Pelvic exenteration for recurrent or advanced gynecologic malignancies – Analysis of outcome and complications

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A B S T R A C T

Pelvic exenterations are known to be a last resort therapeutic option for advanced or recurrent gynecologic malignances, which are known to have poor prognosis.

All women treated with anterior (APE) or total (TPE) pelvic exenteration at our University hospital within a five-year period were identified and their data retrospectively analysed. Parameters such as demographic information, tumor type and stage, previous therapy as well as complication rate and overall survival were evaluated.

47 women were enrolled in this study. Most common indication for PE was cervical cancer (51.1%) followed by carcinoma of the vagina (17%), vulva (10.6%), endometrium (8.5%), ovaries (4.3%) and uterus (2.1%). Patients had received 1, 2 or 3 treatment modalities prior in 12.8%, 38.8% and 21.2% respectively. Predominant urinary diversion was ileum conduit (75.5%). Major complications (Clavien Dindo $\geq$ III) were observed in 40.4%, none in 19.2%. Early mortality was 4.3%. Median Overall Survival (mOS) was 14 months with 2- and 3-year survival rates of 38.8% and 21.2% respectively. After a median follow up of 47 months, 25.5% were still alive. Excluding patients with metastatic disease (n = 10), mOS was 20.6 months with 2- and 3-year survival rates of 46% and 35.2%. OS was significantly worse for patients with positive margins (p = 0.003). Receiving neoadjuvant treatment (25.5%) correlated with negative margins (p = 0.013) but not with overall survival.

PE is feasible with acceptable complication and mortality rates. The long-time benefit is notable bearing in mind the extensive nature of the malignancies and the procedure undertaken.

1. Introduction

Pelvic exenteration (PE) is a last resort operation for advanced or recurring pelvic malignancies. It can be categorized into anterior, posterior and total PE and consists of the radical en bloc resection of (female) reproductive organs in terms of the uterus, fallopian tubes, ovaries and if needed the vagina and vulva. It also entails the removal of adjacent arteries and veins, adherent ligaments as well as either bladder (APE) or rectum (PPE) or both (TPE) in case of tumor infiltration. When first published by A. Brunschwig in 1948, PE was performed as a palliative procedure with high morbidity and mortality rates. In these times, five patients out of 22 (23%) died postoperatively, which represents surgical mortality (Brunschwig, 1948). Over time, early mortality rates decreased due to medical improvements in the fields of preoperative staging, intraoperative patient care and surgical technique. In addition, postoperative treatments and overall cancer therapies, either neo-adjuvant or adjuvant, have changed drastically in the past decades, influencing overall survival after procedures such as PE. Most common gynecologic indication for PE is perceived to be cervical cancer – even

though its incidence has been decreasing gradually (de Gregorio et al., 2019). However, data published by PelvEx Collaborative covering 1293 cases of PE for non-rectal pelvic malignancies, show that beside bladder- and analcancer, most common indication for gynecologic PE was ovarian cancer followed by cervical, vaginal and endometrial cancer (PelvExCollaborative, 2019).

Nonetheless, PE remains a challenging procedure requiring a highly skilled interdisciplinary surgical team. It is rarely performed across the world which is mirrored by the mostly small cohort sizes and/ or wide time frame for analysis in the data published up to date. The aim of the present study was to obtain data especially on mortality and morbidity as a single "high-volume" institution study in order to assess factors influencing overall outcome following PE.

2. Methods

In order to conduct this study, patients who underwent PE at the Department of Gynecology and Obstetrics at University Hospital Marburg within a five-year period between April 2011 and June 2016 were

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identified if they had the documented procedure "exenteration". For this purpose, the German operation- and procedure-coding-system (OPS-Code) was used.

Data from initially 57 patients were retrieved and retrospectively reviewed. Those, who underwent posterior PE (n = 4) as well as those being operated due to an indication other than gynecologic malignancy (n = 3) such as vesicovaginal fistula, were subsequently excluded. Another three cases did not receive PE as such even though having the procedure "PE" noted, leaving 47 cases for final analysis.

