Microbiological characteristics of early and late infectious complications following total pelvic exenteration due to cervical cancer recurrence—the significance of infections in long-term outcomes

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Objective: We analysed microbiological results of early and late infectious complications following total pelvic exenteration (TPE) due to cervical cancer recurrence and evaluated the significance of infections in patient survival. *Methods*: A retrospective study was conducted on 13 out of 31 patients who had undergone TPE due to cervical cancer, from February 2013 to January 2018. *Results*: Early and late infections occurred in 7 (53.8%) patients and 6 (46.1%) patients, respectively. Superficial and deep surgical site infections (SSIs) were the only ones that appeared as early infections. Late infections, besides SSIs (4/13; 30.8%), also included urinary infections (2/13; 15.4%). The most frequently isolated microorganisms were *Enterococcus* spp. (9/28; 32.1%) and *Escherichia coli* (6/28; 21.4%). There was no resistance to vancomycin, teicoplanin and linezolid among *Enterocccus* spp. Among gram-negative rods, there was no resistance to meropenem and imipenem. We found three ESBL (extended-spectrum ß-lactamase) producers. Patients diagnosed with early deep SSIs had a shortened median overall survival (5.0 months vs. 11.5 months, $P = 0.03$). Patient survival was neither related to the occurrence of early superficial infections nor to late infections. *Conclusions*: Our results suggest that early, especially early deep, SSI may worse the prognosis of patients after TPE. The time of infection management after the operation should be especially intensified within 1 month after TPE.

Keywords

Cervical cancer recurrence; Total pelvic exenteration; Post-operative infections

1. Introduction

Total pelvic exenteration (TPE) is a radical surgical procedure most often performed in patients with cervical cancer recurrence [1]. Patients are qualified for surgery after taking into account risk factors, the likely extent of the surgery and the predictable benefits of this procedure [1, 2]. Despite pre-operative assessment, patients undergoing TPE are at higher risk for postoperative complications. Most studies reported approximately 44.0–80.0% prevalence of various postoperative complications after TPE [3–8], with infectious complications accounting for 10 to 23% [2, 3]. However, in some studies, in a selected group of patients, infections were as high as 40–50.0% [6, 9] as a result of overlapping of multiple risk factors. Among pre-operative factors, this applies to prior treatment and advanced tumour stage [3, 4, 10]. Advanced gynaecological malignancies damage natural barriers and predispose to infections with microorganisms inhabiting the female genitourinary tract [11]. Earlier treatment with cytotoxic chemotherapeutic agents disturbs the balance in the intestinal microbiome, damages the gastrointestinal mucosa barrier and facilitates the translocation of endogenous microorganisms colonising the gastrointestinal tract [11, 12]. As a consequence, the microbiome does not protect against colonisation with pathogenic microorganisms [13]. Similarly, previously applied radiotherapy causes tissue damage and increases the risk of complications after surgery [14]. Traditionally, TPE is performed with an open approach, with an extremely long operative time and requiring blood transfusion. Both the need for transfusion and the length of the operation are independent predictors of postoperative infectious complications [15, 16]. Infections following TPE occur within 30 days of surgery (early infections) and in the remote postoperative period, defined as late infections, usually with an indication of the observation period for 31–90 days after surgery [17]. Most often, infectious complications are surgical site infections (SSIs), including superficial SSI, deep SSI, organ/space SSI and pelvic abscesses, as well as urinary tract infections (UTIs) and, albeit less frequently, sepsis and pneumonia [18, 19].

Current literature on TPE often discusses the problem of postoperative infections; however, there are no detailed studies on the microbiological analysis of early and late infections and their importance in long-term treatment outcomes in patients with recurrent cervical cancer. Therefore, we analysed infections, aetiology, resistance to antibiotics and occurrence of multidrug-resistant microorganisms. Additionally, we evaluated an outcome analysis combining early and late

infectious complications and the survival outcome of patients following TPE due to cervical cancer recurrence.

