

Original Article



OPEN ACCESS

Received: Aug 29, 2021

Revised: Sep 21, 2021

Accepted: Oct 28, 2021

Published online: Dec 6, 2021

Correspondence to

Paul Buderath

Department for Gynecology and Obstetrics,
University Hospital of Essen, Hufelandstraße
55, 45147 Essen, Germany.

E-mail: paul.buderath@uk-essen.de

Copyright © 2022. Asian Society of
Gynecologic Oncology, Korean Society of
Gynecologic Oncology, and Japan Society of
Gynecologic Oncology

This is an Open Access article distributed
under the terms of the Creative Commons
Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>)
which permits unrestricted non-commercial
use, distribution, and reproduction in any
medium, provided the original work is properly
cited.

ORCID iDs

Paul Buderath <https://orcid.org/0000-0003-0941-5635>

Maciej Stukan <https://orcid.org/0000-0003-2376-4663>

Wencke Ruhwedel <https://orcid.org/0000-0001-6265-0496>

Deivis Strutas <https://orcid.org/0000-0002-0926-9933>

Gabriele Feisel-Schwickardi <https://orcid.org/0000-0002-1449-2224>

Pauline Wimberger <https://orcid.org/0000-0002-2436-8673>

Rainer Kimmig <https://orcid.org/0000-0003-1118-2199>

Total mesometrial resection (TMMR) for cervical cancer FIGO IB–IIA: first results from the multicentric TMMR register study

Paul Buderath ¹, **Maciej Stukan** ², **Wencke Ruhwedel** ³, **Deivis Strutas** ⁴,
Gabriele Feisel-Schwickardi ⁵, **Pauline Wimberger** ⁶, **Rainer Kimmig** ¹

¹Department of Gynecology and Obstetrics, University Hospital Essen, Essen, Germany

²Department of Gynecologic Oncology, Gdynia Oncology Center, Pomeranian Hospitals, Gdynia, Poland

³Department of Gynecology and Obstetrics, Klinikum Gütersloh, Gütersloh, Germany

⁴Department of Gynecology, University Hospital Zürich, Zürich, Switzerland

⁵Department of Gynecology and Obstetrics, Klinikum Kassel, Kassel, Germany

⁶Department of Gynecology and Obstetrics, University Hospital of Dresden, Technische Universität Dresden, Dresden, Germany

ABSTRACT

Objective: The surgical concept of total mesometrial resection (TMMR) and therapeutic lymphadenectomy (tLNE) for the treatment of early cervical cancer is based on the ontogenetic cancer field model. Unicentric data show excellent locoregional control rates without adjuvant chemoradiation. However, there are so far no prospective, multicentric data supporting the method.

Methods: The multicentric TMMR register study was designed to answer the question whether the concept of TMMR+tLNE could be transferred to different centers and surgeons without compromising the outstanding oncologic results described in a unicentric setting.

Results: In 116 patients with cervical cancer stages IB–IIA, (International Federation of Gynecology and Obstetrics [FIGO] 2018), who underwent TMMR/tLNE, 25.0% were lymph node-positive. pT stages were pT1a in 3 patients (2.6%), pT1b1 in 82 (70.7%), pT1b2 in 18 (15.5%), pT2a in 4 (3.5%) and pT2b in 9 (7.8%). The overall recurrence rate was 7.8% in a median follow-up time of 24 months (6–80). Locoregional recurrences occurred in 6.0% of patients. One patient (0.9%) died from the disease during the observation period.

Conclusion: These are the first multicentric data on the surgical concept of TMMR and tLNE for the treatment of cervical cancer FIGO IB–IIA. We were able to reproduce the excellent oncologic data described for the method albeit with a relatively short median observation time. A randomized controlled trial seems warranted to definitely establish TMMR+tLNE as the method of choice for the treatment of early cervical cancer.

Trial Registration: ClinicalTrials.gov Identifier: [NCT01819077](https://clinicaltrials.gov/ct2/show/study/NCT01819077)

Keywords: Cervical Cancer; Operative Surgical Procedures; Lymphadenectomy; Recurrence

Trial Registration

ClinicalTrials.gov Identifier: [NCT01819077](https://clinicaltrials.gov/ct2/show/study/NCT01819077)

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Conceptualization: B.P.; Data curation: B.P.; Investigation: B.P., S.M., R.W., S.D., F.G., W.P., K.R.; Methodology: B.P.; Project administration: B.P.; Resources: B.P.; Supervision: B.P.; Writing - original draft: B.P.; Writing - review & editing: B.P., S.M., R.W., F.G., W.P., K.R.

Synopsis

Available data on total mesometrial resection and therapeutic lymphadenectomy (TMMR+tLNE) for the treatment of cervical cancer show excellent locoregional control rates without adjuvant chemoradiation. In 116 patients with cervical cancer stages IB–IIA the overall recurrence rate was 7.8% in a median follow-up time of 24 months. Locoregional recurrences occurred in 6.0% of patients.

INTRODUCTION

With more than 500,000 annual new cases and over 300,000 deaths per year, cervical cancer is still a major medical problem worldwide [1]. In Germany, the incidence of the disease has constantly decreased over the last 30 years due to improved genital hygiene as well as the implementation of cytology-based screening. For the future, a further decrease of invasive cervical cancer is expected due to the growing acceptance and ongoing development of the human papillomavirus-vaccine which is recommended in Germany since 2007. However, vaccination rates are still low in Germany and in 2017, 4,540 women were diagnosed with cervical cancer in Germany with 1,506 cancer related deaths [2,3].