Parameters for analysis were evaluated and categorized in pre-, intra- and postoperative. Demographic criteria such as age, body mass index, smoking status and ASA-Score (American Society of Anesthesiologists) were taken into consideration as well as previous treatment in case of recurring or persistent disease along with neoadjuvant intent. Furthermore, tumor features such as entity, histopathological classification in terms of TNM-staging system and grading were studied. Intraoperative parameters represented by length of surgery, intraoperative blood use, type of PE together with type of urinary diversion – in case of anterior or total PE – were taken into consideration. In addition, length of hospital stay along with admission to ICU were noted. Morbidity in regard to postoperative complications was assessed using Clavien Dindo classification (Dindo et al., 2004).

Additionally, a follow-up was conducted with data of Comprehensive Cancer Center Marburg (CCC) to estimate overall survival. All patients were treated exclusively at the University Hospital Marburg. All data were abstracted from patients' routinely reported documents (digital and archived) and anonymized in the process of data collection. Therefore, approval of the Ethics Committee of the Philipps University Marburg was not required according to the German Ethics Committee's regulations. Nevertheless, prior to admission/surgery/therapeutic treatment, patients signed an informed consent form stating that their data would be used for scientific purposes. This study was conducted in accordance with the principles of good clinical practice and the Declaration of Helsinki.

2.1. Statistical analysis

Data was collected using Microsoft Excel for Mac (Version 16.39) and statistically analysed with IBM SPSS Statistics for Mac OS (Version 27.0.0). For nominal variables, descriptive analysis was undertaken, and frequencies calculated. Continuous variables such as age and BMI were estimated using median, mean and range. Differences or correlations between patient groups were assessed using either chi-squared test or Spearman-Rho correlation.

Overall Survival was estimated using Kaplan-Meier Method whereby group differences were assessed with the Log-Rank (Mantel Cox) Test for statistical significance. Time of survival was defined as the time between date of surgery and either day of death or the day last seen by general practitioner or gynecologist. All statistical tests with a p value below 0.05 were deemed significant.

3. Results

3.1. Patient characteristics

A total of 47 patients underwent PE (APE or TPE) for gynecologic malignancies. The mean age across the cohort was 57 years (range 27 to 83 years; median 59.3 years) and median body mass index (BMI) was 25.1 kg/m² (range 15.1–35.7; see Tab. 1). Ten patients had a BMI of 30 or higher by the time PE was undertaken. 31.9% (n = 15) of the patients were smokers or past smokers, however smoking habits could not be assessed for a third of the cohort (n = 18). To evaluate patients' preoperative co-morbidities, the ASA Score was used. ASA Score II and III were assessed predominantly in 51.1% (n = 24) and 40.4% (n = 19) respectively (see Tab. 1).

In total, 72.3% of the cohort received a form of therapy prior to PE –

Table 1
Summarized patient data undergoing Ppelvic exenteration.

Variable	
Age (years)	
Median (mean)	59 (57)
Range	27–83
Body Mass Index (kg/m²)	
Median (mean)	24.6 (25.05)
Range	15.05–34.67
Histological grade	
G1	1 (2.1%)
G2	20 (42.6%)
G3	18 (38.3%)
G4	1 (2.1%)
Tumor type	
Cervical	24 (51.1%)
Vaginal	8 (17%)
Vuvla	5 (10.6%)
Endometrial	4 (8.5%)
Ovarian	2 (4.3%)
Uterus	1 (2.1%)
Others	3 (6.4%)
Tumor stage	
T0	1 (2.1%)
T1	4 (8.5%)
T2	7 (14.9%)
T3	13 (27.7%)
T4	20 (42.6%)
Positive lymph nodes	
N0	14 (29.8%)
N1and higher	16 (34%)
NX	16 (34%)
Positive margins	
R0	30 (63.8%)
R1	10 (21.3%)
R2	1 (2.1%)
Vascular space invasion	
V0	34 (72.3%)
V1	11 (23.4%)
Lymphovascular space invasion	
L0	27 (57.4%)
L1	18 (38.3%)
Distant metastasis	
M0	27 (57.4%)
MX	7 (14.9%)
M1	10 (21.3%)
Recurring disease	
yes	24 (51.1%)
no	22 (46.8%)

25.5% (n = 12) with neoadjuvant intent. Due to the cohort's heterogeneity, different therapy modalities were chosen. Overall, 21.3% (n = 10) received all three types of therapies (surgical, radio- and chemotherapy), another 38.3% (n = 18) received two types of therapies and 12.8% (n = 13) were treated with one modality before PE, leaving another 27.7% (n = 13) with no treatment beforehand therefore receiving primary PE. In total, 52.2% (n = 22) underwent PE due to recurrence, the other half (47.8%, n = 24) because of primary or persistent disease (see Tab. 2).

