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Cancer-field surgery for endometrial cancer by robotic peritoneal mesometrial resection and targeted compartmental lymphadenectomy (PMMR+TCL)

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ABSTRACT

Objective: Cancer-field surgery by peritoneal mesometrial resection and targeted compartmental lymphadenectomy (PMMR+TCL) for the treatment of endometrial cancer (EC) aims at optimal locoregional tumor control without the need for adjuvant radiotherapy. In a previous publication we could demonstrate the feasibility of the method and presented encouraging first oncologic data.

Methods: Following up our 2021 publication, we present data on the treatment of EC by PMMR+TCL in much larger cohort and with longer follow-up.

Results: One hundred and thirty-five patients with EC International Federation of Gynecology and Obstetrics (FIGO) I–IV (75.6% FIGO I) underwent cancer field surgery via PMMR+TCL for EC in the years 2016–2023. Mean follow-up in our cohort was 27.5 months (0, 83; 19.7). The procedure was feasible and safe with favorable intra-and postoperative complication rates. Even though 50.4% of patients had an indication for postoperative radiotherapy following national and international guidelines, the rate of postoperative irradiation administered was 10.4%. The overall recurrence rate was 8.1% and we observed 2 (1.5%) isolated locoregional recurrences.

Conclusion: Our results confirm the feasibility and safety of PMMR+TCL in EC patients. Oncologic data are very encouraging and hint at a superior locoregional control without adjuvant irradiation. Larger studies with longer follow-up will be needed to confirm these results.

Keywords: Endometrial Cancer; Cancer-Field Surgery; PMMR; Gynecologic Oncology, Sentinel Lymph Node Biopsy; Robot Surgery

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Synopsis

We present data on Cancer Field Surgery in Endometrial Cancer in a larger collective with longer follow-up. In a mean follow-up of 27.5 months the recurrence rate was 8.1%. Complication rates were low. We observed 2 isolated locoregional recurrences (1.5%). Our data hint at superior locoregional control without adjuvant irradiation by PMMR+TCL.

Author Contributions
Conceptualization: B.P, K.R.; Data curation: B.P., D.T.M.; Formal analysis: K.R.; Investigation: D.T.M.; Methodology: B.P., K.R.; Project administration: K.R.; Supervision: K.R.; Validation: D.T.M.; Writing - original draft: B.P.; Writing - review & editing: D.T.M., K.R.

INTRODUCTION

With 417,367 new cases in the year 2020, endometrial cancer (EC) is the 7th most common cancer in women worldwide and with around 11,090 newly diagnosed patients per year (forecast for 2020: 10,600), it is the most common female genital cancer entity in Germany [1,2]. The incidence of the disease is increasing worldwide [1], which can be mainly attributed to the increase of obesity, a major risk factor for EC [3,4]. With 97,370 cancer-related deaths in 2020 [1], there is a high medical need to develop optimal treatment strategies for EC patients.

Primary treatment of EC includes hysterectomy and bilateral salpingoopherectomy [5,6]. The indication for systematic pelvic and periaortic lymphadenectomy as well as adjuvant chemo- or radiotherapy depends on histopathologic and molecular risk factors. In recent years, sentinel-lymphadenectomy has been implemented as a treatment option in international guidelines [5].

We have previously published the concept and first results of cancer field surgery by peritoneal mesometrial resection (PMMR) and targeted compartmental lymphadenectomy (TCL) in EC [7-10], which will be briefly summarized below.

EC originates in the Müllerian Compartment. Organ-compartments develop from common precursor tissues and are topologically organized in defined structures—the so-called morphogenetic fields [11]. According to the ontogenetic theory, tumor growth is restricted to the tumor's compartment of origin for a long time. However, increasing malignant progression may facilitate tumor spread across compartment borders in the course of the disease [12,13]. The validity of this concept was demonstrated for cervical, vulvar and rectal cancer [14-16]. The same principles are valid with regard to the spread of tumor cells to the regional lymph vessels, which originate in the embryonal veins and thus belong to the tumor bearing compartment [17].

