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Prognostic factors in pelvic exenteration for gynecological malignancies

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Abstract

Objectives: Analyze morbidity, mortality and prognostic factors after pelvic exenteration (PE) for gynecological malignancies.
Methods: We reviewed a series of 107 individuals who underwent PE at A.C. Camargo Cancer Hospital from August 1982 to September 2010.
Results: Median age was 56.4 years. Primary tumor sites were uterine cervix in 73 cases (68.2%); vaginal, 10 (9.3%); endometrial, 14 (13.1%); vulvar, 7 (6.5%); and uterine sarcomas, 3 (2.8%). Median tumor size was 5.5 cm. Total PE was performed in 56 cases (52.3%), anterior in 31 (29.9%), posterior in 10 (9.3%) and lateral extended in 10. Median operation time, blood transfusion and hospital stay length were 420 min (range: 180–780), 900 ml (range: 300–4500) and 13 days (range: 4–79), respectively. There was no intraoperative death. Fifty-seven (53.3%) and 48 (44.8%) patients had early and late complications, respectively. Five-year progression free survival (PFS), overall survival (OS) and cancer specific survival (CSS) were 35.8%, 27.4% and 41.1%, respectively. Endometrial cancer had better 5-year OS (64.3%) than cervical cancer (23.1%). Lymph node metastasis negatively impacted PFS, CSS and OS. Presence of perineural invasion negatively impacted PFS and CSS. No variable retained the risk of recurrence or death in the multivariate analysis.
Conclusions: PE has acceptable morbidity and mortality and may be the only method that can offer long-term survival in highly selected patients.

Keywords: Pelvic exenteration; Gynecologic neoplasm; Prognostic factors; Morbidity; Mortality

Introduction

Pelvic exenteration (PE) refers to radical en bloc resection of multiple endopelvic and exopelvic organs, followed by surgical reconstruction, to reestablish visceral and parietal function.[1] This procedure was first reported by Alexander Brunschwig[2] in 1948 for the treatment of persistent or recurrent gynecological cancer. Improved perioperative management has recently reduced perioperative mortality rates to 2%–14%.[3–14]

The most common indication for PE is persistent or recurrent cervical cancer after radiation therapy.[1] Twenty-five percent of patients with stage Ib–IIa cervical cancer who are treated with radiation therapy experience a recurrence,[15] but only few are suitable candidates for PE.

The development of new technologies and appropriate patient selection have effected 5-year survival rates following PE that range from 20% to 73%.[7–9,12,14,16–22] Other advances in PE have led to tailored surgery that includes organ sparing when there is no evidence of tumor involvement and to extended operations in which part of the parietal pelvis is resected.[1,4] Further, new techniques for pelvic reconstruction after PE, such as continent urinary diversion and confection of neovagina, have also been described.[23–26]

Several prognostic factors for survival have been reported, such as tumor size, presence of lymphovascular invasion, and positive margins.[12,27] The aim of our study was to retrospectively analyze morbidity, mortality, and the prognostic factors that negatively impact recurrence and survival in patients who underwent pelvic exenteration in AC Camargo Cancer Hospital.

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Patients and methods

This retrospective analysis included 107 individuals with primary and recurrent gynecological malignancies who underwent PE at AC Camargo Cancer Hospital from August 1982 to September 2010. The study was approved by the Institutional Review Board. Eighty-seven patients (81.3%) had PE from January 2000 to September 2010. All patients were treated with curative intent. Patients with extrapelvic metastatic disease, retroperitoneal lymph node metastasis or invasion of the pelvic sidewall that was unsuitable for resection with free margins were excluded.

PE was classified as anterior (APE), posterior (PPE), total (TPE), and total with laterally extended endopelvic resection (LEER). APE refers to the removal of the reproductive tract and bladder; PPE is the removal of the reproductive tract and rectum; and TPE is the removal of reproductive tract, bladder, and rectum. LEER refers to TPE that includes resection of the obturator internus muscle, iliococcygeus muscle, or pubococcygeus muscle. The number of organs or structures (vagina, uterus, bladder, retosigmoid colon, rectum, urethra, anal sphincter, vulva and small bowel) resected and involvement was also evaluated.