3.2. Tumor characteristics

The most common reason for PE was a carcinoma of the cervix (51.1%, n = 24), followed by carcinoma of the vagina (17%, n = 8), the vulva (10.6%, n = 5), the endometrium (8.5%, n = 4) and the ovaries (4.3%, n = 2). In one case, the tumor was dedifferentiated and could only be *assigned* to the uterus (2.1%). In three cases, two simultaneous cancer entities could be identified with one of them being gynecologic; another three underwent PE due to local gynecologic recurrence of a non-gynecologic entity (Anal-Carcinoma, Rectal-Carcinoma, Melanoma).

Regarding tumor size according to TNM staging system, a majority of the tumors was in a pT4 stage (42.6%, n = 20), followed by pT3 and pT2

Table 2

Perioperative data including complications after pelvic exenteration and urinary diversion.

Variable	
Type of pelvic exenteration	
anterior PE	28 (59.6%)
total PE	19 (40.4%)
Previous therapies	
No	13 (27.7%)
Yes	34 (72.3%)
If yes (n = 34)	
1	6 (12.8%)
2	18 (38.8%)
3	10 (21.3%)
Neoadjuvant treatment	
No	35 (74.5%)
Yes	12 (25.5%)
Adjuvant treatment	
No	21 (44.7%)
Yes	25 (53.2%)
Theater time (minutes)	
Mean	373
Range	400 (197–597)
Blood products given	
No	12 (25.5%)
Yes	35 (74.5%)
≤ 2	14 (29.8%)
>2	21 (44.7%)
Urinary Diversion	
Ileum Conduit	36 (76.6%)
Ureterocutaneostomy	8 (18%)
Nephrostomy (PCN)	1 (2.1%)
Pouch	2 (4.3%)
Postoperative complications	
No	9 (19.2%)
Yes	38 (80.8%)
If yes (n = 38)	
Clavien Dindo < III	19 (40.4%)
Clavien Dindo ≥ III	19 (40.4%)
Most common complications	
Urinary tract inf.	10 (21.2%)
Bacteria	5 (10.6%)
Candida	5 (10.6%)
Hydronephrosis	4 (8.5%)
Bowel obstruction	7 (14.9%)
Conservative	5 (10.6%)
Surgical	2 (4.3%)
Wound insufficiency	
VAC pump	4 (8.5%)
Total time hospitalised (days)	
Median (mean)	26 (28.53)
Range	55 (10–65)

stage (27.7%, n = 13; 14.9%, n = 4 respectively).

Approximately a third (29.8%) of the cohort had negative lymph nodes. N1 stage or higher was noted for another third (34%). Lymph node status could not be assessed (NX) in 16 cases (34%). Of those, 13 patients were treated for a recurrence and had received multiple treatment modalities such as radiotherapy or surgery before – 8 had undergone LNE at our institution in the past.

Negative margins were achieved in 63.8% of the cases leaving another 23.4% with positive margins. Unfortunately, margin status could not be assessed in 6 cases as this specific information was missing from the reports. PE was conducted in 21.3% (n = 10) of the cases with palliative intent as patients had distant metastasis present at the time of surgery. Of these, 3 patients had distant lymph node metastasis, another 2 had peritoneal carcinomatosis and one patient had pleura carcinomatosis. In 4 cases either liver or lung metastasis were at least suspected (cM1).

3.3. Surgical intervention

Anterior exenteration (APE) was performed in 59.6% (n = 28) of

cases and total pelvic exenteration in 40.4% (n = 19) of cases. Patients who received posterior PE (n = 4) were retrospectively excluded from this study design as no urologic-interdisciplinary surgery was performed. Infralevator exenteration including a gluteal flap plastic was performed in 2 cases (4.3%).

Mean surgical time was 373 min (range 197 to 597 min). In 74.5% blood transfusions were given perioperatively; in 29.8% a maximum of two packed red blood cells was transfused. Patients' hemoglobin measured pre- and postoperatively showed a significant decrease (p < 0.001) from a mean of 117.5 g/l (range 87–159 g/l) to 95.16 g/l (range 66–122 g/l).