Cancer-field surgery aims at optimal locoregional control by complete resection of the tumor-bearing compartment ("cancer field"). For cervical and vulvar cancer, the techniques of total mesometrial resection and therapeutic lymphadenectomy and of vulvar field resection were developed and described on the basis of these concepts [18]. The uni- and multicentric data published so far convincingly support the expectation of excellent locoregional control without adjuvant irradiation [19-21].

In EC, removal of the cancer field requires complete resection of the Müllerian compartment except of the vagina including the regional draining primary lymph compartments containing the first line nodes. We published the resulting technique of PMMR by minimally invasive, robot-assisted surgery in 2013 [10]. Our group also introduced the technique of TCL which describes the removal of the sentinel nodes following and including the collector lymph vessel leading from the tumor site to the nodes. The technique will therefore be referred to as collector guided lymphadenectomy in future publications. First data including therapeutically intended systematic lymphadenectomy indicate excellent locoregional tumor control rates even without postoperative radiotherapy [7,9]. However, the collectives reported so far were small and the observational times short, limiting the validity of these findings. In this study we therefore present data on feasibility and oncologic safety in a much larger collective.

MATERIALS AND METHODS

Patients who underwent PMMR+TCL for the treatment of EC were identified from our institution's own clinical information system. According to our clinical practice all patients with suspected early-stage EC and no contraindication for myocardial infarction surgery were candidates for the procedure. All results were manually filtered. Perioperative data as well as patient and disease characteristics were collected from the electronic patient charts. The system was also sought for available follow-up information as a portion of our patients remains on routine follow-up at our clinic. Patients were then contacted to obtain actual information on survival and recurrence status.

All patients had received PMMR and pelvic TCL. Periaortic TCL was performed in cases with suspected deep infiltrating, G3 tumors. In the case of macroscopically suspicious lymph nodes these were also resected.

Postoperative complications were counted up to 30 days after surgery and classified according to the Clavien-Dindo classification of postoperative complications [22].

Tumor stages were defined according to the TNM/FIGO scoring modified in 2020 [6].

All statistical analyses were performed using the software SPSS 29.0 (IBM Corp., Armonk, NY, USA).

The study was approved by the local ethics committee (identifier 23-11394-BO).

RESULTS

A total of 135 patients underwent compartment-based surgery via PMMR+TCL for EC in the years 2016–2023. Mean follow-up in our cohort was 27.5 months (0, 83; 19.7).

pT-stage was pT1a in 77 patients (57%), pT1b in 35 women (25.9%), pT2 in 12 cases (8.9%), pT3a in 5 and pT3b in 6 patients (3.7% and 4.4%, respectively). One hundred two patients had FIGO I disease (75,6%), 7 FIGO II (5.2%) and 25 FIGO III (18.5%). One patient was upstaged to FIGO IV postoperatively (0.7%). Lymph nodes were involved in 16 patients (11.9%).

Histopathologic subtype was endometrioid adenocarcinoma in 115 cases (85.2%). Tumor grade was G1 in 62 cases (45.9%), G2 in 45 patients (33.3%) and G3 in 28 women (20.7%).

Mean age of our patients was 59.8 years (29, 89; 11.9), mean BMI 33.8 kg/m^2 (16.7, 83.7; 11.4).

Surgery could be completed minimally-invasively in all 135 cases, no conversion to laparotomy occurred. The intraoperative complication rate was 5.9% (8/135). Among intraoperative complications, lesions of the bowel were the most common with 6 cases. This included 5 cases of serosa lesions which could be sutured robotically by the gynecologic surgeon and one perforation of the colon transversum which required involvement of the general surgeon.

The mean skin-to-skin time was 189 minutes (98, 420; 65.4), mean length of stay 7.9 days (2, 119; 13.2). The mean number of harvested lymph nodes was 11.2 (2, 60; 9.6). In cases with