2. Material and methods

2.1 Hospital setting and study design

The analysis was carried out at the comprehensive cancer centre in the Clinical Department of Gynecological Oncology of the Franciszek Lukaszczyk Oncology Center in Bydgoszcz, Poland, from February 2013 to January 2018. This retrospective study included patients who had been diagnosed with cervical cancer recurrence and had undergone TPE performed by an experienced multidisciplinary team led by an accredited gynecological oncologist. The inclusions criteria for TPE were: cervical cancer recurrence, the history of radical pelvic radiotherapy and the patient's consent to therapy. We included both patients who had recurrence after primary hysterectomy with adjuvant radiotherapy and patients who had recurrence after primary chemoradiation. The data were obtained retrospectively from the patients' medical records (demographic and clinical data, as well as mortality) and the microbiological laboratory database (culture results, antibiotics susceptibility, resistance mechanisms to antibiotics). Information on all patients who died after TPE was retrieved from the database of the Kujawsko-Pomorski regional office of the National Health System of Poland. All data were used to conduct the analysis. The 30-day mortality was defined as death occurring within 30 days after the day of TPE; the 90-day mortality was defined as death occurring within 90 days after the day of TPE.

2.2 Surgical procedure and antibiotic prophylaxis

All patients underwent laparotomy with midline incision. The scope of the total pelvic exenteration included the *en-bloc* removal of the bladder, partial or total resection of the vagina, removal of the uterus or the vaginal vault (in case of previous hysterectomy), removal of the rectum with or without the anus. Additionally, pelvic and/or paraaortic lymphadenectomy were performed. In all patients, the entrance to the pelvis was covered by an omental flap. The resection of the rectum was accompanied with terminal sigmoid colostomy. The following procedures were used for urinary tract diversion: ileocutanaous ureterostomy of Bricker, bilateral ureterocutaneostomy or bilateral nephrostomy. The type of the procedure was dependent on the subjective decision of the surgeon.

Perioperative glycaemic control was implemented to maintain a blood glucose level below 200 mg/dL, with the intent of avoiding severe hyperglycaemia. Antiseptic prophylaxis was carried out in accordance with the recommendation currently in force in our hospital. All patients received parenteral antimicrobial prophylaxis, which was started before they underwent surgery: cefamandole i.v. 2.0 g 8 dose, q 6 h or cephazolin i.v. 1.0 g or 2.0 g (only first dose depending on body weight), next dose 1.0 g, 6 doses, q 8 h, metronidazole i.v. 0.5 g, 6 doses, q 8 h and gentamicin i.v. 1.5 mg/kg, based on the dosing weight (single dose) intraoperatively (in case of

the need for additional prophylaxis), according to the current recommendation of the Hospital Infection Control Committee. In case of severe beta-lactam allergy, as an alternative to cephalosporin, clindamycin i.v. 0.6 g, 3 doses, q 8 h, was administered.

2.3 Infection confirmation

Infectious complications were analysed for the first 90 days following TPE. Surgical site infections (SSIs) including superficial SSIs, deep SSIs and organ/space SSIs including pelvic abscesses and others, such as bloodstream infections (BSIs), urinary tract infections (UTIs) and pneumonia, were registered and classified according to the current criteria of the Center for Disease Control and Prevention (CDC) [20]. All infections were microbiologically and clinically documented. The infections were defined as early ≤30 days after TPE or late >30 days and ≤90 days after TPE. Re-infections were defined as the presence of second and subsequent infections within 90 days following TPE.

2.4 Microbiological cultures, microbial identification and susceptibility test

The results of the microbiological identification and susceptibility assays were obtained from the microbiological laboratory to evaluate the microbiological background of early and late infections. All samples were analysed using routine microbiological methods. Detailed microbiological diagnostic is available as supplemental material.

Screening for ESBLs was performed by a double-disc synergy test (DDST) with disks containing cefotaxime, ceftazidime and amoxicillin with clavulanate [21]. Isolates were tested for the presence of carbapenemases by the boronic acid combined disc test (for KPCs), the synergy test with EDTA (for metallo-β-lactamases; MBLs) and discs with temocillin (for OXA-48-like carbapenemases) [22]. The ESBL-producing isolates were reidentified using matrix-assisted laser desorption/ionisation-time of flight mass spectrometry (IVD MALDI Biotyper Smart System, microflex LT/SH smart, Bruker Daltonik, Bremen, Germany) and examined by The Bruker MBT STAR-Cepha IVD Kit (Bruker Daltonik, Germany) for rapid cephalosporinase diagnostics.

2.5 Statistical analysis

Survival was analysed using Kaplan-Meier survival curves. The difference in patient survival between the studied groups was calculated using the log rank test; a *P*-value less than 0.05 was considered statistically significant. Statistical analysis was conducted using the MedCalc 11.4.2.0 software, MedCalc Software, Seoul, Republic of Korea.

3. Results

3.1 Patient characteristics, origin of the clinical samples, aetiology of infections, type of infection and microbial susceptibility

We identified 31 patients with cervical cancer treated surgically due to cervical cancer recurrence. Of these, 13 patients underwent TPE and formed the study group. Table 1 shows the demographic and clinical characteristics of the analysed patients.