Postoperative morbidity was considered to be early if it occurred earlier than 30 days after the operation or before hospital discharge and late if it occurred after 30 days. Follow-up time was the interval between the date of surgery and the last date for which information was available. Morbidity was analyzed per the National Cancer Institute (NCI) common toxicity criteria.

The database was generated in SPSS, version 16.0. The association between parametric variables was assessed by chi-square or Fischer's exact test. Survival curves were constructed by Kaplan–Meier life table analysis. For all tests, an alpha error up to 5% ($p < 0.05$) was considered significant.

Results

Clinical and pathological data

The patients' clinical and pathological data are summarized in Table 1.

Median age was 56.4 years (range: 28–87). Of the 107 patients who underwent PE, 97 experienced persistent or recurrent disease, with a median interval from the first treatment and PE of 18.8 months and a mean interval of 47.2 months (range: 1–365). Ten cases (9.3%) underwent PE as the primary treatment, all of whom had stage IVA disease, and 2 had vaginal sarcomas, 3 had vaginal squamous cell carcinomas (SCC), 4 had cervical cancers, and 1 had endometrial cancer.

The primary tumor sites in the series were uterine cervix in 73 cases (68.2%); vaginal, 10 (9.3%); endometrial, 14 (13.1%); vulvar, 7 (6.5%); and uterine sarcomas, 3 (2.8%). Sixty-seven patients (62.6%) had SCC, 33 (30.8%) had adenocarcinomas, 6 had sarcomas (3 uterine and 3 vaginal), and 1 had vulvar melanoma.

Table 1
Clinical and pathological characteristics of the 107 patients with gynecological cancer submitted to pelvic exenteration (PE).

Variable		No. of patients	(%)
Median age (*y*)		56.4 years (range, 28–87 years)	
Primary site	Cervix	73	(68.2)
	Uterine corpus	17	(15.9)
	Vagina	10	(9.3)
	Vulva	7	(6.5)
Histologic type	Squamous cell carcinoma	67	(62.6)
	Adenocarcinoma	33	(30.8)
	Sarcoma	6	(5.7)
	Melanoma	1	(0.9)
Type of PE	Total	56	(52.3)
	Anterior	31	(29.9)
	Posterior	10	(9.3)
	Lateral extended resection	10	(9.3)
Organ sparing after Total PE	Anal sphincter	12	(21.4)
	Anal and urinary sphincter	1	(1.7)
Lymph node metastasis	No	41	(67.2)
	Yes	20	(32.8)
Surgical margins	R0	93	(92.1)
	R1	8	(7.9)

Of the 97 patients that had persistent or recurrent disease, 17 (15.9%) were asymptomatic, and the most common symptom was pain (39 cases, 36.5%), followed by bloody discharge (32 cases, 29.9%). The diagnosis was suspected or confirmed by clinical examination in 32 cases (32.9%). In 6 (35.3%) of the 17 asymptomatic patients, the diagnosis was made solely by clinical examination.

Twenty-seven patients (25.2%) were classified as American Association of Anesthesiologists (ASA) grade III. TPE was performed in 56 cases (52.3%), APE in 31 (29.9%), PPE in 10 (9.3%), and LEER in 10 (9.3%). A median of 4 organs was resected (range: 2–7), and a median of 3 organs (range: 1–6) had tumor involvement in the pathology specimen. Of the 56 patients who underwent TPE, 12 (21.4%) had anal sphincter-sparing surgery and colorectal anastomosis and 1 (1.7%) had both anal and urinary sphincter-sparing surgery with an orthotopic neobladder.

Of the 66 patients who underwent TPE or LEER, 44 (66.7%) had concomitant diversion with double-barreled wet colostomy (DBWC), as reported by Guimaraes et al.[28] Empty pelvic floor treatment after TPE or LEER was performed with cecum rotation in 14 cases (21.2%), temporary mechanical support in 13 cases (19.7%) – as previously reported,[29] temporary mechanical support that was associated with cecum rotation in 10 cases (15.1%), marlex mesh in 1 case (1.5%), and a musculocutaneous flap in 1 case (1.5%).

The median operation time was 420 min (range: 180–780), and 95 patients (88.8%) received a blood transfusion (median 900 ml, range: 300–4500). The median length of hospital stay was 13 days (range: 4–79).

Fifty-seven (53.3%) and 48 (44.8%) patients had early and late complications, respectively. However, based on NCI toxicity criteria, 19 (17.8%) had grade III or IV early complications. Fourteen patients (13,1%) had late complications that required surgical intervention.

