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Research Article

Pelvic Exenteration for Cervical Cancer that is Persistent or Recurrent after Radiotherapy or Chemoradiation. Institutional Experience of 51 Years.

Alfonso Torres Lobaton[1*], Rosalva Barra Martinez[2], Maria Yicel Bautista Hernandez[3], Carla America Suarez Juarez[4], Isidro Siañez Rodriguez[4], Fred Morgan Ortiz[5], Juan Carlos Oliva Posada[6], Mónica Alejandra Matta Martínez[4]

[1]Surgeon Oncologist. Technical consultant, Oncology Gynecology Unit, Surgical procedures, Mexico

[2]Surgeon Oncologist. Master of Science, Head of skin cancer unit melanomas soft tissue sarcomas and bone tumors, General Hospital of Mexico, Mexico

[3]Head of the Radiotherapy Unit, Mexico

[4]Gynecologist Oncologist, Mexico

[5]Obstetrician gynecologist. Master of Science. Health Sciences Research Center, Autonomous University of Sinaloa, Statistical analysis, Mexico

[6]Head Surgeon Oncologist of the Oncological Gynecology Unit, Mexico

***Corresponding author**: Alfonso Torres Lobaton, Surgeon Oncologist. Technical consultant, Oncology Gynecology Unit, Surgical procedures, Mexico

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Abstract

Objective: To investigate the morbidity, mortality and results of treatment with pelvic exenteration (PE) in patients with cervical cancer (CC) that was persistent or recurrent following Radiotherapy (RT) or Chemoradiation (CCRT), through 51 years of institutional experience.

Material and methods: This was a retrospective study of 480 patients with CC from the Oncology Service of the Hospital General of Mexico who were treated with PE from January 1966 to December 2006 and from January 2008 to December 2018.

Results: The youngest patient was 24 years old, the oldest was 77 years, and the mean age was 45.8 years. PE was performed on 429 patients in the 1966 to 2006 period (89.3% of total) and on 51 patients (10.6%) in the 2008 to 2018 period. Anterior pelvic exenteration (APE) was performed on 236 patients (49.1%), total pelvic exenteration (TPE) on 234 patients (48.7%), and posterior pelvic exenterations (PPE) on 10 patients (2.0%). The median duration of surgery was 270 min. Major complications developed in 141 patients (29.3%). The overall operative mortality was 9.6%, but decreased from 15.7% before 2000 to 1.9% for the period from 2000 to 2018 ($p<0.0003$). The Kaplan Meier curves showed a 5-year follow up Disease Free Survival (DFS)

and Overall survival (OS) a median of 9 and 19 months respectively and OS of 50.9% for 25 and more months. Multivariate analysis for overall survival (Cox Regression) showed that APE was associated with good prognosis ($p<0.0001$), whereas PPE ($p<0.0001$), parametrial invasion ($p=0.003$), pelvic wall invasion ($p=0.053$) and uterine body invasion ($p<0.0001$) were all associated with worse prognosis. Of the 91 patients with documented failure of PE treatment, 33 (36.2%) presented with distant metastases and of these 19 (42.4%) occurred without locoregional tumor activity.

Conclusions: In this series of CC patients, the use of PE decreased dramatically over time, as well as the rate of operative mortality. Approximately half of patients showed an overall survival rate of more than 24 months, despite having advanced clinical stages of the disease. Patients with PE treatment failure who show distant metastases without pelvic tumor activity could be managed by adjuvant therapy.

Keywords: Cervical cancer; Pelvic exenteration

Abbreviations: PE: Pelvic Exenteration; Pes: Pelvic Exenterations; CC: Cervical Cancer; RT: Radiotherapy; CCRT: Concomitant Chemoradiation; OU: Oncology Unit; GHM: General Hospital of Mexico; CCPR: Cervical Cancer Persistent or Recurrent; APE: Anterior Pelvic Exenteration; TPE: Total Pelvic Exenteration; PPE: Posterior Pelvic Exenterations; PC: Postoperative Complications; MC: Mayor Complications; DFS: Disease Free Survival; FIGO: International Federation of Gynecology and Obstetrics; PET: Positron Emission Tomography; ICU: Intensive Care Unit; GC: Gynecological Cancer; OS: Overall Survival; RTA: Residual Tumor Activity; Gy: Radiation treatment unit