Table 1. Demographic and clinical characteristics of patients (n = 13).

Characteristics	Number of patients	%
Age [years], mean, ± SD, range	55.0 ± 11.0 (37–76)	—
BMI [kg/m^2], mean, ± SD, range	27.3 ± 7.1 (14.4–42.6)	—
FIGO stage at diagnosis		
- IIB	2	15.4
- IIIB	2	15.4
- IVA	7	53.8
- IVB	2	15.4
Diabetes mellitus	1	7.7
Monorenal	1	7.7
Previous treatment	13	100
- radical hysterectomy	1	7.7
- hysterectomy followed by CHTH + RTH	1	7.7
- hysterectomy followed by RTH	2	15.4
- RTH	3	23.1
- radical CHTH + RTH	6	46.1
DFS after primary treatment		
- ≤2 years	3	23.1
- >2 years	8	61.5
- unknown	2	15.4
ASA ≥III	9	69.2
Prophylactic perioperative antibiotics	13	100.00
- metronidazole in combination with cephazolin or cefamandole and gentamycin[1]	12	92.3
- metronidazole in combination with clindamycin	1	7.7
Complicated postoperative course (infectious)		
- early infectious complications (≤30-days following TPE)	7	53.8
- late infectious complications >30-days and ≤90-days following TPE)	6[2]	46.2
Mean operative time [min.]	387 [280–565]	—
Pathology subtype		
- squamous carcinoma	6	46.2
- adenocarcinoma	7	53.8
Margin status		
- negative	11	84.6
- positive	2	15.4
Mean stay ICU [days]	2.0	—
Blood transfusion	10	76.9
- mean units of packed red blood cells transfused	2.9	—
Fresh frozen plasma	5	38.5
Median length of hospital stay [days]	17 [8–44]	—
- hospital stay >28 days	2	15.4
30-days mortality	0	0.0
90-days mortality	1	7.7

[1] gentamycin was administered in case of suspected leakage of intestinal contents into the peritoneal cavity, [2] three of these patients experienced also early infectious complications.

ASA score, operative risk score of the American Society of Anesthesiologists; BMI, body mass index; RTH, radiotherapy; CHTH, chemotherapy; TPE, total pelvic exenteration; ICU, intensive care unit; DFS, disease-free survival; FIGO, International Federation of Gynecology and Obstetrics.

Patient characteristics according to the type of infections and the corresponding aetiological agents of infections are shown in Table 2.

A total of 79 samples of bacterial and fungal cultures, from 13 patients, were analysed for the first 90 days following TPE. Samples were taken from the surgical site (n = 62; 78.5%), the urinary tract (n = 9; 11.4%) and the blood (n = 2; 2.5%); clinical materials collected from other sites were n = 6 (7.6%). For further analysis, only first positive material from first and next episodes of infection was taken. Thus, 11 positive cultures from surgical sites and two cultures from urine were analysed in detail. As a result, a total of 26 bacterial strains, consisting of *E. coli* (n = 6), *E. faecalis* (n = 6), *E. faecium* (n = 3), *Proteus mirabilis* (n = 3), *Pseudomonas aeruginosa* (n = 2),

Table 2. Types and aetiological agents of infections in patients treated with total pelvic exenteration due to cervical cancer recurrence.

Type of infection	Patients (n)	(%)	Mean time to infections	Aetiological agents of infections
Early infection				
Any type	7	53.8	8 days (range 3–24)	
Superficial surgical site infection	1	7.7		*E. faecium (1)*
Deep surgical site infection	6	46.1		*E. coli ESBLs+ (1)*
				E. coli (1)
				K. pneumoniae ESBLs+ (1)
				P. mirabilis (2)
				P. aeruginosa (1)
				E. faecalis (3)
				E. faecium (1)
				F. nucleatum (1)
				B. fragilis (2)
				C. albicans (1)
Wound infection	7	53.8		*E. coli ESBLs+ (1)*
				E. coli (1)
				K. pneumoniae ESBLs+ (1)
				P. mirabilis (2)
				P. aeruginosa (1)
				E. faecalis (3)
				E. faecium (2)
				F. nucleatum (1)
				B. fragilis (2)
				C. albicans (1)
Other	0	0	—————————	—————————
Late infection				
Any type	6	46.1	47 days (range 40–61)	
Superficial surgical site infection	1	7.7		*E. faecium (1)*
Deep surgical site infection	3	23.1		*E. coli (3)*
				E. coli ESBLs+ (1)
				P. mirabilis (1)
				P. aeruginosa (1)
				E. faecalis (3)
				B. uniformis (1)
				F. magna (1)
				C. albicans (1)
Wound infection	4	30.1		*E. coli (2)*
				P. mirabilis (1)
				P. aeruginosa (1)
				E. faecalis (1)
				E. faecium (1)
				B. uniformis (1)
				F. magna (1)
				C. albicans (1)
Other[1]	2	15.4		*E. coli ESBLs+ (1)*
				E. coli (1)
				E. faecalis (2)

[1] Urinary tract.