The patients' data on complications are summarized in Table 2.

There were no intraoperative deaths. Thirteen patients (12.1%) died postoperatively, 9 of whom died (8.4%) before 30 days after surgery. The postoperative deaths were due to sepsis (4 cases, 30.7%), renal failure (2), abdominal dehiscence (2), surgical site bleeding (2), gastric bleeding (1), a cerebral vascular accident (1), and undetermined (1 case).

Age and ASA were the only variables that correlated with the risk of postoperative death. ASA III patients had a 33.3% mortality rate versus 5% for ASA I and II ($p < 0.001$), and patients aged over 70 years had a 42.1% mortality rate compared with 5.7% for younger patients ($p < 0.001$). Further, 57.9% of patients aged over 70 years were also ASA III, for whom the risk of postoperative death was 63.6%.

Thirty-three cases (30.8%) had grade 3 tumors. Median tumor size was 5.5 cm (range: 1–24). Sixty-one patients had pelvic and/or retroperitoneal lymph nodes that were resected; a median of 9 lymph nodes were evaluated (range: 1–136). Twenty cases (32.8%) had lymph node involvement. Sixty-eight patients were evaluated for vascular and perineural invasion. Ten (14.7%) and 35 (51.5%) patients had positive vascular and perineural invasion, respectively. Twenty-six (39.4%) of 66 patients had lymphatic invasion. Surgical margins were considered microscopically free of disease (R0) in 93 patients (92.1%) and positive or involved (R1) in 8 cases (7.9%).

The median follow-up time was 25.7 months (range: 1–122). Forty-eight (44.9%) patients experienced a recurrence. At the end of the follow-up, 30 patients (28%) were alive with no evidence of disease, 39 (36.4%) had died due to cancer, 18 (16.8%) died of other causes, and 7 (6.5%) were alive with evidence of disease.

Table 2
Type of early and late complications of the 107 patients submitted to pelvic exenteration.

Type	No. of patients	(%)
Early complications	57/107	53.3
Bleeding	3	5.2
Deep venous trombosis	3	5.2
Urinary fistula	5	8.8
Intestinal fistula	8	14
Wound infection	15	26.3
Pelvic floor infection	17	29.8
Reoperation (grade IV)	19	33.3
Total	57	100
Late complications	48/107	44.8
Deep venous trombosis	3	6.2
Intestinal fistula	3	6.2
Urinary fistula	5	10.4
Intestinal obstruction	9	18.7
Pelvic floor infection	8	16.7
Urinary obstruction	16	33.3
Reoperation (grade IV)	14	29.2
Total	48	100

Recurrence and survival

The 2- and 5-year progression-free survival (PFS) rates were 50.5% and 35.8%, respectively. The 2- and 5-year overall survival (OS) rates were 49.9% and 27.4%, respectively. The 2- and 5-year cancer-specific survival (CSS) rates were 68.2% and 41.1%, respectively.

Patients with endometrial cancer had a better 5-year OS (64.3%) than those with cervical cancer (23.1%) ($p = 0.016$) (Fig. 1). When primary exenteration for cervical cancer was excluded, the 5-year OS was 24.7%. Regarding CSS, endometrial cancer patients had a 5-year CSS of 79.6% versus 32.9% in cervical cancer patients ($p = 0.017$).

Being asymptomatic prior to PE was associated with a better PFS ($p = 0.028$). Lymph node involvement (5-year PFS: 29.4% vs. 41.7%; $p = 0.017$) and perineural invasion (5-year PFS: 27% vs. 49.8%; $p = 0.041$) negatively impacted the risk of recurrence. Grade 3 disease (5-year OS: 18.9% vs. 33.6%; $p = 0.045$), lymph node involvement (2-year OS: 44,9% vs. 64%; $p = 0.011$) (Fig. 2), and involvement of more than 3 resected organs (2-year OS: 34.3% vs. 53.2%; $p = 0.005$) negatively impacted the risk of death. The median OS for patients with lymph