Introduction

Cervical cancer (CC) causes more than 4,000 deaths per year in Mexico and as such represents an important health problem [1]. Patients with advanced stages of the disease represent 60% of the CC admissions to hospital in this country and receive radiotherapy (RT) as a basic treatment. This population lacks social security, thus explaining the high mortality figures reported previously [2,3]. Pelvic Exenterations (PE) are the last chance for cure in a selected group of patients with recurrent or persistent disease localized to the pelvis [4-6]. These procedures have a high morbidity, with published estimates ranging from 30% to 80% [4,7,8-11]. However, the operative mortality in recent series has been reported to be ≤ 5% [9-11]. In most studies, the 5-year disease free survival (DFS) rate does not exceed 45% [8,9,11-13]. In this article we report on 51 years of experience in our institute on the surgical management of CC patients treated with RT and less frequently chemoradiation (CCRT), and in whom these treatments failed and the patient subsequently underwent PE. The aim of this work was to investigate the role of PE in the treatment of CC patients based on the number of laparotomies performed and the morbidity, mortality, results of surgical procedures, Disease Free Survival (DFS) and Overall Survival (OS) rates, as well as possible causes of treatment failure.

Material and methods

From January 1, 1966 to December 31, 2006 and from January 1, 2008 to December 31, 2018, 1,082 laparotomies were carried out in the Oncology Unit (OU) of the General Hospital of Mexico (GHM) in patients with CC who underwent PE due to persistent or recurrent disease following radiotherapy (50 Gy teletherapy followed by intracavitary radiotherapy, brachytherapy 30 Gy) or complete or incomplete CCRT. This consisted of Teletherapy (50 Gy) + cisplatin or carboplatin at conventional doses+ Brachytherapy (30 Gy) in patients who had an optimal functional reserve and tumor limited to the pelvis, as shown by clinical examination and imaging studies. Anterior Pelvic Exenterations (APE) included resection of the uterus, adnexa, parametria, ureters, urinary bladder, and pelvic lymph nodes. Total Pelvic Exenteration (TPE) also included the rectum, while Posterior Pelvic Exenterations (PPE) included the rectum but preserved the urinary tract. Most of the procedures were superior to the levator muscle of anus [4,14]. Prior to bowel preparation, a supra and infraumbilical median laparotomy were performed and the abdominal and pelvic cavity was reviewed. When there was a suspicion of abdominal activity outside the pelvis or of a tumor fixed to the pelvic wall, an intraoperative biopsy of the lesion was taken and pelvic lymph node dissection was started on the side most affected by the tumor. With a positive report for metastasis of the biopsied tissue, the surgical intervention was terminated and lymph node dissection was completed in the rest of the patients. The specimen was extracted in a block, with sufficient margin to the vagina and removal of the bladder and / or rectum being necessary in some patients with transopertive report of tumor in the vaginal margin, to widen the margin with or without perineal approach for complete extraction of the specimen. Reconstruction of the urinary tract was performed using a defunctionalized segment of the terminal ileum, Bricker's ileal conduit, [14,15] or through a difunctional segment of the sigmoid rectum (sigmoid conduit). A colostomy terminal was carried out in the case of TPE and PPE. For the purpose of analysis, the evaluation of operative morbidity and mortality was divided into four time periods: the first was from 1966 to 1979, the second from 1980 to 1989, the third from 1990

to 2006, and the fourth from 2008 to 2018. The FIGO 2018 version (International Federation of Gynecology and Obstetrics) [16] clinical classification was used here, comprising stage I, IB2 and IB3 lesions and stage III, IIIA and IIIB neoplasms. The morbidity and mortality of each intervention procedure was determined to evaluate the surgeries. Surgical mortality was considered as being death up to 30 days after the intervention. Morbidity was considered to include major complications (MC) that put the patients' life at risk, such as dehiscence of the anastomotic sutures. Complications that did not meet this requirement were considered as minor and included for example the infection of a surgical wound, pelvic or wall abscess, etc. For analysis of the variables, descriptive statistics were used with calculation of the mean and proportions for numerical and categorical variables, as appropriate. Survival analysis was performed using the Kaplan-Meier method and differences between groups were assessed using the log rank test. Univariate and multivariate Cox proportional hazards models were used to identify variables that correlated with DFS and OS, with 95% confidence intervals calculated for the odds ratio (OR). A P value of < 0.05 was considered statistically significant. All statistical analyses were performed with the SPSS 22.0 statistical program.