The classification of cervical cancer follows the International Federation of Gynecology and Obstetrics (FIGO) classification from 2018 [4]. Standard treatment of early cervical cancer (FIGO stages IB and IIA) consists of radical hysterectomy following surgical staging of the pelvic lymph nodes. The aim of the procedure is the removal of the tumor with a circumferential wide margin of cancer-free tissue, preserving the adjacent bladder, ureters, rectum, and pelvic autonomic nerves [5,6].

In the case of lymph node metastases, the disease is usually considered not eligible for surgical treatment and it is recommended not to perform hysterectomy and opt for chemoradiation following pelvic and paraaortic lymph node staging. This strategy aims at avoiding trimodal treatment consisting of radical surgery as well as radio- and chemotherapy. However, also in node-negative patients, adjuvant radiotherapy is part of the standard treatment in the presence of risk factors such as lymph- or vascular space involvement, deep stromal invasion, tumor size >4 cm [7]. Evidence for the adjuvant irradiation to reduce pelvic recurrences stems from a randomized Gynecologic Oncology Group trial published in 1999 [8]. However, no evidence has been presented yet that radiotherapy following surgery prolongs overall survival (OS). Considering the significant side effects of pelvic radiotherapy and the still relevant morbidity of patients with early-stage cervical cancer there is a need to further advance therapy, not least in order to minimize treatment-related morbidity for the commonly young patients.

Cervical cancer originates in the cervical subcompartment of the embryologically determined Müllerian compartment. Compartments are derived from distinct precursor cell populations and after their determination organized in topographically defined structures limited by compartment borders which are rigidly controlled within the organism [9,10]. Current concepts of local tumor spread assume isotropic (randomly diffuse) propagation of cancer cells or cell clusters without respecting tissue borders.

However, this view is falsified by numerous clinical facts including the missing robustness of the surgical margin as predictor of local recurrence [11]. According to the ontogenetic cancer field model, local tumor spread is confined to permissive territories represented by the mature tissue derivatives of the stepwise development of the tissue from which the cancer originates. A subcompartment is the first, a compartment the next permissive cancer field during malignant progression [12].

The validity of the cancer field model has been proven by the spread patterns of hundreds of carcinomas of the lower female genital tract. On the basis of these findings the concept of ontogenetic local tumor staging and the techniques of cancer field surgery have been developed [13,14].

The anatomically distinct cancer fields are the tributary regions for topographically defined lymph node regions including both intercalated and basin nodes [15]. Taking the development of the regional lymphatic system into account first-, second- and third-line lymph nodes can be identified for corresponding cancer fields and selectively resected by therapeutic lymph node dissection.

The aim of different procedures of cancer field surgery is to achieve locoregional tumor control by complete resection of the cancer field and associated first-, second- and third-line lymph node regions of the individual cancer. In this concept, adjuvant irradiation is omitted. In 2001, Höckel [16] first described the cancer field-based surgical concept of total mesometrial resection (TMMR) with therapeutic pelvic and paraaortic lymphadenectomy (tLNE) for the treatment of cervical cancer. As Höckel points out, the surgical anatomy which builds the foundation for conventional techniques of radical hysterectomy represents preparation artifacts rather than developmentally defined anatomical structures [17].

In the most recent analysis, Höckel et al. [6] presented data from 523 patients with cervical carcinoma FIGO stage IB1 to IIB with a median follow-up of 61.8 months. In his cohort, 5-year disease specific survival was 89.4% (95% confidence interval=86.5–92.4) and recurrence-free survival was 83.1% (79.7–86.6). As the authors state, these results compare favorably to those of traditional surgery and adjuvant chemoradiotherapy, in the case of histopathological risk factors, and to primary chemoradiotherapy [18-20].

The surgical technique of TMMR has found a certain amount of followers in the gynecologic community but is still far from being able to be considered as standard. In a 2012 survey among German gynecologic surgeons, 13% reported to perform TMMR by laparotomy for the treatment of early-stage cervical cancer [21]. Robot-assisted TMMR was found to be practiced in a mere 0.5% of the participating centers.

The main criticism brought forth against the method is that of the strictly unicentric nature of the available oncologic outcome data. There are, however, to the best of our knowledge no multi-center prospective data on recurrence rates and survival after TMMR, an issue most likely hindering the more widespread acceptance of the method.

Therefore, in 2013 the multicentric TMMR register study (TMMR-RS) was started to answer the question whether the concept of TMMR+tLNE could be transferred to different centers and different surgeons without compromising the outstanding oncologic results described by the method's inventor. As it remains to be proven that Höckel's results represent the

superiority of the method rather than the craftsmanship of the surgeon, data from cervical cancer patients treated by TMMR at 7 European centers were prospectively collected and evaluated. We present here the first data on oncologic safety and morbidity of TMMR+tLNE in patients with preoperatively assumed cervical cancer FIGO stages IB–IIA.