Table 1. Cohort characteristics

Characteristics	All	FIGO I/II	FIGO III/IV
Age (yr)	59.8 (29, 89; 11.9)	59.2 (29, 89; 12.2)	62.1 (44, 84; 9.9)
BMI (kg/m²)	33.8 (16.7, 83.7; 11.4)	34.4 (16.7, 83.7; 12)	31.6 (20, 50.7; 8.3)
Follow-up (mo)	27.5 (0, 83; 19.7)	28.4 (0, 83; 20.3)	24.1 (2, 75; 16.9)
Length of stay (day)	7.9 (2, 119; 13.2)	7.7 (2, 119; 14.1)	8.7 (3, 36; 8.6)
Skin-to-skin time (min)	189 (98, 420; 65.4)	176.2 (98, 420; 53.5)	242.9 (128, 415; 82.9)
Hb-decrease (g/dL)	−2.1 (−0.2, −5.9; 1.0)	−2.0 (−0.2, −4.6; 0.98)	2.6 (−0.9, −5.9; 1.0)
Lymph nodes harvested	11.2 (2, 60; 9.6)	9.3 (2, 44; 5.9)	19.2 (4, 60; 16.2)

Values are presented as mean (min, max; standard deviation).
BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; Hb, hemoglobin.

pelvic TCL only, a mean of 8.81 nodes (2, 28; 5.1) was resected. Cohort characteristics are summarized in **Table 1**.

Postoperative complications were observed in 18.5% of cases (25/135). Classification of complications according to the Clavien-Dindo Classification revealed the following distribution: 9 patients experienced complications of Clavien-Dindo grade 1, grade 2 complications were documented in another 9 cases. Five women had complications of grade 3. Grade 4 and 5 complications occurred in 1 case each: a 60-year-old woman who had a small bowel lesion which was diagnosed on the second postoperative day. She underwent immediate revisional surgery with lavage and repair of the lesion as well multiple revisional surgeries in the following weeks (Clavien-Dindo grade 4). Unfortunately, she developed a recurrence with disseminated peritoneal carcinosis which could not be adequately treated due to the above-mentioned complications and ultimately died on day 119 after surgery.

The grade 5 complication occurred in an 85-year-old patient who experienced pulmonary embolism which was treated by lysis therapy. Following this, she presented with extensive intraabdominal bleeding and underwent revisional surgery. She died on the intensive care unit on the third postoperative day. **Table 2** presents an overview of the complications observed in our cohort.

Lower grade postoperative complications were mostly voiding disorders, infections and thromboembolic events. A detailed overview of the types of complications is given in **Tables 3** and **4**.

Table 2. Perioperative morbidity

Variables	All	FIGO I/II	FIGO III/IV
Intraoperative complications			
No	127 (94.1)	102 (93.6)	25 (96.2)
Yes	8 (5.9)	7 (6.4)	1 (3.8)
Postoperative complications			
No	110 (81.5)	90 (82.6)	20 (76.9)
Yes	25 (18.5)	19 (17.4)	6 (23.1)
Clavien-Dindo grade			
0	110 (81.5)	90 (82.6)	20 (76.9)
1	9 (6.7)	6 (5.5)	3 (11.5)
2	9 (6.7)	8 (7.3)	1 (3.8)
3	5 (3.7)	3 (2.8)	2 (7.7)
4	1 (0.7)	1 (0.9)	0
5	1 (0.7)	1 (0.9)	0
Conversion to laparotomy			
No	0	0	0

Values are presented as number (%).
FIGO, International Federation of Gynecology and Obstetrics.

Table 3. Types of intraoperative complications

Complications	Frequency (%)
Bowel lesion	1 (0.7)
Isolated serosa lesion	5 (3.5)
Bladder lesion	1 (0.7)
Vessel lesion	1 (0.7)

Values are presented as number (%).

Table 4. Types of postoperative complications

Complications	Frequency (%)
Infection	5 (3.7)
Hematoma	2 (1.5)
Voiding disorder	4 (3.0)
Organ injury	1 (0.7)
Wound complications	1 (0.7)
Thrombembolism	4 (3.0)
Others	8 (5.9)

Values are presented as number (%).

To assess the effect of the concept of PMMR+TCL on the treatment strategy for EC patients, we compared the treatment patients received to the actual German S3- and ESMO-ESGO-ESTRO guideline recommendations. Patients who had an indication for adjuvant radiotherapy but did not receive irradiation due to the concept of cancer field resection were counted as "radiotherapy omitted".

Radiotherapy was spared in 54 women (40%). In total, only 14 women (10.4%) received postoperative radiotherapy, compared to 68 patients (50.4%) who had a recommendation according to actual guidelines.