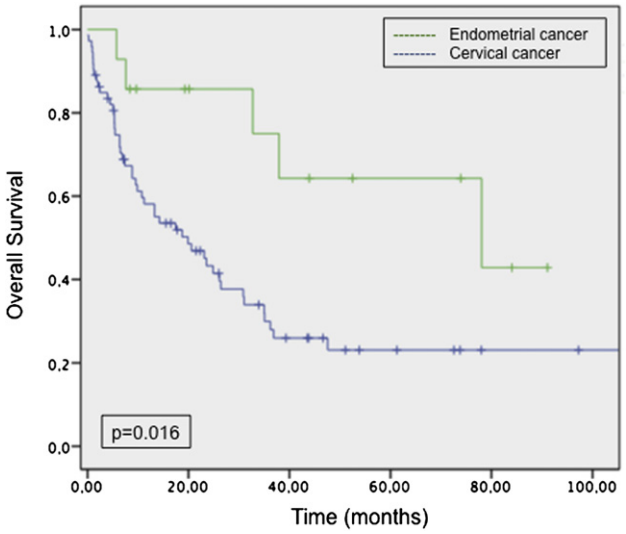

Figure 1. Overall survival curves for patients with primary endometrial and cervical cancer ($p = 0.016$).

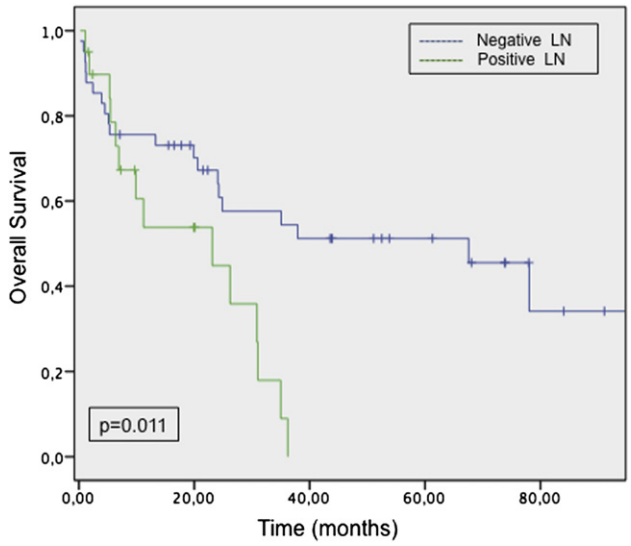

Figure 2. Overall survival curves for patients with positive and negative lymph node (LN) metastasis ($p = 0.011$).

node involvement was 23.1 months and no patient survived more than 36 months. Lymph node involvement (2-year CSS: 50% vs. 63.8%; $p = 0.001$), perineural invasion (3-year CSS: 32.5% vs. 73.7%; $p = 0.004$), and involvement of more than 3 resected organs (3-year CSS: 24.6% vs. 59.6%; $p = 0.048$) also negatively impacted the risk of death from cancer.

Tumor size >5 cm did not correlate with the risk of recurrence ($p = 0.52$), risk of death ($p = 0.19$), or risk of death from cancer ($p = 0.066$).

Patients for whom the interval from the first treatment to PE was greater than 24 months had a better OS ($p = 0.053$) and CSS ($p = 0.062$). However, it did not achieve statistical significance.

Negative margin (R0 resection) did not correlate with a lower risk of recurrence ($p = 0.093$), death ($p = 0.23$), or death from cancer ($p = 0.057$). When patients with cervical or vaginal cancer were analyzed separately, R0 resection positively impacted PFS (2-year CSS: 16.7% vs. 41.6%; $p = 0.026$) and CSS (2-year CSS: 33.3% vs. 65.2; $p = 0.024$) but not OS ($p = 0.21$).

No variable retained the risk of recurrence or death in the multivariate analysis.

Discussion

Exenteration is a major surgical procedure, entailing long operating times that range from 5 to 14 h,[3,4,6,9,11,27] significant blood loss (2300–4000 cm^3),[3,6,11–13,27] and prolonged hospital stays.[3,9,27]

We have noted 5-year overall and cancer-specific survival rates of 27.4% and 41.1%, respectively, consistent with other series, in which median 5-year survival has ranged from 30% to 60%.[3,7,9,11,12,16,22,30–33] Our data reflect a heterogeneous population with associated illnesses, in which 25.2% of subjects were ASA III. We also included extremely locally advanced tumors—the median tumor size in our series was 5.5 cm, and 9.3% underwent exenterative procedures that extended to the pelvic sidewall.

