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Original Article

Predictive factors of surgical complications after pelvic exenteration for gynecological malignancies: a large single-institution experience

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ABSTRACT

Objective: To evaluate pre-operative predictors of early (<30 days) severe complications (grade Dindo 3+) in patients with gynecological malignancy submitted to pelvic exenteration (PE).
Methods: We retrospectively analyzed 129 patients submitted to surgery at Fondazione Policlinico Gemelli between 2010 and 2019. We included patients affected by primary or recurrent/persistent cervical, endometrial, or vulvar/vaginal cancers. Post-operative complications were graded according to the Dindo classification. Logistic regression was used to analyze potential predictors of complications.
Results: We performed 63 anterior PE, 10 posterior PE, and 56 total PE. The incidence of early severe post-operative complications was 27.9% (n=36), and the early mortality rate was 2.3% (n=3). More frequent complications were related to the urinary diversion and intestinal surgery. In univariable analysis, hemoglobin ≤10 g/dL (odds ratio [OR]=4.2; 95% confidence interval [CI]=1.65–10.7; p=0.003), low albumin levels (OR=3.9; 95% CI=1.27–12.11; p=0.025), diabetes (OR=4.15; 95% CI=1.22–14.1; p=0.022), 2+ comorbidities at presentation (OR=5.18; 95% CI=1.49–17.93; p=0.012) were predictors of early severe complications. In multivariable analysis, only low hemoglobin and comorbidities at presentation were independent

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

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predictors of complications.
Conclusion: Pelvic exenteration is an aggressive surgery characterized by a high rate of post-operative complications. Pre-operative assessment of comorbidities and patient health status are crucial to better select the right candidate for this type of surgery.

Keywords: Cervical Cancer; Endometrial Cancer; Pelvic Exenteration; Nutritional Status

Synopsis
Pelvic exenteration is a salvage procedure heavily related to a high risk of complication. Currently there are no valid predictors of risk of complications. We identified low hemoglobin and albumin levels, diabetes, and comorbidities at presentation as predictors of early severe complications. Identified factors could promote future studies in building validated scores to predict surgical risk related to pelvic exenteration. Moreover, nutritional status will have to be furtherly assessed in this context.

INTRODUCTION

Pelvic exenteration (PE) is a very extensive surgery characterized by the en-bloc removal of all pelvic organs, including the bladder, anorectum and internal reproductive organs. After the first pioneering experience [1], techniques and indications for surgery have evolved, heading towards curative intents and a more accurate selection of patients. The mortality rate significantly improved over time from 23% in the first series reported to the actual <5% [2,3]. However, the complexity of this surgery still carries a high number of post-operative complications, ranging between 51% and 82%, with a rate of severe complications of 22%–32%. Moreover, this data is not supported by an excellent outcome in terms of long-term survival with an estimated 5-year overall survival (OS) of 40% [4,5]. Indeed, this could be the result of the extension of the indication to pelvic exenteration for both curative and palliative intent.

In the field of curative intent, PE aims to completely eradicate tumor, especially in patients in which other therapeutic approaches failed. PE is also indicated in a palliative treatment of all disabling symptoms related to the advanced disease, impairing quality of life, such as intractable pain, bleeding, urinary and pelvic sepsis, obstruction, and fistula formation.

Moreover, candidates for this surgery often have advanced disease, a history of previous oncological treatment (radiation therapy and/or chemotherapy), and poor performance status.

The complexity of PE, the high rate of severe complications and the relatively poor oncologic outcome make the selection of patients challenging. In this context, pre-operative nutritional status is commonly assessed and has been associated with an increased risk of complication [6]. The causes of pre-operative malnutrition in oncological patients is multifactorial. Impaired intake is the most important etiological factor, moreover, sarcopenia is often associated with effects of multimodal therapy [7]. Indeed, malnutrition is a modifiable risk factor for surgery. Perioperative nutritional support is very effective in decreasing post-operative complications and the length of hospital stay in malnourished patients [8]. Therefore, it is of utmost importance, to properly identify patients with increased risk of post-operative complications, who are susceptible of preoperative nutritional support.