ESBLs, extended spectrum ß-lactamases.

Klebsiella pneumoniae (n = 1), *Bacteroides fragilis* (n = 2), *B. uniformis* (n = 1), *Fusobacterium nucleatum* (n = 1) and *Finegoldia magna* (n = 1) and 2 strains of yeast-like fungi, *Candida albicans,* were analysed. The occurrence of microorganisms depending on the time of the onset of infections is presented in Fig. 1. We did not notice any significant differences in the diversity of microorganisms depending on the time of appearance of the infectious complications. Seven (53.8%)

patients were diagnosed with early infections, whereas six (46.1%) experienced late infection, of whom three patients (3/13; 23.1%) presented re-infection. Early infections concerned only the site, whereas late infections, apart from the surgical site, also included urinary infections. All surgical site infections were wound infections. We did not observe pneumonia, BSIs and pelvic abscess among the analysed patients. Concerning three patients who presented re-infections, in one patient, it was deep-wound infection first and then UTI; two patients experienced deep wound infections twice within 90 days after TPE. The types of the infection, according to the site of the infection and the time of the occurrence, are summarised in Table 2.
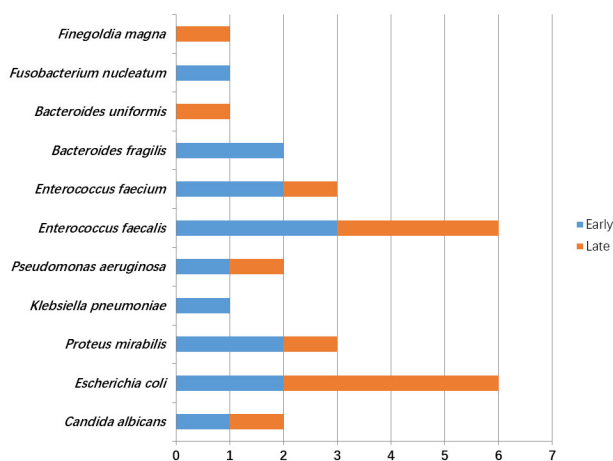

Fig. 1. Occurrence of microorganisms depending on the time of the onset of infection. Aetiological agents of early and late infectious complications (X axis—number of isolates).

The most frequently isolated microorganisms were *Enterococcus* spp. (9/28; 32.1%) and *E. coli* (6/28; 21.4%). Among the less frequently isolated microorganisms were *P. mirabilis* (3/28; 10.7%), *P. aeruginosa* (2/28; 7.1%) and *K. pneumoniae* (1/28 3.6%). Polymicrobial infections accounted for the majority of the cases and were confirmed in 8 cases in 7 out of 10 patients (70.0%). Concerning mixed SSIs, apart from *E. coli* and *Enterococcus* spp., *P. mirabilis* was a reported cause of SSIs in three cases of these infections among two patients, and *P. aeruginosa* in two cases in two patients. Mixed infections caused by both aerobic and anaerobic species were also confirmed. Anaerobic bacteria of the genera *Bacteroides, Fusobacterium* and *Finegoldia* were isolated in three patients. In two patients, growth of yeast-like fungi of the genus *Candida* was observed. Urinary infections were caused by two microorganisms, *Enterococcus* spp. and *E. coli*. In two patients, ESBL-positive infections were confirmed.

Among the 12 examined aerobic, gram-negative bacilli, 33.0% (4/12) were susceptible to ciprofloxacin. For the third-generation cephalosporins, susceptibility rates to ceftazidime and cefotaxime were 67.0% (8/12) and 58.0% (7/12), respec-

tively. For the fourth-generation cephalosporins, the susceptibility rate was 67.0% (8/12). Susceptibility to piperacillin-tazobactam was observed at a rate of 67.0% (8/12). Susceptibility rate to carbapenems was 100% (12/12) for meropenem; none of the isolates was resistant to imipenem, excluding characteristics such as an intrinsically low activity of imipenem against *P. mirabilis.* None of the tested isolates produced carbapenemases. More than four-fifths of the isolates were susceptible to gentamycin and amikacin (10/12; 83.0% for each).