MATERIALS AND METHODS

The multicentric TMMR-RS started to enroll patients in August 2013 and continues to do so to this day. A total of 15 centers were initialized for participation in the trial. However, 5 centers withdrew or did not enroll any patients, so that there are 10 active centers at the time of writing. Reasons for withdrawal were changes of personnel or a lack of resources for follow-up and documentation. Three centers recruited minimally-invasive cases exclusively and thus did not include any patients in the current analysis of open TMMR. A list of the active, enrolling centers included in this analysis is given in **Table 1**.

The study was approved by the local ethics committee of the University of Duisburg-Essen (ethical approval ID 12-5190 BO) and registered in the international register of clinical trials (ClinicalTrials.gov Identifier: NCT01819077).

1. Criteria for participating centers

In order to standardize treatment, requirements for participating centers included.

Study design

1. Didactic training: self-study of stepwise educational video how to perform the TMMR-procedure (Höckel M, Leipzig 2010; Kimmig R, Essen 2012).
2. Passed participation of 2-day educational training concerning TMMR at the “Leipzig School of Radical Pelvic Surgery”.
3. Performing at least 10 TMMR procedures at participating institution/year.
4. Evaluation of surgical technique at the participating institution by Höckel M (Leipzig) or Kimmig R (Essen) or substitute determined by them. Substitute had to be trained to perform TMMR by either Höckel M or Kimmig R.

Table 1. Cohort characteristics

Characteristics	Value
Age (yr)	48.9 (28–74)±11.8
BMI (kg/m ²)	25.8 (18–37.6)±4.6
Lymph nodes removed	54.4 (20–130)±19.6
Hb decrease (g/dL)	3.0 (0.1–7.1)±1.4
Length of stay (days)	10.6 (5–37)±4.6
Catheter time (days)	6.4 (1–51)±5.6
Residual urine at discharge (mL)	65.6 (0–600)±109.0
Name of center	
Essen	11 (9.5)
Köln	5 (4.3)
Dresden	6 (5.2)
Kassel	27 (23.3)
Zürich	16 (13.8)
Gütersloh	5 (5.2)
Gdynia	45 (38.8)

All values are given as mean (minimum–maximum)±standard deviation or number of patients included per center (%). BMI, body mass index; Hb, hemoglobin.

5. Securing standardized workup of the surgical specimen by pathologists according to the study protocol (Horn LC, Leipzig). The detailed protocol is available from the authors.
6. Acceptance of study participation by the responsible project leader and commitment of online documentation of primary histopathological and clinical data as well as follow-up data (when assessed).

The TMMR-RS was designed as a prospective multicentric register study. All patients gave fully informed consent prior to the procedure. Data were documented by the physician in charge on the data documentation forms handed out by the study coordinators. All data were pseudonymised prior to sending them to the central study unit in Essen.

Data assessed included preoperative characteristics of the patient and the tumor, intraoperative data such as route of surgery, skin-to-skin-time and blood loss, histopathologic results and data concerning postoperative morbidity.

All patients were asked to complete questionnaires on quality of life (QoL) (European Organization for Research and Treatment of Cancer–Quality of Life Questionnaire 30 [EORTC QLQ-C30] [22]), pelvic floor function (German Pelvic Floor Questionnaire [23]) and sexual function (Sexual Activity Questionnaire [SAQ] [24]) at baseline as well as during the structured follow-up.

All patients were instructed to undergo gynecologic oncologic follow-up every 3 months. Follow-up at the respective study center was performed at 6, 12 and 24 months after surgery and included an interview, pelvic gynecologic examination and the completion of the questionnaires mentioned above. Afterwards, patients were contacted once yearly for the assessment of survival and recurrence status.

Inclusion and exclusion criteria can be found below. Patients who received adjuvant irradiation were excluded from the study. However, adjuvant chemotherapy was allowed.

Inclusion criteria

1. Histologically proven cervical cancer: squamous cell carcinoma or adenocarcinoma; FIGO stages IB–IIA (preoperatively); Karnofsky-Index ≥ 70 ; unrestricted operability; body mass index (BMI) < 35 ; age ≥ 18 years.
2. Individual decision for treatment of TMMR and tLNE without adjuvant radiotherapy by the responsible clinic (clinician) on a clinical routine basis.
3. Informed consent of the patient.

Exclusion criteria

1. Neuroendocrine differentiation and all preoperative FIGO stage IA or > IIA.
2. Distant metastases except in paraaortic lymph nodes; scleroderma, lupus erythematosus, mixed connective tissue disease; secondary malignancy; previous radiotherapy of the pelvis.
3. Patients with diseases of the connective tissue will be excluded because of unforeseeable (e.g., neurological) symptoms and disorders after surgery. Patients with a BMI ≥ 35 will be excluded because of very high risks regarding wound healing, infections and thrombosis independent on the type of surgery.

2. Surgical procedure

TMMR and tLNE was performed according to the descriptions of the method by Höckel M and the according surgical videos [6,25]. The tLNE included complete pelvic lymphadenectomy. Paraaortic lymphadenectomy was only performed if pelvic lymph node involvement was proven by frozen section.