Nevertheless, only few reports have tried to investigate the association between poor nutritional status and operative outcomes in PE, and most of them included a low number of patients, with retrospective design, and, even more importantly, included different types of tumor [9-11]. The aim of this study is to provide criteria for estimating the risk of early and post-operative complications after PE in a gynecological setting, taking into account the pre-operative nutritional status and therefore trying to yield surgeons, a more adequate and detailed counseling before surgery.

MATERIALS AND METHODS

We retrospectively analyzed patients undergoing pelvic exenteration for gynecological malignancy at Fondazione Policlinico A. Gemelli IRCCS, Roma between June 2010 and May 2019. All patients gave their written consent to the use of clinical data for research purposes, and the study was approved by the Institutional Review Board (ID: 3879, Prot No. 0011322/21). We included patients with primary and recurrent gynecological tumors diagnoses, including cervical cancer, endometrial cancer, vulvar cancer, and vaginal cancer, aged between 18 and 75 years. We excluded patients diagnosed with ovarian cancer due to the different patterns and extent of disease; patients with non-oncological disease in which pelvic exenteration is performed for symptomatic purpose (i.e., fistula after mesh erosion for pelvic organ prolapse); and patients diagnosed with a different, non-gynecological tumor 5 years before the surgery date. The primary endpoint was to identify prognostic factors of early severe complications (grade 3 or higher).

Demographic data, comorbidities, surgical data, pathologic reports, and post-operative complications were extracted from the medical reports. Demographic data included age, body mass index (BMI), ASA score, pre-operative albumin, hemoglobin, and creatinine levels. Patient comorbidities included hypertension requiring medication and/or other cardiovascular disease (CVD), diabetes mellitus, chronic obstructive pulmonary disease (COPD) or recent pneumonia, renal failure, transient ischemic attack (TIA) or cerebrovascular accident (CVA), autoimmune disease, and depression. The disease characteristics included the type of cancer and the timing of the disease. It was defined as "primary" when pelvic exenteration was performed as the upfront treatment of the disease or after neoadjuvant chemotherapy or radiation, as "recurrent" when it was performed to treat the relapse occurring at least 6 months after the first treatment, as "persistent" when the recurrence happened within 6 months from the previous treatment. We also collected data about previous radiation treatment, including patients who underwent external beam radiation ± vaginal brachytherapy, and previous chemotherapy, meaning patients who underwent systemic chemotherapy.

The surgical approach (open abdominal, laparoscopic, or robotic-assisted) was individualized based on surgeon preference and patient characteristics. The extent of pelvic exenteration was defined as anterior, posterior or total according to Magrina classification [12]. In case of anterior exenteration, the urinary diversion technique included the execution of Bricker or Wallace anastomosis (all refluxing techniques).

Post-operative complications were graded according to Dindo classification [13]. We evaluated early complications (within 30 days from surgery) and late complications (within 6 months from surgery). We evaluated severe complications, grade 3, that are defined as

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events requiring endoscopic, radiological, or surgical intervention and grade 4 defined as life-threatening complications requiring intensive care unit (ICU) management. Dindo grade 5 complication is the death of the patient due to surgery. The rate of early and late severe complications was recorded for each patient.

1. Anthropometry, body composition, and sarcopenia assessments

Weight and height obtained from the patient's chart were recorded by hospital staff. These anthropometric measurements were performed using a professional balance beam scale with a height rod (Seca 700 Physician's Balance; Seca GmbH, Hamburg, Germany). BMI was calculated using the formula weight in kilograms divided by height in meters squared (in kg/m^2). Skeletal muscle (SM), visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), and intramuscular adipose tissue (IMAT) were analyzed from computed tomography (CT) images. The CT scanner, Revolution Maxima GE Healthcare (GE Healthcare, Chicago, IL, USA) was used. A single DICOM image was extracted from pre-operative CT imaging at the the third lumbar vertebra level (L3). The DICOM images were then exported to SliceOmatic software v5.0 (Tomovision, Montreal, Quebec, Canada). Image analysis was performed by 2 investigators with imaging experience and blinded to outcomes to minimize the introduction of bias. Using pre-established Hounsfield unit (HU) thresholds, areas of specific tissues were identified and quantified in cm2 as follows: −29 to +150 HU for SM, −190 to −30 HU for SAT, −150 to −50 HU for VAT, and −190 to −30 HU for IMAT. Skeletal muscle index (SMI), visceral adipose index (VAI), subcutaneous adipose index (SAI), and intramuscular adipose index (IMAI) were calculated by normalizing areas of SM, VAT, SAT, and IMAT for squared height (in m^2). According to the sex-specific consensus definitions of Fearon et al. [14], sarcopenia was defined as SMI <39 cm^2/m^2 in women.