Thirty out of the 135 women received adjuvant chemotherapy (22.2%). Adjuvant therapy is summarized in **Table 5**.

During the observational period, 11 women experienced a recurrence (8.1%). Two of these presented as isolated locoregional recurrences, the remaining 9 women developed distant metastases.

The 2 isolated locoregional recurrences are described in detail below: a 58-year-old patient with a pT1a, pN0, G1, L0, V0, R0 endometrioid adenocarcinoma (p53wt, L1CAM neg.)

Table 5. Adjuvant therapy

Adjuvant therapy	All	FIGO I/II	FIGO III/IV
Adjuvant radiotherapy according to guidelines			
No	67 (49.6)	67 (61.5)	0
Yes	68 (50.4)	42 (38.5)	26 (100.0)
Adjuvant radiotherapy received			
No	121 (89.6)	108 (99.1)	13 (50.0)
Yes	14 (10.4)	1 (0.9)	13 (50.0)
Adjuvant radiotherapy omitted			
No	81 (60.0)	68 (62.4)	13 (50.0)
Yes	54 (40.0)	41 (37.6)	13 (50.0)
Adjuvant chemotherapy			
No	105 (77.8)	101 (92.7)	4 (15.4)
Yes	30 (22.2)	8 (7.3)	22 (84.6)

Values are presented as number (%).
FIGO, International Federation of Gynecology and Obstetrics.

experienced a vaginal cuff recurrence 2.5 years after PMMR. She received a radical partial colpectomy with R0-resection and postoperative chemotherapy as well as irradiation. So far, no further recurrence or progression occurred in this patient.

Another woman with pT1b pN0 (0/14) G2 L0 V0 R0 endometrioid adenocarcinoma developed a vaginal cuff recurrence 19 months after PMMR. She received partial colpectomy with R0-resection as well. As postoperative histology revealed circumscribed peritoneal carcinosis of the bladder peritoneum, this patient received chemotherapy with carboplatinum and paclitaxel postoperatively.

One suspected locoregional recurrence turned out to be a secondary malignancy: a 36-year-old woman who suffered from endometrioid cancer pT1a pN0 (0/11) L0 V0 G1 R0 presented with a metastatic lymph node in the left internal iliac region 9 months after surgery which was resected robotically. Histopathology revealed a squamous cell cancer thus not concordant with the initial tumor type. Thorough examination did not reveal any primary so that the patients was treated as squamous-cell carcinoma of unknown primary. The patient developed disseminated lymph node metastases shortly after and is currently stable under immunotherapy with pembrolizumab.

Five out of the 135 patients had died at the time of analysis. In addition to the grade 4 and 5 complications described above these included one patient who died from metastatic disease and 2 women who died from other causes without any sign of recurrence. **Table 6** shows detailed information on disease characteristics an oncologic outcome.

We then performed analyses for FIGO stages I/II and III/IV separately.

Demographic data did not differ significantly between early and more advanced stages. Skin-to-skin time was longer in FIGO III/IV patients although this effect did not reach statistical significance (242.9 vs. 176.2 minutes). Significantly more lymph nodes were removed in advanced stages (19.2 vs. 9.3; p=0.003). The rates of intra- and postoperative complications did not differ significantly between groups. However, both the grade 4 and 5 complication did occur in FIGO I/II patients.

A significantly higher percentage of patients in the FIGO III/IV group had tumor grade G2/3 or non-endometrioid histology (p<0.001, respectively).

Adjuvant therapy showed significant differences between groups.

Of the 109 patients in FIGO stages I and II, only one woman received postoperative radiotherapy (0.9%). Forty-two of these women had a guideline-recommendation for adjuvant irradiation. Thus, radiotherapy was omitted in 41 patients (37.6%) in FIGO stages I and II.

In advanced stages, 13/26 patients received radiotherapy while all patients had an indication according to guidelines. Adjuvant chemotherapy was given in 7.3% of cases in stage I or II (8/109) and in 84.6% of cases in FIGO stages III or IV (22/26).

