9%). In contrast, the relapse rate for patients without the Sedlis criteria and high-risk factors (57 patients) was 8.8% (5 patients, with a median follow-up of 30 months). There was no statistically significant difference in DFS (P = 0.36) (Graph 1). A total of 33 patients (26.6%) had high-risk factors and 4 relapses (12.1%) occurred in this subgroup. The median follow-up was 29 months. There were no statistically significant differences in DFS compared to patients without high-risk factors (P = 0.58) (Graph 2).

## Discussion

In this study, we present the first multicenter retrospective cohort of patients treated according to the cancer field theory through total mesometrial resection and therapeutic lymph node dissection with original protocol deviation. The main point was the omission of the intraoperative frozen section for every single case. In contrast, the extension of tLND was planned according to the preoperative tumor size and gross intraoperative findings. The overall relapse rate was 8.1%, despite the omission of radiation therapy. This result corresponds with previously published data [18,19].

We found no differences in DFS for patients with or without the Sedlis criteria. This finding aligns with data previously published by Cibula [4]. The omission of adjuvant radiation therapy in this group of patients does not appear to affect tumor control, but it may prevent overtreatment with life-long consequences.

The analysis of high-risk patients showed comparable results to the standard of care, with a 12.1% relapse rate in patients with metastatic lymph nodes, parametrial involvement, and R1 resection (vaginal margin). Interestingly, there were no relapses among the 8 patients who had stage IIB without lymph node metastasis. The main challenge relates to the preoperative evaluation of the extent of parametrial involvement, for which the therapeutic potential of TMMR may be adequate. For a patient with a positive vaginal margin, strict follow-up was selected, and no relapse was detected 26 months after surgery. Patients without node metastasis but classified as high-risk avoided any adjuvant therapy in the intention-to-treat cohort. However, patients who had lymph node




**Graph 2. Disease-free survival of patients with or without high-risk factors.**

metastasis received 6 cycles of carboplatin + paclitaxel chemotherapy to reduce the distant relapse rate. The rationale for this approach is based on the suggestion of a higher distant relapse rate than local relapse. However, there is no high-quality data to confirm this protocol.

Despite the promising results of TMMR and therapeutic lymph node dissection, we encountered several obstacles during the implementation of the procedure. First, the concept behind TMMR is based on a completely different approach to pelvic anatomy. Some terms (e. g., distal mesoureter or mesometria) might be misleading for gynecological oncologists, pathologists, and radiologists and require additional explanation in correlation with conventional anatomy [20]. Second, the learning curve is challenging but replicable. Despite the Buderath's study, none of the surgeons in this study operated under direct supervision by Höckel or his substitutes. Nevertheless, we maintained contact with the Höckel's team, especially during the learning curve. The fact that a portion of the patients included in the analysis were operated on during the learning curve may have negatively impacted the results. Third, some patients sought a second opinion at other centers and were assigned radiation therapy. Ten patients were excluded from the analysis because they chose to be irradiated after the decision-making process.

We emphasize that conducting a randomized controlled trial in this field is almost impossible. Cervical cancer has become relatively rare in gynecological surgery services even in developing countries. Consequently, only a few surgeons are dedicated to performing radical cervical cancer surgery. Modifying the operation technique is time-consuming, and it is challenging to standardize radical hysterectomy techniques without a surgeon who is experienced in other styles of surgery. Moreover, convincing an experienced surgeon to adopt a different type of surgery can be difficult.

## Conclusions

The preliminary results of our study are encouraging; however, longer follow-up and prospective data collection are necessary to gather stronger evidence concerning the oncological efficacy of TMMR.

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