Furthermore, a significant improvement in Creatinine could be shown dropping from 0.92 mg/dl (range 0.37–1.65 mg/dl) at the date of admission to 0.82 mg/dl (range 0.28–1.7 mg/dl) at the date of discharge. Median length of hospital stay was 26 days (range 10–65 days).

3.4. Urinary diversion

Ileal conduit was the most common choice for urinary diversion (76.6%, n = 36). In 17% (n = 8) an ureterocutaneostomy alongside with nephrectomy of the opposite site due to hydronephrosis and secondary loss of kidney function was performed – 7 of these patients were treated for cervical cancer. Two patients received a pouch (4.3%), in one case percutaneous nephrostomy was the only option (2.1%) because of far advanced ureter infiltration.

3.5. Complications

To evaluate complication rates, Clavien Dindo Classification was used to ensure comparability. Nine patients (19.1%) had no postoperative complications (Clavien Dindo 0). In 40.4% (n = 19) of cases minor complications occurred – classified as Clavien Dindo grade I or II (17% and 23.4% respectively). Another 40.4% suffered major complications, defined as those in need of surgical, endoscopic or radiological interventions.

Interventions performed without general anesthesia (Clavien Dindo III a) were needed in 8.5% (n = 4) compared to 25.5% (n = 12) of those under general anesthesia (III b). Clavien Dindo grade IV represents complications, which required ICU treatment due to single organ dysfunction (IV a, 2.1%, n = 1) or multi organ dysfunction (IV b, n = 0). Urinary tract infections, either due to bacteria or candida (10.6% each) were the most frequent complication as they occurred in 21.2% of the cases. Most common major complication was urinary tract obstruction treated with a percutaneous nephrostomy (8.5%, n = 4) as well as wound healing disorder treated with a vacuum assisted closure (VAC) pump (8.5%, n = 4). Both patients who received infralevator exenteration and a gluteal flap plastic suffered wound insufficiency that needed surgical intervention. Relaparotomies were necessary in 6 cases (12.8%).

Early morbidity represented as Clavien Dindo Grade V was 4.3% as 2 patients died within the first 30 days after surgery. Both patients had notable comorbidities. One patient had a history of thrombotic thrombocytopenic purpura and showed postoperative hemorrhage complications. Despite surgical re-intervention, the patient died due to E. coli sepsis, candidiasis of the lung and multiple arterial embolisms. In the second case the patient suffered a severe pulmonary embolism.

Looking at urological complications in particular, 7 patients presented with bowel obstruction (14.9%), which could be treated conservatively in 5 cases (8.5%; representing CD II) and operatively in 2 cases (4.3%). Two of these underwent TPE, the other 5 APE. Four patients (8.5%) developed hydronephrosis after surgery, which was treated with temporary percutaneous nephrostomy (CD III b).

No correlation (according to Spearman-Rho) could be found between minor or major complications and age divided into three equal groups (p = 0.132), a BMI below or above 30 (p = 0.717) or assessed ASA-Score

(p = 0.516).

Adjuvant therapy was administered in 53.2% (n = 25) of cases. Ten patients (21.3%) received chemotherapy, 8 (17%) received radiotherapy and 7 patients (14.9%) were treated with both modalities.

All patient data are summarized in table 1 and table 2.

3.6. Survival

Median Overall Survival (mOS) was 14 months (range 0.4–39.5 months) for the entire cohort. 2- and 3-year overall survival was 38.8% and 21.3% respectively (see Fig. 1). In total, 25.5% were alive by the time of follow up with a median follow-up period of 47 months.

Excluding patients with metastatic disease (n = 10), median OS increased to 20.6 months with an improved 2- and 3-year overall survival of 46% and 35.2% respectively (see Fig. 2). For those 10 patients with oligo distant metastatic disease a median overall survival of 6.1 months (range 0.5 to 11 months) was evaluated, which was significantly worse (p < 0.001) than the OS of patients without metastases.

Survival was significantly worse (p = 0.003) for patients with positive margins (mOS 6.8 months; range 0.4–39.5 months) compared to those with free margins (mOS 24 months; range 4–35.6 months; see Fig. 3). Achieving negative margins showed some correlation with receiving neoadjuvant therapy (p = 0.013). However, this observation did not remain significant regarding OS – no difference between patients, who received neoadjuvant therapy versus those who did not, could be found (p = 0.805).