Results

Of the 1,082 operated patients, 480 (44.3%) underwent PE. The proportion of patients undergoing PE has decreased over the years, as shown in Table 1. Almost 90% (429/480, 89.3%) of the procedures were carried out in the period from 1966 to 2006, with only 51 (10.6%) carried out in the period from 2008 to 2018.

Period	PE/laparatomy cases	Percent
1966-1979	171/351	48.7
1980-1989	132/331	39.8
1990-2006	126/249	50.6
2008-2018	51/151	33.1
Total	480/1082	44.3
*429/480 (89.3%) of all PE were performed from 1966 to 2006, and 51/480 (10.6%) from 2008 to 2018.		

Table 1: Relationship of pelvic exenterations to laparotomies during four different time periods*.

Clinicopathological characteristics of the 480 patients who underwent PE are shown in Table 2. The youngest patient was 24 years old, the oldest was 77 years and the mean age was 45.8 years. The most common histopathological type was squamous cell carcinoma (92.2% of cases), the large majority of patients (95%) were diagnosed at an advanced stage, and 89.3% received a complete pelvic cycle of RT as the initial treatment. APE (49.1%) and TPE (48.7%) were performed at almost identical frequency. For the urinary diversions, ileal conduits were made in 397 (82.8%) patients and sigmoid conduits in 80 (16.6%) patients. Only 3 patients (0.6%) underwent continent urinary diversions.

Variable	No. of Patients	Percent
Age		
21-30	22	4.5
31-40	127	26.4
41-50	183	38.1
51-60	110	22.9
61-70	29	6
71-80	9	1.8
<24, >77, median: 45.8 years		
Pathology		
Squamous cell carcinoma	443	92.2
Adenocarcinoma	37	7.7
Clinical Stage		

I	31	6.4
II	213	44.3
III	148	30.8
IVA	44	9.1
Not classifiable	44	9.1
Schedule of Radiotherapy		
Complete Pelvic Cycle*	429	89.3
**Radiotherapy + Chemotherapy	51	10.6

*External beam radiotherapy: 45-50 Gy + Brachytherapy: 30-35 Gy (RT).

** External beam radiotherapy/Chemotherapy + Brachytherapy or External beam radiotherapy/Chemotherapy.

Table 2: Clinicopathological characteristics of the 480 patients who underwent PE.

The duration of the surgical procedures ranged from 3 to 6 hours, with an average of 4.45 hours. The average blood loss was 1200 c.c. (range 400 - 7,500 c.c.) and the days of hospitalization ranged from 7 to 61 with an average of 15 days.

Morbimortality: Postoperative Complications (PC) were documented in 232 (48.4%) patients. These occurred in 86/171 (50.2%) of patients treated from 1966 to 1979, in 50/132 (37.8%) of those treated from 1980 to 1989, in 76/126 (59.5%) of those treated from 1990 to 2006, and in 20/51 (39.2%) of those treated from 2008 to 2018. The 59.5% increase observed in the period from 1990 to 2006 was due to completion of the training program for surgeons and admission to their specialty. MC occurred in 141/480 (29.3%) patients and of these 28 (19.8%) required further surgery. The most frequent MCs were due to dehiscence of the ureteral and intestinal sutures, and sepsis (Table 3).

Complication	Number	Percent
Urinary fistula	51	31.4
Intestinal fistula	28	17.2
Septicemia	23	14.1
Gastrointestinal bleeding	15	9.2
Intestinal obstruction	15	9.2
Postoperative bleeding	12	7.4
Necrosis of the ileal conduit	8	4.9
Pneumonia	7	4.3
Other	3	1.8
Total:	141/479	29.4

* 29 patients (20.5%) presented with more than one complication

Table 3: Major postoperative complications observed in 141 patients.

More than one MC was observed in 29 (20.5%) patients. Minor complications were observed in 91 (18.9%) patients and were mostly due to infection of the surgical wound and to pelvic abscess. Forty-six (9.5%) of the 480 patients died within the first 30 postoperative days. Postoperative mortality showed a decline from 15.7% in the 1966-1979 period to just 1.9% for the 2000-2018 period (P=0.0003) (Table 4 and Figure 1).