The overall recurrence rate in FIGO stages I/II was 3.7% (4/109). Out of these, 2 patients developed isolated pelvic recurrence (1.8%). In FIGO stages III/IV, the recurrence rate was 26.9%, all of which presented with distant metastases (7/26).

Table 6. Disease characteristics and outcome

Characteristics and outcome	All	FIGO I/II	FIGO III/IV
FIGO-stage			
FIGO I	102 (75.6)	102 (93.6)	0
FIGO II	7 (5.2)	7 (6.4)	0
FIGO III	25 (18.5)	0	25 (96.2)
FIGO IV	1 (0.7)	0	1 (3.8)
pT-stage			
1a	77 (57.0)	74 (67.9)	3 (11.5)
1b	35 (25.9)	28 (25.7)	7 (26.9)
2	12 (8.9)	7 (6.4)	5 (19.2)
3a	5 (3.7)	0	5 (19.2)
3b	6 (4.4)	0	6 (23.1)
Nodal status			
pN0	119 (88.1)	109 (100.0)	10 (38.5)
pN1/2	16 (11.9)	0	16 (61.5)
Histopathologic grading			
G1	62 (45.9)	59 (54.1)	3 (11.5)
G2	45 (33.3)	35 (32.1)	10 (38.5)
G3	28 (20.7)	15 (13.8)	13 (50.0)
Histopathologic subtype			
Endometrioid	115 (85.2)	100 (91.7)	15 (57.7)
Other	20 (14.8)	9 (8.3)	11 (42.3)
Periaortic nodes assessed			
No	109 (80.7)	96 (88.1)	12 (46.2)
Yes	26 (19.3)	13 (11.9)	14 (53.8)
Recurrence			
No	125 (91.9)	105 (96.3)	20 (73.1)
Yes	11 (8.1)	4 (3.7)	7 (26.9)
Distant metastases			
No	126 (93.3)	107 (98.2)	20 (73.1)
Yes	9 (6.7)	2 (1.8)	7 (26.9)
Isolated pelvic recurrence			
No	133 (98.5)	107 (98.2)	26 (100.0)
Yes	2 (1.5)	2 (1.8)	0
Death			
No	129 (95.6)	106 (97.2)	24 (88.5)
Yes	6 (4.4)	3 (2.8)	3 (11.5)

Values are presented as number (%).
FIGO, International Federation of Gynecology and Obstetrics.

DISCUSSION

We present here data on feasibility and safety of cancer-field surgery by PMMR+TCL for the treatment of EC in a cohort of 135 consecutive patients. With around 60 years, the mean age of our patients was slightly younger than described for the German population (68 years) [2]. Regarding cancer stages, 67% of patients are diagnosed in UICC stage I in Germany, compared to 75.6% in our cohort. These discrepancies are well explainable as the German cancer statistics includes all newly diagnosed EC cases in Germany whereas we only analyzed patients eligible for primary minimally invasive surgical treatment by PMMR+TCL, meaning only women with a preoperative stage of FIGO I and II. Postoperative upstaging occurred in the case of metastatic lymph nodes, or in one case the retrospective diagnosis of pulmonary filiae.

The low intraoperative complication rate of 5.9% and the fact that there were no conversions to laparotomy demonstrate the feasibility of robotic cancer field surgery in EC. Postoperative complications occurred in 18.5% of cases, 5.9% of patients had complications of Clavien-Dindo grade 3 and higher. These data seem very reasonable compared to the literature. In a

randomized controlled trial of laparoscopic vs. robotically assisted surgery including 99 EC patients, Mäenpää et al. [23] reported a rate of 10% major early complications in the robotic group. A retrospective cohort study of 1,433 women with a diagnosis of complex atypical hyperplasia and EC managed by minimally invasive hysterectomy and surgical staging by Barrie et al. [24] showed a postoperative complication rate (any grade) of 21.7% in the robotic cohort. In a retrospective cohort study of 12,283 patients who underwent hysterectomy for EC in the US in the years 2008–2014, Casarin et al. [25] reported a rate of 3.2% major complications in 7,737 women after minimally-invasive surgery. However, complications were not classified according to Clavien-Dindo in this publication. In the same study, surgery-related deaths were reported in 0.3% of cases. A Danish study from the year 2017 reported one surgery-related death in a cohort of 202 EC patients treated by robotic hysterectomy (5%) [26]. Though our cohort might be too small to draw definite conclusions on surgical mortality, the occurrence of one grade 5 complication in 135 women (0.7%) seems to be inside the expectable range. The question could be raised whether an average operative time of more than 3 hours is justified. However, operative time reported for conventional treatment of EC by hysterectomy and sentinel lymph node (SLN) differ greatly in the literature. In a study by Togami et al. [27], operative time was 204 minutes which is not much different from our study. In total, as morbidity is not increased and considering the oncologic results reported we don't consider this to be a major issue.