Upon designing the TMMR-RS, the decision about the route for surgery was left to the participating surgeon. Thus, patients operated via open abdominal, conventional laparoscopic as well as robotic surgery were enrolled in the study. However, after publication of the data from the Laparoscopic Approach to Cervical Cancer (LACC)-study, indicating higher recurrence rates after minimally-invasive surgery for cervical cancer [20], an interim-analysis of our own collective was performed concerning recurrence rates and surgical approach. Although follow-up data were still immature at the time, we observed a trend towards a higher recurrence rate in minimally-invasive procedures. Thus, enrollment of patients with minimal-invasive surgery was stopped in 2019 and open surgery was recommended to all participating centers. For the current analysis, we decided to focus on patients treated by laparotomy only, in order to 1) exclude the possible detrimental effect of minimally-invasive surgery on oncologic outcome irrespective of the surgical strategy and 2) obtain a cohort comparable to those of Höckel's publications, who performs TMMR+tLNE via laparotomy only.

RESULTS

1. Study cohort

Between August 2013 and November 2020, 133 patients were enrolled in the laparotomy arm of the TMMR-RS in 7 participating centers. Patients who demanded adjuvant (chemo) irradiation (n=4) were excluded from the analysis in order to assess the postulated optimal locoregional tumor control by the surgical procedure alone. Only patients who had a follow-up of at least 6 months available were included in the oncologic outcome analysis, resulting in the exclusion of another 13 patients.

Following these criteria, 116 patients from 7 centers were included in the final analysis. Patients' characteristics are presented in **Table 1**. Twenty-nine patients had lymph node metastases (25.0%). For the classification of the disease, the most recent version of the FIGO-classification (2018) was used [26]. In the preoperative clinical staging, 55 patients were classified as having FIGO IB1 disease, 35 patients FIGO IB2, 21 patients FIGO IB3 and 5 patients FIGO IIA1 (47.4%, 30.2%, 18.1% and 4.3%, respectively). Pathological workup revealed pT1a1 disease in 2 patients (1.7%), pT1a2 in 1 (0.9%), pT1b1 in 82 (70.7%), pT1b2 in 18 (15.5%), pT2a in 4 (3.5%) and pT2b in 9 (7.8%) women. As the subdivision into tumors smaller than 2 cm and 2 cm and larger in biggest diameter is not reflected in the current TNM-classification of pT1b disease, we analyzed this factor separately for pT1b disease. Forty-four tumors (44.0%) were smaller than 2 cm, 56 (56.0%) 2 cm and larger. Overall mean tumor size was 28.6 mm (3–73). Disease characteristics are summarized in **Table 2**.

The number of patients recruited per center ranged from 5 to 45 (**Table 1**). As is clear from the numbers, not all centers met the aim of including 10 patients per year. However, centers were kept in the study as long as they included and documented patients according to the study protocol.

Table 2. Disease characteristics

Characteristics	Value
FIGO stage	
IB1	55 (47.4)
IB2	35 (30.2)
IB3	21 (18.1)
IIA1	5 (4.3)
pT stage	
pT1a1	2 (1.7)
pT1a2	1 (0.9)
pT1b1	82 (70.7)
pT1b2	18 (15.5)
pT2a1	1 (0.9)
pT2a2	3 (2.6)
pT2b	9 (7.8)
Tumor size (in pT1b disease; cm)	
<2	44 (44.0)
≥2	56 (56.0)
Histological subtype	
Squamous cell carcinoma	91 (78.4)
Adenocarcinoma	24 (20.7)
Other	1 (0.9)
Nodal status	
pN0	87 (75.0)
pN1	29 (25.0)
Adjuvant chemotherapy	
Yes	24 (20.7)
No	92 (79.3)
Recurrence	
9 (7.8)	
Localization of recurrence	
Vaginal stump	3 (2.6)
Pelvis	4 (3.4)
Distant	2 (1.7)
Death	2 (1.7)

All values are given as total number (%).

FIGO, International Federation of Gynecology and Obstetrics.

2. Treatment-related morbidity

Intraoperative complications occurred in 2 cases (1.7%). In one case, an intraoperative bladder lesion occurred which could be managed surgically. The other intraoperative complication was a lesion of the diaphragm with consecutive pneumothorax during the application of the central venous catheter by the anesthesiologist.

Data on postoperative complications were available for all 116 patients. Thirty of these women experienced postoperative complications Clavien-Dindo grades \geq II (25.8%). Two of the complications occurring in our collective (1.7%) were grade IIIb: one patient experienced compartment syndrome of both lower legs and required surgical intervention. Another patient experienced pulmonary embolism and a postoperative intraabdominal hemorrhage treated by laparoscopic revision surgery. It should be mentioned however that 2 patients died in the postoperative period. One patient suffered myocardial infarction on the first postoperative day and cerebral infarction 2 days later. She died on the fifth postoperative day. The patient was 80 years old, had diabetes type 2, negative anamnesis for cardiac disease, performance status (PS) estimated for 0, and American Society of Anesthesiologists (ASA) II. The surgical treatment was applied to her because there was a prolapse of the cervix (Pelvic Organ Prolapse Quantification-3), that disabled planning and radical treatment with chemoradiotherapy. Another patient died of cardiac arrest 4 weeks after surgery. No autopsy

Table 3. Surgical morbidity

Characteristics	Value
Frequency and severity	
Intraoperative complications	2 (1.7)
Postoperative complications	
Total	40 (34.5)
Clavien-Dindo	
Grade I	10 (8.6)
Grade II	15 (12.9)
Grade IIIa	13 (11.2)
Grade IIIb	2 (1.7)
Frequency of the most common postoperative complications	
Positioning lesion	2 (1.7)
Thrombosis/embolism	1 (0.9)
Infection	11 (9.5)
Voiding disorder	20 (17.2)
Lymphedema	1 (0.9)
Other	5 (4.3)
Long-term morbidity (6–24 months)	
Persistent voiding disorder	10 (8.6)
Lymphedema	10 (8.6)

All values are given as total number (%).

was performed but pulmonary thromboembolism was regarded as the most probable cause of death. The patient was 72 years old, PS-1, ASA II, she suffered from diabetes mellitus type 2, hypertension, chronic renal disease, hyperlipidemia and anxiety/depression disorders. Both patients were not included into the oncologic analysis.