2. Statistical analysis

Continuous variables were described as a mean and standard deviation for normally distributed data, or median and interquartile range (IQR). Categorical variables were reported as frequencies and percentages. Variables were evaluated for their association with complications based on univariate logistic regression models. Associations were summarized using the odds ratios (ORs), and corresponding 95% confidence intervals (CIs) were estimated from the final multivariable logistic regression models. All p-values were two-sided and a value of <0.05 was considered statistically significant. We included in the multivariable models all factors reaching p<0.200 at the univariable analysis.

RESULTS

We included in the analysis 129 patients. Cervical cancer was the most common malignancy (n=90, 69.8%), followed by endometrial cancer (n=24, 18.6%) and vulvar and vaginal cancer (n=15, 11.6%). In a small percentage of cases, pelvic exenteration was the upfront treatment, while in 76.7% of cases, it was a savage surgery for relapse or persistence of disease. In 82.2% of patients, radiation treatment has already been a treatment strategy before exenteration. Demographic characteristics are listed in **Table 1**.

The median age was 59 years (range, 30–86). Most of patients had normal weight, while 35.6% were overweight or obese, and 10.9% were morbidly obese. The most frequent comorbidity was hypertension requiring medication (n=35, 27.1%), followed by diabetes (n=12, 9.3%), depression or anxiety (n=8, 6.2%), COPD or pulmonary disease (n=7, 5.4%),

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Table 1. Demographic and disease characteristics of 129 patients undergoing pelvic exenteration between June 2010 and May 2019

Characteristic	Values
Patient characteristic	
Age (yr)	
≥70	27 (20.9)
<70	102 (79.1)
BMI (kg/m²)	25 (14–54)
<25	60 (46.5)
25–34.9	46 (35.6)
35+	14 (10.9)
Unknown	9 (7.0)
ASA score	
1–2	90 (69.8)
3	8 (6.2)
Unknown	31 (24.0)
Hemoglobin (g/dL)	
≤10	25 (19.3)
>10	86 (66.7)
Unknown	18 (14.0)
Creatinine (mg/dL)	0.8 (0.5–4.1)
≤1.2	96 (74.4)
>1.2	15 (11.6)
Unknown	18 (14)
Albumin (mg/dL)	38 (20–48)
<30	15 (11.6)
≥30	94 (72.9)
Unknown	20 (15.5)
Comorbidities at presentation	
None	72 (55.8)
1	42 (32.6)
2+	13 (10.1)
Unknown	2 (98.4)
Frequencies of comorbidities	
CVD/hypertension requiring medications	35 (27.1)
Diabetes mellitus	12 (9.3)
Depression or anxiety	8 (6.2)
COPD or recent pneumonia	7 (5.4)
Autoimmune disease	3 (2.3)
Renal failure (acute/chronic)	3 (2.3)
TIA	2 (1.6)
Disease characteristics	
Primary site	
Cervical cancer	90 (69.8)
Endometrial cancer	24 (18.6)
Vaginal/vulvar cancer	15 (11.6)
Timing	
Primary treatment	30 (23.3)
Recurrence	79 (61.2)
Persistence	20 (15.5)
Previous EBRT	
Yes	106 (82.2)
No	23 (17.8)
Previous chemotherapy	
Yes	93 (72.1)
No	36 (27.9)

Values are presented as number of patients (%) or median (range).
ASA, American Society of Anesthesiologists; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; EBRT, external beam radiotherapy; TIA, transient ischemic attack.