Lymph node status could be assessed for 30 patients of whom 14 had negative and 16 had positive lymph nodes. Median OS for those with N0 was 28 months compared to that of patients with N1 which was 10 months (2/16 alive, 12.5%). This difference did not reach significance (p = 0.08; see Fig. 4).

There was no significant difference in OS concerning demographics such as age (divided into three equal groups, p = 0.816; age above 65 years (n = 13), p = 0.847)) and BMI over 30 (p = 0.819). Neither was there a significant difference between patients with relapsed versus primary disease (p = 0.822), between patients with none, one, two or three different previous therapy modalities before PE (p = 0.145), between patients with neoadjuvant therapy or without (p = 0.805), between patients with or without adjuvant therapy (p = 0.071), between patients with cervical, vaginal or vulva carcinoma (p = 0.653), between patients with tumor grading G2 versus G3 (p = 0.697), between patients with pT2 versus pT3 versus pT4 status (p = 0.365), between patients with lymphovascular space invasion and those without (p = 0.758), between patients with vascular space invasion and those without (p = 0.497), between patients with perineural space invasion and those

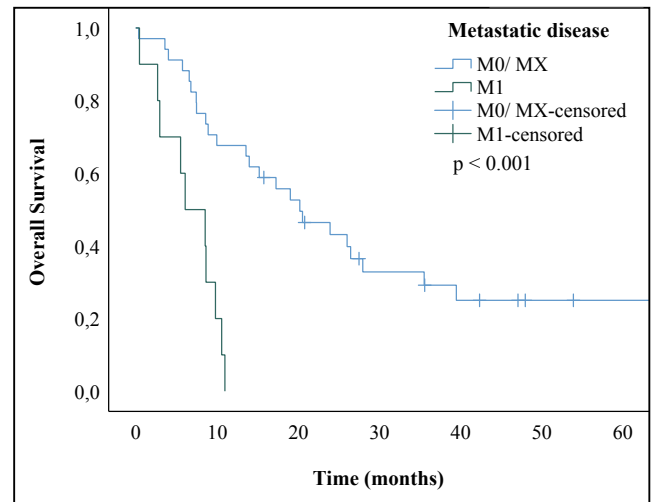Fig. 1. Overall Survival for the entire cohort.

Fig. 2. Overall Survival according to metastasis present at the time of PE.

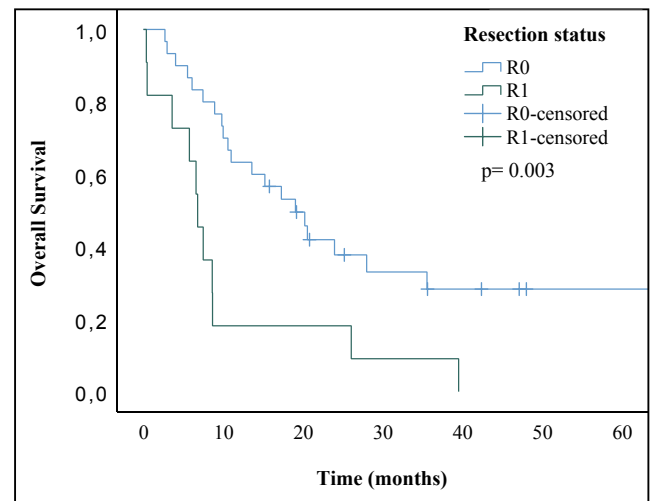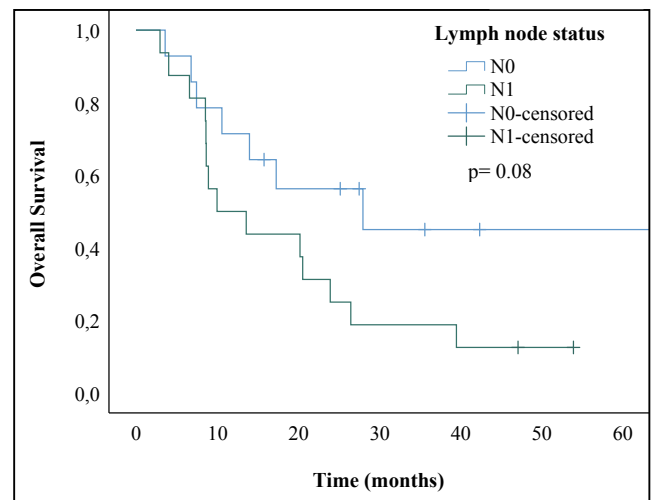Fig. 3. Overall Survival according to resection status.