One *K. pneumoniae* isolate (1/1) and two *E. coli* isolates (2/6) were ESBL producers. The presence of cephalosporinase activity in ESBL producers was confirmed by mass spectra.

Concerning only ESBL-producers, the examined strains were fully resistant to third-generation cephalosporins (cefotaxime and ceftazidime), fourth-generation cephalosporins (cefepime) and fluoroquinolones (ciprofloxacin). The isolate *K. pneumoniae* was also resistant to piperacillin-tazobactam. Other analysed resistance mechanisms were not detected.

Among aerobic gram-positive cocci, we isolated only *Enterococcus* spp., which showed no resistance to vancomycin, teicoplanin and linezolid.

3.2 Survival analysis

We found a significantly shortened survival period of patients who were diagnosed with early surgical site infections ($P = 0.02$, Fig. 2A) and patients with early, deep surgical site infections ($P = 0.03$, Fig. 2B). Patient survival was neither related to the occurrence of early superficial infections nor to late infections. The data concerning patient survival and the type of the infection are summarised in Table 3.

We observed a significantly shortened overall survival period of patients infected by *P. mirabilis* when compared to patients without *P. mirabilis* infection ($P < 0.01$, Fig. 2C). We found no association between patient survival and infection with the other studied microorganisms. The data concerning patient survival and type of identified microorganisms are presented in Table 4.

4. Discussion

Despite of significant advantages of TPE, a number of studies reported that this extensive surgery in the pelvic region is a procedure with a high risk of various complications [3–6, 23]. Some studies pointed out that most of the complications are caused by infections [6, 24]. Indeed, the infections are the most common adverse events following TPE. However, most of the previous studies focused on the identification of the risk factors for adverse events following TPE, identifying the risk factors for infection. In this study, we analysed a homogenous group of patients who had undergone TPE due to cervical cancer recurrence. We analysed the type of the infection, identified the aetiological agents responsible for infection and evaluated the association between infection and long-term outcome. Because TPE is a seldomly performed surgery, data concerning the types of the infection

Table 3. Survival of patients treated with total pelvic exenteration due to cervical cancer recurrence depending on infection appearance.

Early infection	Patients (n)	%	Median overall survival (months)	Survival range	P-value
Any type					
Absent	6	46.2	11.4	7–85.8	P = 0.02
Present	7	53.8	7.4	1.06–16.4	
Superficial surgical site infection					
Absent	12	93.3	10.7	1.06–85.8	P = 0.15
Present	1	7.7	16.4	NA[1]	
Deep surgical site infection					
Absent	7	53.8	11.5	7–85.8	P = 0.03
Present	6	46.2	5.0	1.06–11.3	
Late infection					
Any type					
Absent	7	53.8	7.34	4.9–85.8	P = 0.88
Present	6	46.1	10.76	1.06–11.7	
Superficial surgical site infection					
Absent	12	93.3	10.4	1.06–85.8	P = 0.80
Present	1	7.7	11.4	NA	
Deep surgical site infection					
Absent	10	76.9	10.7	1.06–85.8	P = 0.64
Present	3	23.1	4.7	3.9–11.8	
Wound infection					
Absent	9	60.9	11.3	1.06–85.8	P = 0.42
Present	4	30.1	10.6	46–11.7	
Other					
Absent	11	84.6	10.4	1.06–85.8	P = 0.21
Present	2	15.4	7.85[1]	3.9–11.8	

NA, not available. [1] Due to the low sample number, we report the mean survival instead of the median.

Table 4. Survival of patients treated with total pelvic exenteration due to cervical cancer recurrence in regards to the aetiological agents of infections.

Microorganism/resistance mechanism	Patients (n)	%	Median overall survival (months)	Survival range	P-value
Enterococcus faecalis					
Absent	8	61.5	9.1	4.6–85.8	P = 0.95
Present	5	38.5	11.3	1.06–11.7	
Enterococcus faecium					
Absent	10	76.9	10.4	1.06–85.8	P = 0.89
Present	3	23.1	11.4	4.6–16.4	
Extended spectrum beta-lactamases (ESBLs)					
- producing *Enterobacterales*					
Absent	11	84.6	10.4	1.06–85.8	P = 0.92
Present	2	15.4	6.6[1]	3.9–11.4	
Pseudomonas aeruginosa					
Absent	11	84.6	11.4	4.9–85.8	P = 0.10
Present	2	15.4	6.26[1]	1.06–10.4	
Proteus mirabilis					
Absent	11	84.6	11.4	3.9–85.8	P < 0.01
Present	2	15.4	2.83[1]	1.06–4.6	

[1] Due to the low sample number, we report the mean survival instead of the median.

and the aetiological agents responsible for infection after TPE are sparse.