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renal failure (n=3, 2.3%), autoimmune disease (n=3, 2.3%), and TIA/cerebrovascular accident (n=2, 1.6%).

The median operative time was 540 min (range, 100–900). We included in the analysis 63 anterior exenterations, 56 total pelvic exenterations and 10 posterior exenterations. The surgeon decided the surgical approach according to his own preference. We performed 100 (77.5%) open abdominal procedures and 29 (22.5%) minimally invasive procedures, among which 12 were laparoscopies and 17 robotic-assisted surgery. The surgical approach was not influenced by the type of disease (cervical cancer, endometrial cancer, and vulvar/vaginal cancer were performed with minimally invasive surgery (MIS) respectively in 18.7%, 33.3%, and 26.7% of cases, p=0.225), the timing of disease (primary, persistent, and recurrent disease were performed with MIS respectively in the 30%, 10%, 26.3% of cases, p=0.312), or age group. However, we observed that morbid obese patients (BMI >35 kg/m^2) were more likely to be treated by MIS, compared with overweight/obese (BMI 25–35 kg/m^2) and normal weight patients (BMI <25 kg/m^2), respectively in 60%, 22.2% and 16.4% of cases, p=0.002 (data not shown). Surgical characteristics are listed in **Table 2**.

Among 129 patients, 36 (27.9%) experienced severe early post-operative complications within 30 days from surgery. Among these, the highest complication was of grade 3 in 31 (24%) patients, requiring radiological or endoscopic interventional radiology or reoperation. In two (1.6%) patients, the highest complication was of grade 4. Mortality within 1 month from surgery was 2.3% (grade 5). The rate of readmission was 8.5% (11 patients). Type of early complications are listed in **Table 3** and **Fig. S1**.

Moreover, late complications were experienced by 23.8% of patients. Among these, 28 (22.2%) experienced grade 3 complications, and 2 patients died (1.6%). In a sub-analysis focusing on cases of urinary complications, we found an overall rate of 21.7%, meaning that 28 patients had complications related to urinary diversion. The most common urinary complication was ureteral stenosis (n=13, 46.4%) and it has been reported in the late post-operative period, followed by leak of ureteral anastomosis (n=8, 28.6%) that is often diagnosed within 30 days from surgery. Six patients needed reoperation, while for 22 cases, interventional radiology procedures were adequate to treat the complication (**Table 4**).

In the univariable analysis (**Tables 5** and **6**), we found that levels of hemoglobin ≤10 g/dL were associated with increased incidence of early post-operative complications (56% vs. 23.3%, OR=4.2; 95% CI=1.65–10.7; p=0.003). More interestingly, we found a significant increase of risk in case of low albumin levels with (OS=3.9; 95% CI=1.27–12.11; p=0.025). Age and BMI did not affect the rate of early complications. The risk of early complications slightly increased as the number of comorbidities of the patient (23.6% for no comorbidities, 26.2% 1 comorbidity and 61.5% for 2+ comorbidities, p=0.012). However, the diagnosis of diabetes was the only statistically significative parameter for early complications (58.3% vs. 25.2%, OR=4.15; 95% CI=1.22–14.1; p=0.022). Previous external beam radiation treatment ± vaginal brachytherapy and previous chemotherapy were not associated with an increased risk of early complications. Surgical characteristics were not also associated with the risk of severe complications. The mean length of stay (standard deviation) was 35 days for patients with severe complications and 17 days for patients with no severe complications (p=0.001).