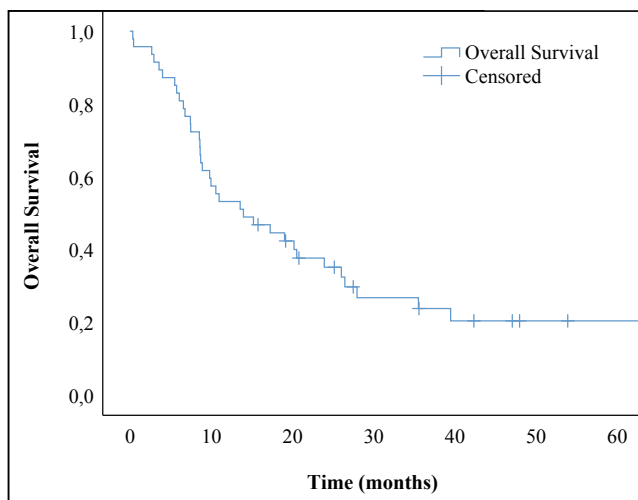Fig. 4. Overall Survival according to lymph node status.

without (p = 0.336) and between patients with a history of smoking vs non-smokers (p = 0.432).

Comparing OS for patients with an operation time longer than six hours, a significantly worse outcome was observed (p = 0.03) with a mOS of 10 months versus a mOS of 24 months. No correlation could be shown between operation and extent of complications (p = 0.207).

4. Discussion

Since first published in 1948 (Brunschwig, 1948), an attempt has been made to identify patients that would benefit most from PE (Brunchschwig and Daniel, 1960). However, to date no certain correlation could be found between demographic criteria such as age, BMI and comorbidities and complication rate or overall survival – neither in this study nor in others (Maggioni et al., 2009; Shingleton et al., 1989).

Central aim of this study was to evaluate morbidity in order to improve peri- and post-operative treatment. Applying the Clavien Dindo classification system (Dindo et al., 2004) ensures comparability, but – as most staging systems do – lacks a thorough assessment as patients often suffer concomitant complications. For instance, for a patient experiencing wound dehiscence treated with a VAC pump as well as urinary tract infection treated with antibiotics, only the higher rated complication would be noted within the classification.

Complication rate described in the current literature on PE differs greatly as some report that "nearly every patient experienced a complication" (Westin et al., 2014) whereas others stated that up to 62% of the cohort did not have any (de Gregorio et al., 2019). Most authors agree upon the conception that infection, mostly of the urinary tract or wound, make up for most of the complications (Berek et al., 2005; de Gregorio et al., 2019). In this series 21.2% of the patients experienced urinary tract infection, underlining the statement made above.

In our cohort, most common major complications calling for surgical intervention was wound dehiscence as well as postoperative hydronephrosis (8.5% each), which is in line with recent studies (Baiocchi et al., 2012; Chiantera et al., 2014; de Gregorio et al., 2019; Urh et al., 2013; Westin et al., 2014). Small bowel obstruction (10.6%) and symptomatic ileus with need of surgical intervention (4.3%) are also well-known complications of urinary diversions as reflected in our figures (Berek et al., 2005; Fotopoulou et al., 2010; Jäger et al., 2013). In our cohort, early mortality occurred in 2 cases, which is consistent with the data reported by other groups (0–5%) (Berek et al., 2005; Chiantera et al., 2014; de Gregorio et al., 2019; Kaur et al., 2012; Westin et al., 2014).

Many factors influence the choice of urinary diversion from which the patient would benefit most, such as the prior treatment received (surgical, radio- and/ or chemotherapy), patients' fitness and compliance as well as the risk of postoperative complications (Dessole et al., 2018; Westin et al., 2014). In our cohort 76.6% of the patients received an ileal conduit, which is in accordance with other studies (Chiantera et al., 2014; Goldberg et al., 2006; Urh et al., 2013). Striking a balance between reconstructive surgery, increased risk of postoperative complications, and patient satisfaction is not without its challenges. This is underlined by Goldberg and co-workers showing that 54% of patients who received a pouch experienced challenges in daily living. They report that patients would undoubtedly choose an ileum conduit, if the surgery could be repeated (Goldberg et al., 2006).