Period	No. of cases	Percent
1966-1979*	27/171	15.7
1980-1989	11/132	8.3
1990-1999	Jun-73	8.2
2000-2006**	Feb-53	3.7
2008-2018**	0/51	0
Total:	46/480	9.5

*1966-1979: 27/271 (15.7%) vs 2000-2018**: 2/103 (1.9%), p=0.0003.

Table 4: Thirty-day postoperative mortality from Pelvic Exenteration.

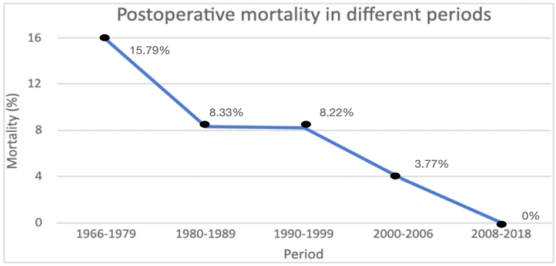

Figure 1: Postoperative mortality for 480 cases that underwent PE in different time periods.

The postoperative mortality according to the type of exenteration performed was 28/234 (11.9%) for TPE, 21/236 (8.9%) for APE, and 0/10 (0%) for PPE. There was no significant difference between the mortality rates for TPE and APE (P = 0.277).

Pathology Reports for 430 surgeries: Table 5 shows the location of tumor activity according to the pathology report for the 480 EPs. No patient in this series received additional treatment post-Pelvic exenteration..

Variable	Total of cases	Percent
Central recurrence		
No	317	66
Yes	163	33.9
Parametria recurrence		
No	266	55.4
Yes	214	44.5
Hydronephrosis		
No	444	92.5
Yes	36	7.5
Pelvic wall extent		
No	443	92.2
Yes	37	7.7
Bladder extent		
No	416	86.6
Yes	64	13.3
Rectum extent		
No	459	95.6
Yes	21	4.3
Uterine body extent		
No	454	94.5
Yes	26	5.4
Adnexa extent		
No	471	98.1
Yes	9	1.8
Lymph node metastases		
No	395	82.2
Yes	85	17.7

Table 5: Pathology reports for 480 surgeries.

Results of surgical treatment: The Kaplan Meier curves showed for DFS and OS, in the 480 exenterations a median of 9 and 19 months respectively, Figure 2.

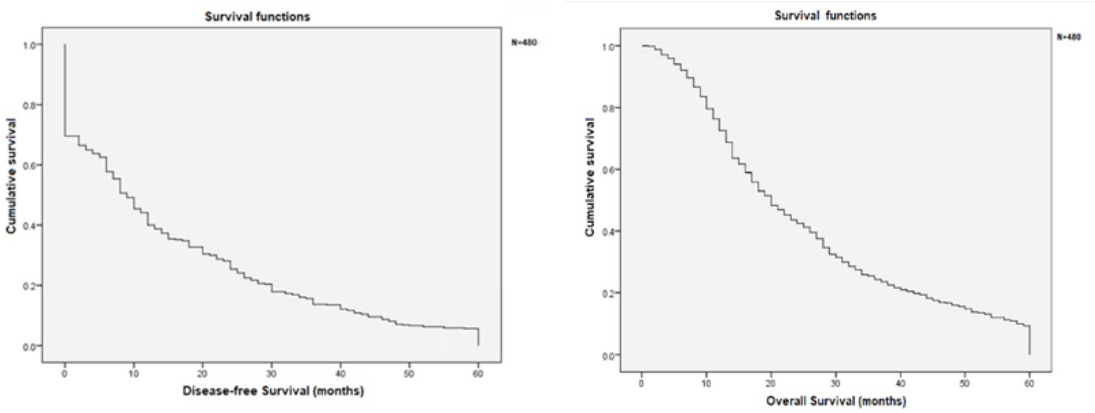

Figure 2: A median of DFS and OS to five years in the 480 exenterations: 9 and 19 months respectively.

When comparing for DFS the periods 1966-2006 vs 2008-2018, the figures were 9 and 9 months (Log Rank Test p=0.964) and 19 and 20.0 months for OS (Log Rank Test, p=0.802), Figure 3.