In the analysis of nutritional status, we found a trend toward an increase of early complications among patients with a lower index of visceral, subcutaneous, and

Table 2. Surgical characteristics of 129 patients undergoing pelvic exenteration

Surgical characteristics	Values
Surgical approach	
Open abdominal	100 (77.5)
Laparoscopy	12 (9.3)
Robotic	17 (13.2)
Extent of surgery	
Anterior pelvic exenteration	63 (48.8)
Posterior pelvic exenteration	10 (7.8)
Total pelvic exenteration	56 (43.4)
Operative time (min)	540 (100–900)
<540	54 (41.9)
≥540	75 (58.1)
Surgical intent	
Curative	93 (72.1)
Palliative (carcinosis, N+)	36 (27.9)
Carcinosis	
Yes	14 (10.9)
No	115 (89.1)
Vulvectomy	
Yes	9 (7)
No	120 (93)
Loop diverting ileostomy	
Yes	8 (6.2)
No	121 (93.8)
Side wall	
Yes	33 (25.6)
No	96 (74.4)
Colpectomy	
Partial	31 (24)
Total	98 (76)
Pelvic floor reconstruction	
Yes	4 (3.1)
No	125 (96.9)
Lymph node dissection	
Yes	81 (62.8)
No	48 (37.2)
Positive node (n=81 total lymphadenectomy)	
Yes	25 (30.9)
No	56 (69.1)
Length of stay (days)	14 (6–150)
<14 days	53 (41.1)
≥14 days	72 (55.8)
Unknown	4 (3.1)
Estimated blood loss (mL)	700 (100–3,500)
<700	31 (24.0)
≥700	36 (27.9)
Unknown	62 (48.1)
Tumor dimension (mm)	40 (0–150)
<40	45 (34.6)
≥40	56 (43.1)
Unknown	29 (22.3)

Values are presented as number of patients (%) or median (range).

intramuscular adipose tissue, even if not statistically significant. We observed a statistically significant reduction of skeletal muscle fat in patients with early complications. Sarcopenia, defined ad SMI <39 cm^2/m^2, did not reach a statistically significant impact on complications; however, the 75% of patients with sarcopenia had early complications compared to the 52.7% of patients with normal SMI.

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Table 3. Frequencies and description of post-operative early and late complications according to Dindo classification

Complications	Values
Highest early complication (grade 3<)	36/129 (27.9)
Grade 3	31 (24.0)
Grade 3a (invasive procedure without general anesthesia, such as endoscopic, interventional procedure)	12
Percutaneous nephrostomy	8
Drainage of abdominal abscess	5
Catheter embolization	1
Wound dehiscence not requiring GA	1
Grade 3b (operation under general anesthesia)	19
Leakage of intestinal anastomosis/bowel perforation	10
Complications of urinary reconstruction (leak/fistula/ischemia)	5
Peritonitis	4
Abdominal bleeding/haemoperitoneum	2
Grade 4 (organ system failure, ICU)	2 (1.6)
Renal failure	1
Sepsis/acute ischemia of lower extremity/ICU	1
Grade 5 (death)	3 (2.3)
Highest late complication (grade 3<)	30/126 (23.8)
Grade 3	28 (22.2)
Grade 3a	16
Percutaneous nephrostomy	12
Drainage of abdominal abscess	5
Grade 3b	12
Bowel fistula/occlusion/stenosis	8
Complications of urinary reconstruction (leack/fistula/ischemia)	1
Peritonitis	3
Grade 5 (death)	2 (1.6)

Values are presented as number of patients (%) or frequency.
GA, general anaesthesia; ICU, intensive case unit.

Table 4. Description of early and late urinary complications of 129 patients undergoing pelvic exenteration

Complications	Values
Urinary complications	TOT=28
Early (within 30 days)	10 (35.7)
Leak Bricker anastomosis	8
Fistula (ureteral, vescico-vaginal)	1
Stomia	1
Requiring interventional radiology procedure	6
Requiring reoperation	5
Late (within 6 months)	17 (60.7)
Stenosis	13
Leak	4
Requiring interventional radiology procedure	16
Requiring reoperation	1
Bowel complications	TOT=22
Early (within 30 days)	11 (50.0)
Leakage of bowel anastomosis	9
Stomia	2
Requiring reoperation	11
Late (within 6 months)	11 (50.0)
Fistula	5
Occlusion	5
Ischemia	1
Requiring interventional reoperation	9

Values are presented as number of patients (%) or frequency.
TOT, total.