The key findings of this study are that the most common infectious complications that arise after TPE due to cervical cancer recurrence are early SSIs. Furthermore, although we did not observe early SSI infections as the direct cause of death, we also found that early, especially deep, SSIs were associated with shortened OS.
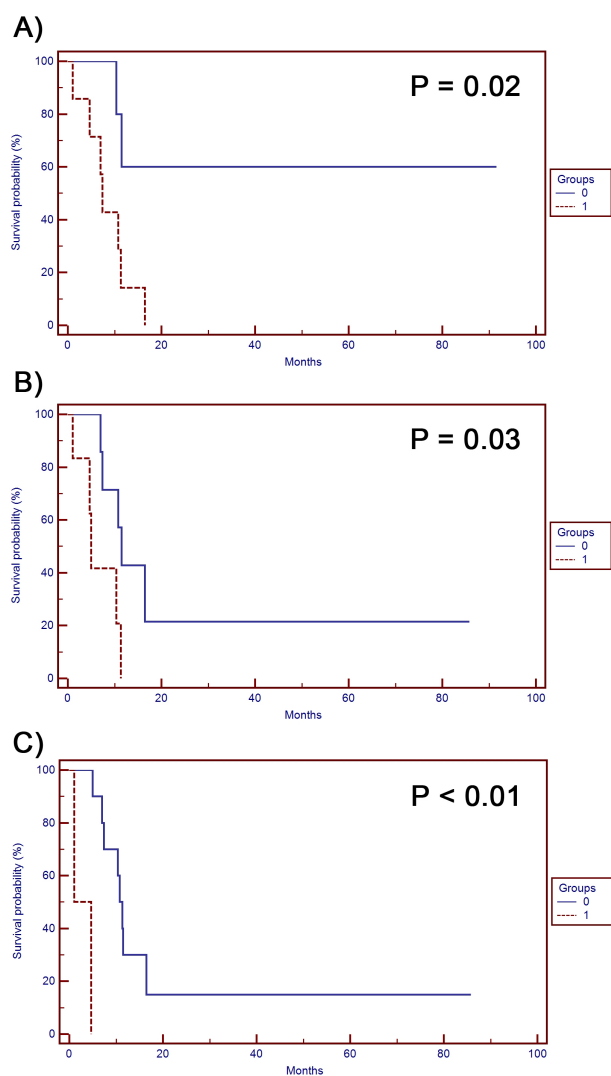
Fig. 2. Survival after total exenteration due to cervical cancer recurrence according to the type and the aetiological agent of the infection. (A) Group 0: patients without early surgical site infection, median overall survival (mOS) = 11.4 months (range 7–85.8); Group 1: patients with early surgical site infection present, mOS = 7.4 months (1.06–16.4). (B) Group 0: patients without deep, early surgical site infection, mOS = 11.5 months (7–85.8); Group 1: patients diagnosed with deep, early surgical site infection present, mOS = 5.0 months (1.06–11.3). (C) Group 0: patients without *Proteus mirabilis* identified in the culture, mOS = 11.4 months (3.9–85.8); Group 1: patients with *P. mirabilis* identified in the culture, mean OS = 2.83 months (1.06–4.6).

The TPE is a complex and extensive operation with an extremely long operative time. The duration of the operation period varies among studies; in extreme cases, it can be up to 17 hr [3]. In the present study, the mean operation time was 6 hr, comparable to previous series [6, 23]; in no case, the operation exceeded 10 hr. Vigneswaran *et al.* [16] found a relationship between an operation period in TPE longer than 6 hr and early wound infection occurrence. The relationship between operation duration and rate of infectious complica-

tions is known in the surgical literature. In a systemic review by Cheng *et al.* [25], the authors reported that the likelihood of SSI increased with every 60 min of operation time. A higher risk of infections is probably connected with other post-operative complications.

The tissue concentration of antibiotics used in perioperative prophylaxis declines over time. Hence, in TPE, further doses of antibiotics are given. The guidelines of the Polish National Antibiotics Protection Program [26] recommend that antibiotics should be used to prevent infections before and during surgery only, discouraging postoperative continuation. However, the overall rate of different infections observed after TPE shows the need of postoperative antimicrobial prophylaxis. We therefore adopted the policy of using intravenous antibiotics routinely also following surgery.