Among the less severe postoperative complications, the most common were voiding disorders (n=20; 17.2%) and infections, predominantly of the surgical site (n=11; 9.5%). Perioperative morbidity is summarized in **Table 3**.

Over the course of the first 24 months of follow-up, a detailed assessment of long-term morbidity was done at 6, 12 and 24 months after surgery. The most common long-term complications were bladder voiding disorders and lymphedema, each occurring in 10 patients (8.6%; **Table 3**).

3. Adjuvant therapy

No adjuvant irradiation was performed in the TMMR-RS. However, adjuvant chemotherapy was allowed at the discretion of the attending physician. Twenty-four patients (20.7%) received adjuvant chemotherapy with mostly platinum-containing regimens.

4. QoL

Baseline QLQ-C30 was available from 96 patients and revealed a mean global health score of 63.5. Over the course of the follow-up visits, QoL as measured by the QLQ-C30 gradually increased (6 months: 67.3; 12 months: 71.3; 24 months: 72.2).

The SAQ was completed by patients who were sexually active at the time of interrogation only. Eighteen patients refused to answer this questionnaire. Of the remaining 98 women, 35 (35.7%) reported to be sexually active before surgery. This rate increased until 12 months later (39/68; 57.4%). At 24 months after surgery, only 41 patients were evaluable regarding their sexual activity of whom 18 were sexually active (43.9%).

Table 4. Results of the EORTC QLQ-C30

Characteristics	V0 (n=94)	V1 (n=85)	V2 (n=69)	V3 (n=46)
Global health	63.48±22.89	67.28±19.34	71.28±18.07	72.20±19.19
Physical function	87.25±14.88	80.44±17.20	82.92±15.43	82.76±19.16
Role functioning	79.19±30.27	77.64±29.40	82.16±22.54	84.85±21.93
Emotional functioning	58.11±27.63	70.80±26.49	80.21±19.93	71.61±26.31
Cognitive functioning	83.58±22.81	90.16±69.83	89.39±16.74	86.20±20.56
Social functioning	75.35±28.70	79.19±25.50	84.27±23.02	81.43±28.30
Fatigue	31.74±25.56	32.31±25.28	24.94±19.75	32.65±25.97
Nausea/vomiting	4.56±10.72	6.07±16.80	3.57±12.00	5.11±12.13
Pain	20.47±24.47	25.64±27.44	17.37±21.63	16.74±22.76
Dyspnea	11.06±23.98	17.14±25.29	15.17±24.51	12.98±22.71
Insomnia	31.52±32.62	33.26±33.38	26.59±30.38	29.63±28.37
Appetite loss	18.70±29.35	12.03±19.61	8.04±18.27	2.87±9.40
Constipation	13.19±23.46	30.25±34.18	23.44±29.54	29.70±30.86
Diarrhea	10.35±19.48	3.41±10.05	2.80±10.88	10.13±20.96
Financial difficulties	15.56±25.09	20.03±28.86	16.38±28.09	15.91±29.61

Values are given as mean±standard deviation. V0: preoperative status; V1: 6 months after surgery; V2: 12 months after surgery; V3: 25 months after surgery.

EORTC QLQ-C30, European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire 30.

Table 5. Results of the SAQ

Characteristics	V0 (n=96)	V1 (n=86)	V2 (n=66)	V3 (n=41)
Sexually active	35/98 (35.7)	39/89 (43.8)	39/68 (57.4)	18/41 (43.9)
Pleasure	10.74±4.59	9.92±4.04	10.13±4.50	10.05±4.86
Discomfort	0.89±1.09	1.56±1.65	1.37±1.50	1.26±1.10
Habit	1.12±0.88	1.00±0.77	1.21±0.81	1.05±1.13

Values are given as number (%) or mean±standard deviation. V0: preoperative status; V1: 6 months after surgery; V2: 12 months after surgery; V3: 25 months after surgery.

SAQ, Sexual Activity Questionnaire.

Detailed results of the QLQ-C30 and SAQ are given in **Tables 4** and **5**.

5. Number and location of lymph node metastases

The mean number of removed lymph nodes was 54.4 (20–130). In the case of pN1 status, the number of involved lymph nodes ranged from 1 to 7 with a mean of 2.9.

6. Recurrences and survival

Follow-up time ranged from 6 to 80 months (median: 24 months). During this period, 9 recurrences were observed (7.8%). Stage-dependent recurrence rates were 0% (0/3) for pT1a, 9.0% (9/100) for pT1b and 0% for pT2a (0/4) as well as pT2b (0/9).

Recurrence rate for node-positive patients was 10.3% (3/29), in node-negative disease 6.9% of patients experienced a recurrence (6/87).