Multivariable analysis confirmed low hemoglobin (OR=9.8; 95% CI=1.9–50; p=0.006) and comorbidities at presentation, in particular, 2+ comorbidities (OR=19.9; 95% CI=2.79–142.1; p=0.003) were independent prognostic factors for early complications (**Table S1**).

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Table 5. Logistic regression analysis of predictors of early (<30 days) postoperative complications

Patient characteristic	Early complication G3-4 (n=36)	Unadjusted OR (95% CI)	p
Age (yr)			
<70	27 (75.0)	1	
≥70	9 (25.0)	1.39 (0.56–3.46)	0.527
BMI (kg/m^2)			
<25	14 (43.7)	1	
25–34.9	14 (43.7)	1.44 (0.6–3.42)	0.414
35+	4 (12.5)	1.31 (0.35–4.85)	0.745
ASA score			
1–2	25 (92.6)	1	
3	2 (7.4)	0.87 (0.16–4.58)	0.926
Hemoglobin (mg/dL)			
>10	20 (58.8)	1	
≤10	14 (41.2)	**4.2 (1.65–10.7)**	**0.003**
Creatinine (mg/dL)			
≤1.2	28 (82.4)	1	
>1.2	6 (17.6)	1.62 (0.53–4.98)	0.414
Albumin (mg/dL)			
≥30	26 (74.3)	1	
<30	9 (25.7)	**3.9 (1.27–12.11)**	**0.025**
Comorbidities at presentation			
None	17 (47.2)	1	
1	11 (30.6)	1.15 (0.48–2.76)	0.734
2+	8 (22.2)	**5.18 (1.49–17.93)**	**0.012**
CVD/hypertension requiring medications			
No	23 (63.9)	1	
Yes	13 (36.1)	1.77 (0.77–4.1)	0.242
Diabetes mellitus			
No	29 (80.6)	1	
Yes	7 (19.4)	**4.15 (1.22–14.1)**	**0.022**
COPD or recent pneumonia			
No	35 (97.2)	1	
Yes	1 (2.8)	0.4 (0.05–3.49)	0.418
Depression or anxiety			
No	33 (91.7)	Ref	
Yes	3 (8.3)	1.58 (0.36–6.99)	0.523
Renal failure (acute/chronic)			
No	34 (94.4)	1	
Yes	2 (5.6)	5.29 (0.46–60.3)	0.223
Autoimmune disease			
No	35 (97.2)	1	
Yes	1 (2.8)	1.27 (0.11–14.5)	0.814
Previous EBRT ± VBRT			
No	6 (16.7)	1	
Yes	30 (83.3)	1.12 (0.4–3.11)	0.838
Previous chemotherapy			
No	10 (27.8)	1	
Yes	26 (72.2)	1.01 (0.43–2.38)	0.917
Primary site			
Endometrial cancer	7 (19.4)	0.82 (0.2–3.3)	0.842
Cervical cancer	24 (66.7)	0.73 (0.23–2.34)	0.626
Vulvar and vaginal cancer	5 (13.9)	Ref	
Timing			
Primary	8 (22.2)	1	
Persistence	5 (13.9)	0.91 (0.25–3.35)	0.939
Recurrence	23 (63.9)	1.13 (0.44–2.9)	0.837
Surgical approach			
Laparotomy	30 (83.3)	1	
Laparoscopy/Robotic	6 (16.7)	0.61 (0.26–1.65)	0.329

(continued to the next page)

Table 5. (Continued) Logistic regression analysis of predictors of early (<30 days) postoperative complications