The usefulness of extended antibiotic prophylaxis in the immediate postoperative period in TPE remains limited. Koh *et al.* [27] suggest that prolonged courses of antibiotic administration in PE may reduce septic complications, which is in contrast to the findings of Ishibashi *et al.* [28] on patients undergoing surgery for rectal cancer; the authors did not observe a significant reduction in SSI incidence among patients receiving a single dose of postoperative antibiotics vs. multiple-dose antibiotics. Other authors argue that prolonged courses of antibiotic prophylaxis may cause the risk of increasing microbial resistance infections [29, 30]. However, in a large retrospective cohort study by Cohen *et al.* [31], among 689 patients with post-operative infections, there was no association between antibiotic prophylaxis and post-operative antibiotic-resistant infections.

Despite the use of extended antibiotic prophylaxis in TPE, mainly cephalosporines and metronidazole, the rate of infectious complications remains high. After TPE, up to 50% of patients experienced infections [6, 9]. This observation is in line with our results, where early infections affected slightly more than 50.0% of the patients. It is worth noting that prolonged antibiotics have not been found to reduce the rate of infectious complications in our study, however we did not identified any case of sepsis in our patients.

It seems to be that the complexity of the surgical procedure is one of the factors contributing to the occurrence of a number of infectious complications. In the literature, most studies reported data in PE in total, lacking results for the exact type of exenteration performed. However, this would likely correlate with the obtained results. More advanced gynecological malignancies with higher tumour mass and damage of natural barriers are inherently at higher risk of infections. Our assumption is confirmed by the findings of Petruziello and colleagues [6] in a series of 28 patients undergoing PE due to gynaecologic malignancy. The authors found that TPE was a more morbid procedure than non-TPE exenteration; they also noted the differences in the occurrence of infections and reported about 43.0% of SSIs in patients that had undergone TPE and 7.0% of SSIs in patients after non-TPE. Our rate of SSIs was slightly higher than that received by the cited au-

thors. In turn, the rate of pelvic abscess after PE is 2.0–17.0% [3, 4], whereas in our study, we did not recognise any such case. The absence of pelvic abscess formation in our patients may be a result of the routine use of an omental flap to prevent empty pelvis syndrome.

We reported that the most common infections following PE were SSIs and UTIs. These infections occur both as early ones, appearing up to 30 days after the procedure, and as late ones, appearing later than 1 month after the procedure. However, the share of different types of infections and the time of their appearance varies among studies. In previous studies, UTIs rather dominated. For example, in their series, Martinez *et al.* [32] reported UTIs in approximately 50% of the cases, both as early and late infections. The occurrence of urinary tract infections may be connected with surgical techniques for the urinary tract diversion used. Patients operated by the Bricker's method are less likely to obtain urinary infections [33]. In our study, UTIs occurred only as late complication, in 2 out of 13 patients (15.4%), and the time to infection appearance was approximately 2 months. It is worth noting that patients may experience re-infection, and this was the case with one patient who experienced UTI after early deep SSI and one patient with a fistula, requiring surgical re-intervention.

The most serious infection following TPE is sepsis. The prevalence of sepsis varies among studies. Lago *et al.* [4], in medium-late complications, found a sepsis rate as high as 26.0% in a small number of cervical cancer patients in their study. Li *et al.* [5], also analysing a small series of patients with recurrent and persistent cervical cancer, recognised sepsis in 10.0% of patients. A similar result was obtained by McLean *et al.* [34]; however, in a group of 44 patients with gynecological malignancies who underwent PE after chemoradiation, the authors observed sepsis in 14.0%. In turn, Matsuo *et al.* [8], in their population-based study (2647 cases) on PE for gynecological malignances, reported a sepsis rate of 8.4%. This differs from our study, where we did not observe sepsis among our patients. The most likely causes of our results are the implementation of sepsis prevention programs in our hospital, and antibiotic prophylaxis.

Nowadays, SSIs following TPE, especially deep SSIs, are difficult to treat, most likely because of the extended profiles of the microorganisms that cause infections in gynaecological malignancies and increasing microbial resistance. The majority of these infections are polymicrobial and caused by aerobic and anaerobic bacteria and, occasionally, by yeast-like fungi. The aetiological agents of infections are mainly the main genera of the gut and genitourinary tract microbiota [11, 35]. However, fewer data exist on the aetiological agents of infections after TPE. In available publications, the most commonly reported microorganisms among aerobic bacteria are *E. coli* and *Enterococcus* spp., whereas in terms of anaerobic bacteria, *Bacteroides* is most common. The most frequently detected yeast-like fungus is *C. albicans* [36].