OS for the whole cohort and progression-free survival for node-positive and node-negative patients, respectively are given in **Fig. 1**.

Analyzing the patients who experienced recurrence, 7 (6.3%) recurrences can be classified as locoregional recurrences (3 vaginal recurrences, 4 pelvic recurrences) and 2 (1.8%) as distant metastases.

One patient experienced a recurrence at the left pelvic side wall which was treated by chemoradiotherapy. The patient survived free of recurrence until 2 years later when she refused to be contacted for follow-up.

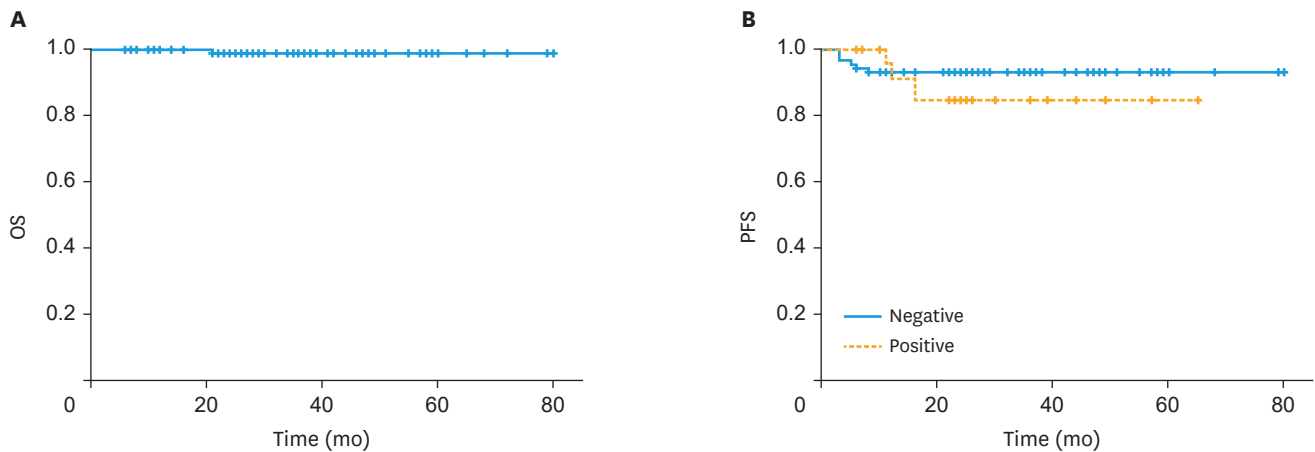


Fig. 1. (A) OS of the whole cohort and (B) PFS for node-negative and node-positive patients. Kaplan-Meier estimate. OS, overall survival; PFS, progression-free survival.

Another pelvic recurrence was diagnosed and treated at a third-party hospital from where no further information could be obtained.

The third pelvic recurrence occurred after 12 months of follow-up. Laparotomy revealed a tumor in the left pelvis, involving the internal iliac vessels, the ureter and infiltrating the wall of the sigmoid colon. The tumor was also fixed to the left pelvic wall and adherent to the musculus levator ani without infiltrating the muscle. A second tumor in the same patient was found on the promontorium, infiltrating the periosteum and the posterior wall of the common iliac vein. Both tumors were resected but free margins could not be achieved. Thus, postoperative irradiation is planned at the time of writing this manuscript.

The fourth pelvic recurrence, occurring 22 months after surgery, involved the right pelvic side wall and the bladder. Data on therapy and follow-up are missing.

Of the vaginal recurrences, one patient experienced a vaginal stump recurrence only 3 months after TMMR. She received salvage chemoradiotherapy and is currently without evidence of disease at 2 years follow-up.

The second vaginal recurrence was treated by total colectomy followed by radiochemotherapy. So far, the woman remained recurrence-free for 6 years afterwards.

The most recent case of vaginal recurrence occurred 6 months after TMMR and was treated by robotic radical partial colectomy. At the time of writing, the patient has just finished adjuvant chemoradiotherapy.

Of the patients experiencing distant recurrence, one woman was diagnosed with inguinal lymph node metastases and peritoneal recurrence involving the ascending colon mesentery 8 months after surgery. She was operated again, underwent a partial colectomy and right inguinal lymphonodectomy, complete surgical resection was obtained, she received adjuvant chemotherapy, however the disease progressed and the patient died 7 month after treatment of recurrence.

The second distant recurrence occurred in a patient who had periaortic lymph node metastases 16 months after surgery. Surgical resection was tried to perform but aborted due to inoperability. Chemoradiotherapy was administered but the patient died in the course of the disease.

DISCUSSION

We present here the first multicentric data on the concept of TMMR+tLNE for the treatment of cervical cancer.

Patients in the TMMR-RS showed very low rates of intraoperative and severe (Clavien-Dindo grades III and higher) postoperative complications. The total rate of postoperative complications was 34.5% including 25.8% moderate (Clavien-Dindo grades II and IIIa) scores. This is comparable to the rates Höckel presented in his most recent analysis (21% grade 2, 3% grade 3) [6]. Thus, abdominal TMMR compared favorably to data regarding treatment-related morbidity after radical hysterectomy [19]. In a recent nation-wide cohort study of 472 women treated by radical hysterectomy in the Netherlands, an overall perioperative complication rate of 35% was described [27]. Analyzing the influence of the surgical approach, the investigators found a complicative course in up to 73% of patients who underwent laparotomy.