In contrast to other series, we observed better survival rates for subjects with endometrial cancer (5-year OS 64.3%).[22] Despite its disparate mechanisms and metastatic pathways compared with cervical cancer, we recommend that PE be an option for select patients with recurrent endometrial cancer with pelvic disease who are unsuitable for other curative treatments.

The perioperative mortality within 30 days of PE is 0%–14%.[3–14,22] We noted a high postoperative death rate that correlated with age over 70 years and preexisting medical illness (ASA III). Matthews et al.[19] reported a series of 63 patients aged over 65 years who underwent PE, observing an operative mortality rate of 11%. Our findings support other reports[3,34] that have suggested that advanced age and the presence of systemic disease render these patients unsuitable candidates for this extensive procedure. However, Maggioni et al.[22] demonstrated no postoperative mortality, in agreement with other reports that have concluded that physiological, rather than chronological, age should be considered in selecting patients.[19,35]

Our morbidity rate after PE is consistent with reported values of 32%–84%,[11,22,31] with a reintervention rate of 26%–32%.[36] In our series, the rate of early and late complications was 53.3% and 44.8%, respectively. However, based on NCI toxicity criteria, only 17.8% had grade III or IV early surgical complications.

The most common early complications were related to wound (29.8% of 57 patients) or pelvic infections (26.3%), but they were nearly always treated conservatively. The most threatening complications were those that affected the urinary and gastrointestinal systems. Eight (7.4%) patients had intestinal fistulas, and 5 had urinary fistulas (4.6%), similar to Maggioni et al. (4.6%).[22]

We reported[29] an alternative method of treating the empty pelvic floor with a temporary mechanical support, as performed in 23 cases. Briefly, a silicone expander device previously indicated as a urinary bladder modelator was used. The 300 ml capacity apparatus presents a filiform tube for filling/emptying. After total PE, we placed the device on the pelvic floor and the filling tube was externalized through the perineum or abdominal wall. The device was then filled with a saline solution to settle in the small pelvis. Due to its size and mobility, whenever possible we dissected the caecum from the right parietocolic space at about 5 cm from parietal peritoneum, turned it inferomedially and placed it carefully and tensionless on the silicone device. After the procedure we did a peritoneal reflection restoration by suturing the pericecal peritoneum to the remaining parietal peritoneum on the silicone expander. We removed the silicone device with median of 10 days after PE. After patient's sedation, we emptied the device through its externalized filiform tube and then pulled and removed it.

The patients who underwent TPE or LEER using a mechanical device were more likely to develop early or late pelvic infections—53.8% of such cases experienced a pelvic infection versus 18.6% of those without the device ($p = 0.002$). Further, our overall early pelvic infection rate was 15.8%, and we believe that a musculocutaneous flap, such as Vertical Rectus Abdominis Myocutaneous (VRAM) flap, when associated with cecum transposition is the ideal choice for most patients. The musculocutaneous flap may substitute permanently the mechanical support provided by the silicone expander as previously described.

The majority of late complications in our series was related to urinary diversions (33.3%), the most frequent of which was hydronephrosis. Most patients were managed conservatively or by positioning ureteral stents when moderate hydronephrosis was found.

In our data, 30.8% of patients underwent any surgical intervention (including stents) during follow-up, because 33.3% and 29.2% of early and late complications, respectively, required surgery. Maggioni et al.[22] reported a 23.3% rate of reoperation.

Margin status appears to be the factor that is most consistently associated with prognosis.[34,37] Fotopoulou et al.[30] observed that complete tumor resection correlated with better overall and progression-free survival. Numa et al.[38] reported a 5-year survival of 51.3% for an R0 resection compared with 0% for an R1 resection. Further, in series by Berek et al.[3] and Shingleton et al.,[12] no patient survived 3 years following exenteration when the margins of the surgical specimen were tumor-involved. Lawhead et al.[7] reported that 8 of 9 patients with tumor-involved resection margins died from the disease. The series in Marnitz et al.[39] included only cervical cancer patients, and the 2-year survival rate was 10.2% for patients with positive margins and 55.2% (5-year survival rate of 44.8%) for those who had negative margins ($p = 0.0057$).