The overall recurrence rate in our cohort was 8.1%. In a 2006 review, Fung-Kee-Fung et al. [28] described a recurrence rate of 13% for EC of all risk stratifications. Other authors describe rates of 7%–15% for stage I–II EC [29]. In a population-based cohort study including 1,630 women, Akesson et al. [30] reported an overall recurrence rate of 8.3% for EC stages FIGO IA to IIIC treated in accordance with current guidelines. In early stages, recurrence rates ranged from 4.9% (FIGO IA) to 14.1% (FIGO II). The rate of postoperative irradiation (alone or with concomitant chemotherapy) was 31.8% in this study.

The stage-dependent recurrence rate for stage I and II disease was 3.7% in our cohort, comparing favorably to the treatment results reported above for the conventional treatment of early-stage EC. In the 26 women with stage III/IV disease, the recurrence rate in our cohort was 26.9%. A meta-analysis of 1868 patients with FIGO stage III EC which underwent radical surgery followed by either adjuvant chemotherapy or chemoirradiation reported recurrence rates of 34.9% and 27.6% respectively. Thus, overall as well as stage-dependent recurrence rates in our study are lower than reported in the available literature.

These favorable findings must be interpreted in the context of the adjuvant treatment administered: Only 10.4% of our patients received adjuvant radiotherapy, compared to a rate of 50.4% who would have been irradiated according to current guidelines. The abandonment of postoperative radiotherapy did thus not lead to a compromise in oncologic safety.

In stages I and II, 7.3% of our patients received adjuvant chemotherapy. A study by Jebens Nordskar et al. [31] including 108 patients undergoing robotic surgery and SLN mapping reported a 5-year recurrence-free survival of 98.9% in stage I, which is even lower than in our cohort. However, adjuvant chemotherapy was administered in 24% of women stage I in this study which raises the question of the role of adjuvant therapy in low-risk collectives.

However, with respect to the ontogenetically derived concept of cancer-field surgery the prevention of locoregional recurrence is the measure of surgical efficacy and proof of concept

at the same time. The locoregional recurrence rate was as low as 1.8% in stage I/II EC even though adjuvant radiotherapy was omitted in all patients but one. In comparison, a randomized controlled study of open vs. laparoscopic surgery in stage I EC reported a local recurrence rate of 15.8% and 5.0%, respectively even with adjuvant treatment administered in half of the cases [32]. A European multicenter study including 645 patients with FIGO IA, G1–2 tumors comparing intravaginal brachytherapy to observation reported vaginal recurrence rates of 3.1% and 1.2%, respectively in this low-risk population [33]. In intermediate/high-risk early-stage EC, a randomized controlled study of external beam radiation vs. no adjuvant therapy has reported locoregional recurrences in 3% and 6%, respectively [34]. Our data therefore hint at an excellent locoregional disease control by cancer field surgery without adjuvant irradiation.

It must be noted that the observational time was still rather short at 27.5 months. However, as most recurrences occur during the first 2 years after primary treatment, we don't expect a dramatic increase in recurrences with a longer follow-up time [35,36].

In conclusion, our findings demonstrate the feasibility and safety of PMMR+TCL and support the concept of cancer-field surgery for the treatment of EC. In contrast to the concept of hysterectomy and sentinel node excision it may spare adjuvant irradiation without compromising locoregional control. Larger, prospective trials will be needed to compare the ontogenetic approach to that of current guideline treatment of EC. Therefore we have initiated the prospective PMMR trial which is currently recruiting (NCT04504006).

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