Analysis of QoL revealed a significant improvement of the QLQ-C30 global health status from the baseline before surgery to the final assessment 24 months after TMMR. This result is well in line with the few data available of QoL after radical hysterectomy [28]. An analysis of QoL favoring TMMR in comparison to the Wertheim-Meigs procedure published in 2014 produced similar results for the TMMR group [29]. However, this is to the best of our knowledge the first study to evaluate the gradual improvement of QoL during the course of therapy and recovery.

So far, the unicentric data published by Höckel remain the only valid reference point for the oncological safety of TMMR [6]. Höckel was able to achieve a 5-year recurrence-free survival of 83.1% in his cohort of 495 patients treated by TMMR and tLNE for cervical cancer FIGO stages IB1 to IIB. The overall recurrence rate in our cohort was 7.8% after a median follow-up of 24 months. There are to our knowledge no large observational studies reporting the stage-dependent recurrence rates after treatment according to actual guidelines for cervical cancer patients. However, in the available literature the 5-year recurrence rate for cervical cancer FIGO stages IB to IIA is reported to be about 25% [18,19]. Although a longer observational period is definitely needed in order to compare these results to those of Höckel, the finding of only 7 locoregional recurrences and 1 death in 116 patients is very encouraging and hints at an excellent locoregional tumor control as postulated by the TMMR concept.

Moreover, none of the patients experiencing locoregional recurrences in our cohort died of the disease. Recurrences were treated by salvage radiotherapy and/or surgery. Those patients who were followed up for years after the recurrence remained free of disease following salvage therapy. This means that the toxicity of adjuvant radiotherapy could be avoided for the vast majority of patients and irradiation could be spared for those patients experiencing recurrence without compromising in terms of OS.

There are, however, limitations of our study. First of all, median follow-up in our cohort was 24 months, only. Thus, the data concerning oncological outcome are still immature. Especially in the recurring patients, observational time is not long enough to state if local

recurrences after TMMR could be cured by salvage therapy. Second, the number of patients is still low with only 116 women. This reflects several difficulties we experienced during the course of the study. First of all, the results of the LACC-trial forced us to concentrate on open abdominal surgery only, excluding about half of the patients already recruited from the analysis. Second, the relatively slow recruitment mirrors the challenge of motivating participants to perform extensive data documentation and follow-up without financial compensation.

In summary, these first multicentric data demonstrate an outcome comparable to that reported by Höckel for the treatment of women with cervical cancer FIGO IB–IIA by TMMR+tLNE. The multicentric TMMR study thus hints at a general reproducibility of the so far only unicentric data on the method. TMMR+tLNE is feasible also in a multicentric approach and achieves locoregional control rates superior to any established surgical concept. A randomized controlled trial would be needed now to draw a definitive comparison to the established treatment concepts for these patients. However, this will be very challenging to design as participating surgeons would have to master both procedures in equal quality. Moreover, surgeons who perform TMMR/tLNE will have serious ethical reservations against performing classical radical hysterectomy if the patient is randomized in the control arm.

REFERENCES

1. Cohen PA, Jhingran A, Oaknin A, Denny L. Cervical cancer. *Lancet* 2019;393:169-82.
[PUBMED](#) | [CROSSREF](#)
2. Robert Koch-Institut. Krebs in Deutschland 2013/2014. Berlin: Robert Koch-Institut; 2017.
3. Schneede P. One decade of HPV vaccination in Germany. *Urologe A* 2017;56:728-33.
[PUBMED](#) | [CROSSREF](#)
4. Saleh M, Virarkar M, Javadi S, Elsherif SB, de Castro Faria S, Bhosale P. Cervical cancer: 2018 revised International Federation of Gynecology and Obstetrics staging system and the role of imaging. *AJR Am J Roentgenol* 2020;214:1182-95.
[PUBMED](#) | [CROSSREF](#)
5. Landoni F, Bocciolone L, Perego P, Maneo A, Bratina G, Mangioni C. Cancer of the cervix, FIGO stages IB and IIA: patterns of local growth and paracervical extension. *Int J Gynecol Cancer* 1995;5:329-34.
[PUBMED](#) | [CROSSREF](#)
6. Höckel M, Wolf B, Schmidt K, Mende M, Aktas B, Kimmig R, et al. Surgical resection based on ontogenetic cancer field theory for cervical cancer: mature results from a single-centre, prospective, observational, cohort study. *Lancet Oncol* 2019;20:1316-26.
[PUBMED](#) | [CROSSREF](#)
7. Association of the Scientific Medical Societies in Germany (AWMF). Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): S3-Leitlinie Diagnostik, Therapie und Nachsorge der Patientin mit Zervixkarzinom, Langversion, 1.0, 2014, AWMF-Registernummer: 032/033OL [Internet]. Frankfurt am Main: AWMF; 2014 [cited 2016 Jun 27]. Available from: <http://leitlinienprogramm-onkologie.de/Leitlinien.7.0.html>.
8. Sedlis A, Bundy BN, Rotman MZ, Lentz SS, Muderspach LI, Zaino RJ. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: a Gynecologic Oncology Group study. *Gynecol Oncol* 1999;73:177-83.
[PUBMED](#) | [CROSSREF](#)
9. Wolpert L. Positional information and the spatial pattern of cellular differentiation. *J Theor Biol* 1969;25:1-47.
[PUBMED](#) | [CROSSREF](#)
10. Dahmann C, Oates AC, Brand M. Boundary formation and maintenance in tissue development. *Nat Rev Genet* 2011;12:43-55.
[PUBMED](#) | [CROSSREF](#)
11. Höckel M, Horn LC. The puzzle of close surgical margins is not puzzling. *Gynecol Oncol* 2013;130:224-5.
[PUBMED](#) | [CROSSREF](#)