However, microscopic margin involvement can be detected during the final histopathological review and cannot be determined preoperatively in all cases.[38] In the Maggioni series,[22] when cervical and vaginal cancer were reported separately, 27 of 83 (32.5%) patients had positive margins in the final pathological examination, and survival rates differed between patients with involved margins (25% at 5 years) and disease-free resection margins (60% at 5 years) ($p = 0.043$). Nevertheless, in Rutledge and McGuffee's study,[40] negative margin status was associated with longer disease-free survival ($p = 0.01$) but not with CSS or OS.

We found that 7.9% of our patients had R1 margins and that survival did not differ from patients who underwent PE with microscopic negative resection margins (R0) on the surgical specimen. This finding may be attributed to the heterogeneity of the group. However, as reported in other series, when we analyzed only cervical and vaginal cancers, R0 resection impacted PFS ($p = 0.026$) and CSS ($p = 0.024$) positively.

Tumor diameter at the preoperative clinical evaluation has been reported to be a prognostic factor, although the appropriate cutoff remains to be defined. Some groups have proposed a cutoff of 3–5 cm.[1,12,37] Shingleton et al.[12] and Höckel at al.[4] suggested that recurrent tumor diameter can predict the prognosis, whereas Morley et al.,[9] Symmonds et al.,[14] and Maggioni et al.[22] failed to conclude such a correlation.

In our series, the median tumor size was larger than in other series (5.5 cm), and neither extreme (3 cm or 5 cm) was a significant factor with regard to survival. In contrast, tumor invasiveness—ie, the involvement of more than 3 organs—negatively impacted survival; thus, these data may be more significant than tumor size itself.

The prognostic significance of the interval between primary treatment and PE is controversial. It appears that tumors that take longer to recur are more indolent and more likely to be controlled or cured. Some studies have shown that longer intervals are associated with a better prognosis,[3,9,12,13,39] whereas others have not observed such a correlation.[11] We noted better overall survival for patients who recurred after 24 months of treatment, albeit insignificantly. Notably, PFS after PE was better for asymptomatic patients—the first such finding. It is unclear whether asymptomatic patients are more likely to have more indolent tumors or whether earlier disease development is more amenable to salvage therapy.

Several groups have described lymph node metastasis as an important negative prognostic factor,[17,22,34,37,41] and others consider it a contraindication for PE.[9,16,42] Yet, Rutledge and McGuffee[40] concluded that lymph node status was unrelated to survival and that long-term survival can be achieved, even with positive lymph node involvement, if they are completely resected. In patients with positive lymph nodes, 36% remained alive after 3 years of follow-up versus 26% at 5 years. In addition, Marnitz et al.[39] and Ketcham et al.[6] failed to describe lymph node involvement as a significant factor of survival.

We consider lymph node status an important prognostic factor and propose that lymph node evaluation might take part of the surgical procedure to better stratify those patients who are more likely to recur and benefit from adjuvant treatment trials. In our series no patient with lymph node involvement had prolonged survival.

The preoperative determination of lymph node status remains problematic, but preoperative radiological studies by CT scan, MRI, or, more recently, PET-CT, which has a sensitivity of 100% and a specificity of 73% in detecting sites of extrapelvic metastasis,[42] should be mandatory for restaging. Since 2005, all patients who underwent PE in our institution have had a PET-CT scan with negative findings for distant disease.

Overall, our series have a comparable sample size to the most important studies of this kind and may add important information to literature. Nevertheless, our data may help to select patients to PE and better stratify those with higher risk of recurrence and death after PE.

In summary, lymph node involvement and presence of perineural invasion negatively impacted the risk of recurrence and death from cancer. Number of organs involved rather than tumor size should be considered as a prognostic factor. For cervical and vaginal cancer, R0 resection correlates to better outcome. However, no variable retained the risk of recurrence or death in the multivariate analysis. Finally, PE should not be offered to patients classified as ASA III and also aged over 70 years.

Our series suggests that PE is a feasible therapeutic option that avoids intraoperative death and has acceptable morbidity and mortality. Careful patient selection, meticulous operative techniques, multiple-surgeon effort, intensive postoperative management, and the creation of specific and adequate referral centers remain the cornerstones of reducing the complication rates and maximizing the success of this aggressive operation. PE might be the only approach that effects long-term survival in highly select patients with persistent or recurrent gynecological malignancies.

Conflict of interest statement

All authors declare that there is no conflict of interest.

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