Patient characteristic	Early complication G3-4 (n=36)	Unadjusted OR (95% CI)	p
Operative time (min)			
<540	11 (30.6)	1	
≥540	25 (69.4)	1.95 (0.86–4.43)	0.151
Surgical intent			
Palliative	8 (22.2)	1	
Curative	28 (77.8)	0.66 (0.27–1.64)	0.437
Carcinosis			
No	32 (88.9)	1	
Yes	4 (11.1)	1.04 (0.3–3.55)	0.913
Extent of surgery			
Anterior	16 (44.4)	1	
Posterior	2 (5.6)	0.73 (0.14–3.82)	0.725
Total	18 (50.0)	1.39 (0.63–3.1)	0.451
Stoma			
No	16 (44.4)	1	
Yes	20 (55.6)	1.33 (0.6–2.89)	0.514
Side wall			
No	27 (75.0)	1	
Yes	9 (25.0)	0.96 (0.39–2.32)	0.914
Colpectomy			
Partial	6 (16.7)	1	
Total	30 (83.3)	1.84 (0.68–4.94)	0.347
Plastic reconstruction			
No	34 (94.4)	1	
Yes	2 (5.6)	2.7 (0.36–19.76)	0.321
Lymph node dissection			
No	13 (36.1)	1	
Yes	23 (63.9)	1.07 (0.48–2.37)	0.914
Positive node (n=82 total LND)			
No	18 (78.3)	1	
Yes	5 (21.8)	0.53 (0.17–1.63)	0.348
Length of stay (days)			
<14 days	8 (24.2)	1	
≥14 days	25 (75.8)	**2.99 (1.22–7.32)**	**0.016**
Estimated blood loss (mL)			
<700	9 (37.5)	1	
≥700	15 (62.5)	1.74 (0.63–4.84)	0.326

Bold styled p values indicate below 0.05.
ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; EBRT, external beam radiotherapy; LND, lymph node dissection; OR, odds ratio; VBRT, vaginal brachytherapy.

Table 6. Anthropometric results for patients included in this study according to postoperative complications

Nutritional status	No early complications grades 3–4	Early complications grades 3–4	p-value
VAT index (cm^2/m^2)	96.8±78.6	83.8±60.4	0.403
SAT index (cm^2/m^2)	225.1±142.2	209.3±120.8	0.591
IMAT index (cm^2/m^2)	10.1±6.5	9.8±7.04	0.872
Sarcopenia	29 (52.7)	18 (75.0)	0.064
Sarcopenia	OR=2.69	95% CI=0.92–7.8	0.072

Values are presented as mean±standard deviation or number (%).
CI, confidence interval; IMAT, intramuscular adipose tissue; OR, odds ratio; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

Readmission rate was 8.5% and 3 patients (2.3%) died within 30 days from surgery due to infectious complications.

In the analysis of late post-operative complications we evaluated 126 patients. Thirty patients experienced severe complications (grade 3 or higher). Mortality rate was 1.6% (n=2) within

6 months. One patient died of cardiac failure after pulmonary embolism, the other one died of infectious complication more than 30 days after surgery. No predictors of late severe complications were found.

DISCUSSION

This is one of the largest single-institution retrospective studies focusing on post-operative complications after PE in gynecological setting and considering nutritional status. We evaluated both early and late complications because, due to the complexity of this surgery, recovery time may be longer than other surgeries, and complications could arise even later than 30 days after surgery. In fact, we noticed different type of complications between the early and late post-operative period.

In our series, we observed that: 1) PE is a complex surgical procedure: 27.9% of patients experience severe complications within 30 days from surgery, and 23.8% have late severe complications; 2) the overall mortality rate is 3.8%, and 3/129 patients (2.3%) die within 30 days, in line with literature data; 3) the most frequent surgical complications are related to the urinary reconstruction and to bowel reconstruction; 4) low pre-operative hemoglobin levels and presence of comorbidities are independent factors affecting early severe complications rate. We did not find any predictor of late complications.

In this study, the frequencies of post-operative complications and mortality appear in line with the current literature. All surgical procedures have been carried out by a dedicated team of expert surgeons, involving gynecologic oncologist, urologists and general surgeons with enhanced perioperative assessment.

We have confirmed that the age of patients and BMI should not be considered an absolute limitation to this surgery [15,16]. Obesity has previously been reported as a risk factor for early complications in other series [17,18], and even more frequently for wound dehiscence [15]. However, we cannot confirm this data, maybe due to an increased use of minimally invasive techniques as laparoscopy and robotic-assisted surgery (60% of severe obese patients underwent MIS) in this subset of patients [19-21].