12. Höckel M. Morphogenetic fields of embryonic development in locoregional cancer spread. *Lancet Oncol* 2015;16:e148-51.
[PUBMED](#) | [CROSSREF](#)
13. Höckel M, Hentschel B, Horn LC. Association between developmental steps in the organogenesis of the uterine cervix and locoregional progression of cervical cancer: a prospective clinicopathological analysis. *Lancet Oncol* 2014;15:445-56.
[PUBMED](#) | [CROSSREF](#)
14. Höckel M, Trott S, Dornhöfer N, Horn LC, Hentschel B, Wolf B. Vulvar field resection based on ontogenetic cancer field theory for surgical treatment of vulvar carcinoma: a single-centre, single-group, prospective trial. *Lancet Oncol* 2018;19:537-48.
[PUBMED](#) | [CROSSREF](#)
15. Yang Y, Oliver G. Development of the mammalian lymphatic vasculature. *J Clin Invest* 2014;124:888-97.
[PUBMED](#) | [CROSSREF](#)
16. Höckel M. Total mesometrial resection: nerve-sparing extended radical abdominal hysterectomy. *Zentralbl Gynakol* 2001;123:245-9.
[PUBMED](#) | [CROSSREF](#)
17. Cibula D, Abu-Rustum NR, Benedetti-Panici P, Köhler C, Raspagliesi F, Querleu D, et al. New classification system of radical hysterectomy: emphasis on a three-dimensional anatomic template for parametrial resection. *Gynecol Oncol* 2011;122:264-8.
[PUBMED](#) | [CROSSREF](#)
18. Landoni F, Maneo A, Cormio G, Perego P, Milani R, Caruso O, et al. Class II versus class III radical hysterectomy in stage IB-IIA cervical cancer: a prospective randomized study. *Gynecol Oncol* 2001;80:3-12.
[PUBMED](#) | [CROSSREF](#)
19. Landoni F, Maneo A, Colombo A, Placa F, Milani R, Perego P, et al. Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. *Lancet* 1997;350:535-40.
[PUBMED](#) | [CROSSREF](#)
20. Ramirez PT, Frumovitz M, Pareja R, Lopez A, Vieira M, Ribeiro R, et al. Minimally invasive versus abdominal radical hysterectomy for cervical cancer. *N Engl J Med* 2018;379:1895-904.
[PUBMED](#) | [CROSSREF](#)
21. Mangler M, Zech N, Schneider A, Köhler C, Marnitz S. Aspects of therapy for cervical cancer in Germany 2012 - Results from a survey of German gynaecological hospitals. *Geburtshilfe Frauenheilkd* 2013;73:227-38.
[PUBMED](#) | [CROSSREF](#)
22. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85:365-76.
[PUBMED](#) | [CROSSREF](#)
23. Baessler K, Kempkensteffen C. Validation of a comprehensive pelvic floor questionnaire for the hospital, private practice and research. *Gynakol Geburtshilfliche Rundsch* 2009;49:299-307.
[PUBMED](#) | [CROSSREF](#)
24. Thirlaway K, Fallowfield L, Cuzick J. The Sexual Activity Questionnaire: a measure of women's sexual functioning. *Qual Life Res* 1996;5:81-90.
[PUBMED](#) | [CROSSREF](#)
25. Höckel M, Horn LC, Fritsch H. Association between the mesenchymal compartment of uterovaginal organogenesis and local tumour spread in stage IB-IIB cervical carcinoma: a prospective study. *Lancet Oncol* 2005;6:751-6.
[PUBMED](#) | [CROSSREF](#)
26. Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri. *Int J Gynaecol Obstet* 2018;143 Suppl 2:22-36.
[PUBMED](#) | [CROSSREF](#)
27. Wenzel HH, Kruitwagen RF, Nijman HW, Bekkers RL, van Gorp T, de Kroon CD, et al. Short-term surgical complications after radical hysterectomy—A nationwide cohort study. *Acta Obstet Gynecol Scand* 2020;99:925-32.
[PUBMED](#) | [CROSSREF](#)
28. Plotti F, Terranova C, Capriglione S, Crispino S, Li Pomi A, de Cicco Nardone C, et al. Assessment of quality of life and urinary and sexual function after radical hysterectomy in long-term cervical cancer survivors. *Int J Gynecol Cancer* 2018;28:818-23.
[PUBMED](#) | [CROSSREF](#)
29. Sowa E, Kuhnt S, Hinz A, Schröder C, Deutsch T, Geue K. Postoperative health-related quality of life of cervical cancer patients - A comparison between the wertheim-meigs operation and total mesometrial resection (TMMR). *Geburtshilfe Frauenheilkd* 2014;74:670-6.
[PUBMED](#) | [CROSSREF](#)