In addition, PE is performed to improve patients' chances of survival in the event of advanced pelvic carcinoma. Histopathological parameters influence survival significantly, especially in case of PE. Our date confirms that negative margin resection is the most consistent with an impact on overall survival. Also, neoadjuvant treatment correlated strongly with achieving negative margins. However, it did not correlate with overall survival. Landoni et al. observed similar findings in their study when comparing patients receiving up-front PE with those receiving neoadjuvant therapy (Landoni et al., 2013). A multicentric study that evaluated the outcome of 523 patients receiving PE due to gynecologic malignancies showed that neoadjuvant treatment was associated with improved survival for endometrial or ovarian cancer but worse survival for cervical cancer (PelvExCollaborative, 2019).

The presence of positive lymph nodes may also influence overall survival. Westin et al. showed that survival strongly correlated with lymph node status, which remained significant in multivariate analysis (Westin et al., 2014). This also has been reported by other groups (Fleisch et al., 2007; Maggioni et al., 2009; Seagle et al., 2016; Shingleton et al., 1989; Symmonds et al., 1975). In our study, lymph node status did not influence survival significantly, but a trend could be noted. The decision of offering PE to patients with positive lymph nodes may also be based on the prospect to extend life or to improve of quality of life, regardless of a curative intent (Rutledge and McGuffee, 1987).

This might also be valid for PE for women who presented with distant metastasis. It is difficult to compare present studies because *"palliative"* is defined differently by each author. A review of Guimarães et al. reported that 67% to 90% of patients voiced symptom relief or an improved quality of life following palliative PE (Guimarães et al., 2011; Höckel and Dornhöfer, 2006; McCahill et al., 2003; Stanhope and Symmonds, 1985; Symmonds et al., 1975).

For patients whose carcinoma is locally advanced, PE would offer a possibility of cure (Fleisch et al., 2007; Westin et al., 2014). This is reflected in our data with a median OS of 20.6 months and remarkable 2- and 3-year survival year of 46% and 35.2%, representing a real chance of long-term survival. Reported 5-year overall survival rates differ greatly within a range of 21% to 64% (Baiocchi et al., 2012; Benn et al., 2011; Berek et al., 2005; de Gregorio et al., 2019; Fleisch et al., 2007; Goldberg et al., 2006; Jäger et al., 2013; Kaur et al., 2012; Maggioni et al., 2009; McLean et al., 2011; Schmidt et al., 2012; Urh et al., 2013; Westin et al., 2014). Most likely, these differences occur due to very heterogenous study populations not only in terms of tumor entities but also in regard to patient selection. Schmidt et al. reported a 5-year survival rate of 64% for patients with cervical cancer, but they excluded patients with R1-resection (Schmidt et al., 2012). Goldberg et al. showed 5-year survival rates of 47% excluding patients with positive lymph nodes (Goldberg et al., 2006). Besides patient selection, different approaches to PE can lead to different results worldwide. Marnitz et al. conducted a study comparing these approaches in American and German clinics using a questionnaire (Marnitz et al., 2009). They found that in the case of cervical cancer, 43% of German clinics and none of American clinics offered PE to those with FIGO IVA stage cancer (Marnitz et al., 2009). Furthermore, PE was recommended in case of bladder and/ or rectum fistula by 61% of German clinics compared to 29% in the US (Marnitz et al., 2009). These results reflect on the different approaches to PE across the globe resulting in differing overall survival rates.

Because PE is an ultraradical procedure representing chance of survival but also negatively influencing Quality of Life, patients have to be counselled on the effects of PE (Nelson et al., 2018).

Limitations of our study are the monocentric and retrospective character, the relative short follow-up time and the consideration of various tumor entities including different previous therapies. However – given the extend and the challenging character for hospital staff involved as well as the limited number of patients suitable for PE - small retrospective studies like this one remain *viable* in order to understand pelvic exenteration as a last resort intervention for recurrent or advanced gynecologic malignancies with the goal to improve patient outcomes.

Author contribution

AH and UW conceptualized the project. AH administered and supervised, JB and LtG collected the data, LtG conducted statistical analysis and wrote the original draft, AH, UW and JB reviewed and edited the draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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