Looking at patient characteristics and health status before surgery we found that low hemoglobin levels are independently associated with higher complications. This data has already been reported in literature, specifically on pelvic exenteration [18]. Many studies underline the importance of albumin levels, showing that a poor pre-operative nutritional status is associated with an increased incidence of any complications [9,22]. In a large series of pelvic exenteration for gynecological, urological and colorectal malignancies, preoperative Albumin lower than 3.5 g/dl was found to be associated with increased incidence of any post-operative complications (85.9% vs. 72.3%, p=0.034) [9]. Similarly, Bogani et al. [22], described low albumin levels (<3.5 g/dL) strongly correlated to 90-days morbidity (OR=16.2; 95% CI=2.85–92.8; p=0.002). In our series, we found an increase in severe complication for albumin <3 mg/dL from 27.7% to 60% (p=0.025). Moreover, these findings are consistent with the data in advanced ovarian cancer and several other kind of surgeries [17,23]. Furthermore, in the same direction, we confirmed that a poor nutritional status, in terms of sarcopenia, has been associated to a higher risk of early complications even if we did not reach statistical significance (OR=2.69; 95% CI=0.92–7.8; p=0.072). We

believe that nutritional status is a crucial point in the pre-operative evaluation of the fitness of the patient, and statistical significance could be achieved with a larger sample size or in a multicentric external validation. Probably the trend toward a higher risk of complications for sarcopenic patients with the lack of significance may be due to a low number of patients analyzed (50 missing data) and to a low median SMI of our population that contributed to not clear evidence of differences among groups). Smilarly to our series, L3 CT-scan images were assessed to quantify body composition in a study of 227 pelvic exenteration for locally advanced rectal cancer. Authors did not find any correlation between complications rate and skeletal muscle density [24]. This lack of correlation might lead us to think that radiological characterization of body composition should be considered along with other functional and nutritional aspects, to yield reliable prognostic information.

Looking at the overall health status, patients undergoing pelvic exenteration are often characterized by the presence of multiple comorbidities. Previous studies showed that the presence of comorbidities (OR=1.34; 95% CI=1.01–1.78; p=0.040) and diabetes (OR=1.6; 95% CI=1.1–2.4; p=0.012) predicted post-operative complications in both univariable and multivariable analysis [25]. Accordingly with other gynecological malignancies, the patient's capability to tolerate a surgical extensive treatment is strongly correlated with overall health status [26-28]. We confirmed this data and, in particular, the increasing number of comorbidities independently correlates with post-operative complications.

On the other hand, we did not find a correlation between previous radiation treatment and severe complications. This is a debated topic, since many studies in the literature report a higher risk of anastomosis complications in patients receiving chemoradiation [29]; however, in our and in other previous studies on pelvic exenterations, this correlation did not occur, probably due to the unbalanced rate of patients submitted to radiation therapy before surgery.

In this study, surgical data, such as median operative time, median estimated blood loss and length of stay are superimposable with other experiences [30], meaning the overall standardization of the technique, the importance of performing this surgery in highly specialized centers, and the fact that complications are directly related to the intrinsic complexity of this surgery.

This study's strength relies in the relatively high number of patients treated in a single institution. The large number of body composition data collected in this study, provides a solid basis to promote future trials assessing the impact of pre-operative health condition and nutritional status in gynecologic pelvic exenteration patients. The main limitation is due to the retrospective study design. Moreover, the high number of patients for whom radiological images were not available might have hampered the assessment of correlations between complications and body composition. Finally, data regarding perioperative nutritional support were not available. We believe that this kind of information should be assessed in further prospective trials.

In conclusion, we identified pre-operative factors related to early severe post-operative complications in gynecological cancer patients undergoing pelvic exenteration. Moreover, we believe that the global health status and, above all, nutritional status should be better analyzed in the assessment of risk of post-operative complications, in larger multicentric study. Our data could help the surgeon in the pre-operative assessment of the risk with subsequent more personalized counseling with patients.

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SUPPLEMENTARY MATERIALS

Table S1

Multivariable logistic regression of predictors of early post-operative complications in 129 patients

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Fig. S1

Rate and grade of early (<30 days) and late (>30 days) post-operative complications.

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