These results are similar to those seen in our present study. Most deep SSIs were polymicrobial infections. Next to the most common bacteria, such as *Enterococcus* and *E. coli*, we isolated other *Enterobacterales*, such as *K. pneumoniae* and *P. mirabilis* and gram-negative nonfermenting rods of the species *P. aeruginosa*. Apart from *Bacteroides*, we also found the anaerobic genera *Fusobacterium* and *Finegoldia*. We did not find non-albicans *Candida* spp., which tend to be more resistant to fluconazole than *C. albicans.* There was no difference in the microbial composition between early and late infections. This seems to be an interesting observation, as the causative microorganisms of infections usually change with the length of the hospitalisation period.

We did not observe a significantly shortened overall survival of patients depending on the bacteria detected, apart from the association found between patient survival and infection with *P. mirabilis*. This species is intrinsically less susceptible to imipenem than other bacteria of *Enterobacterales* and is frequently a part of polymicrobial infections [37, 38]. However, our observation requires further research.

Most studies on gynaecological malignancies report superficial infections together with deep and organ/space SSIs. However, superficial SSIs involve only skin and subcutaneous tissue of incision [20], which probably influences the aetiological agents of the infection. In this study, 18.0% of the confirmed infections were superficial, and the only aetiological agent was *E. faecium*. Enterococci are naturally resistant to many commonly used antimicrobial agents and also exhibit high-level resistance to cephalosporins. In our study, we did not observe glycopeptide-resistant and linezolid-resistant strains among the analysed enterococci. However, linezolid resistance and vancomycin resistance among enterococci are currently a major emergence in some hospitals, making the treatment of enterococcal infections challenging [39]. This should be taken into account, especially since enterococci were the predominant flora in our study.

Furthermore, we found more than 20% of ESBL producers among *Enterobacterales*. The production of ESBL is often connected with resistance to third-generation cephalosporins, which have been recommended for infection treatment. The remaining treatment option is an antibiotic from the carbapenems group [39]. As we did not observe carbapenem-resistant Gram-negative bacteria in our study, we therefore recommend the use of carbapenems as the first-line treatment for early and late infections following TPE caused by ESBL-producing bacteria.

To our knowledge, there are no studies on antibiotic susceptibility of microorganisms isolated from infections after TPE. Thus, we cannot directly compare the susceptibility results. In our present study, maximum resistance was shown for fluoroquinolones (67.0%), followed by third- and fourth-generation cephalosporins (slightly less than 40.0%). The most effective antibiotics for gram-negative bacteria were carbapenems and aminoglycosides. However, this study was only conducted at one oncological centre, and empirical antibiotic selection should be based on the knowledge of local

prevalence of bacterial organisms and antibiotic susceptibilities.

We found that patient with early SSIs, mainly deep-SSIs, had a shortened survival period compared to patients who were not diagnosed with early infection. These patients had complicated postoperative courses of non-infectious nature, and some required additional surgery, which may explain the lowest survival for this group of patients. However, an infection may have been the cause of these complications. Thus, the prevention of postoperative early SSIs is a major issue, with the main goal of reducing SSIs.

The main limitation of this study is its retrospective character, as it is based on data obtained from medical reports. Another limitation is the small series analysed; however, this procedure is highly uncommon. However, our study group was homogenous, and we focused on the type of the infection, the separate analysis of superficial and deep infections and the identification of aetiological agents, which is a new sight in the literature. Despite the limitations, this report provides further data on infectious complications in patients with cervical cancer recurrence who underwent TPE. We point out the need for closer pre- and post-operative management of these patients to enhance patient care.

5. Conclusions

In conclusion, our results suggest that early, especially early deep, SSI may worse the prognosis of patients after TPE. Therefore, the time of infection management after the operation should be especially intensified within 1 month after TPE.

Author contributions

Conceptualisation, MS; Methodology, MS; Formal Analysis, MS; Resources, MS; Data Curation, MS; Writing—Original Draft Preparation, MS; Writing—Review & Editing, MS, SS; Visualisation, MS, SS; Supervision, SS.

Ethics approval and consent to participate

This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study received the Centre of Postgraduate Medical Education Ethical Committee approval (7/PB/2020).

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Conflict of interest

The authors declare no conflict of interest.

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