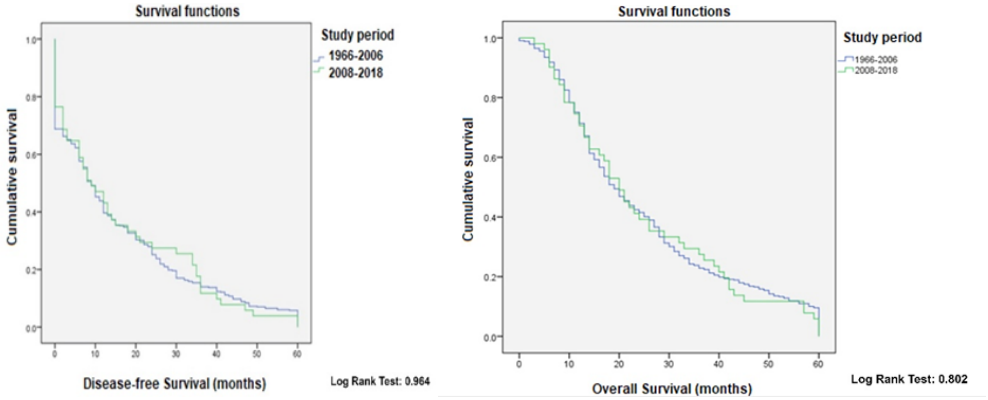

Figure 3: DFS the periods 1966-2006 vs 2008-2018, the figures were 9 and 9 months (Log Rank Test p=0.964) and 19 and 20.0 months for OS (Log Rank Test, p=0.802).

Out of 332 patients, 480 patients (69.1%) exhibited a disease-free follow up. The median DFS of these patients was 24.2 months (95% CI: 21.9 – 26.6), while the mean OS was 34.4 months (95% CI: 30.7), Figure 4.

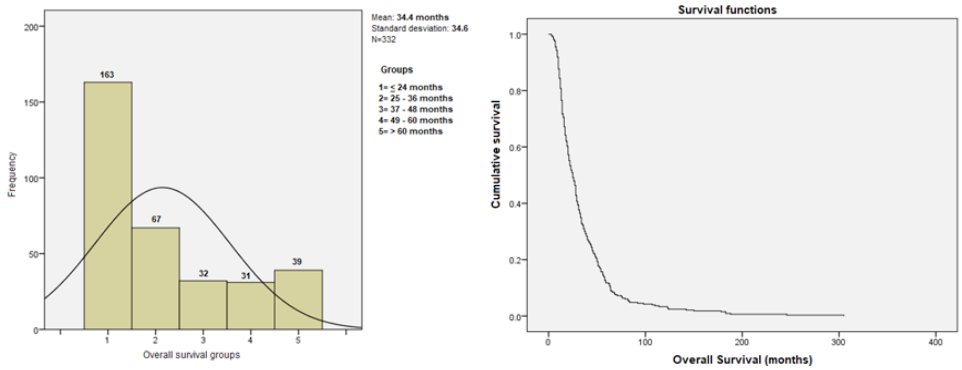

Figure 4: (Kaplan Meier survival curves) Overall Survival in months of 169/332 patients (25–60 months 50.9%).

A total of 208 patients (62.6 %) lost their follow up during the first 24 months following surgery with no evidence of disease. because of this , we do not know the presence or not of tumor activity in these patients. There were 148 therapeutic failures in this series. Of these, 91 were due to tumor recurrence and the patients died with tumor activity (Table 6). Another 46 died during the first 30 days postoperatively. (Table 4) and 14 patients died due to tumor activity during the first 24 months of follow-up without finding the cause of death in the records.

Prognostic factors: In univariate analysis, the variables that indicated OS with favorable influence on prognosis were age 21-30 years (p=0.044), FIGO Stage I and II (p=0.002), APE (p=0.001), and surgery performed one year after the diagnosis of tumor recurrence (p<0.0001). The variables associated with a negative influence on prognosis were parametrial recurrence (p<0.0001), pelvic wall invasion (p<0.0001), hydronephrosis (p<0.0001), bladder invasion (p=0.002), uterine body invasion (p<0.0001), and lymph node metastases (p<0.0001). Table 6

Variable	Median	N	Min	Max	P Value
Age group					0.044
21 – 30	30	22	7	123	
31 – 40	17	127	1	150	
41 – 50	19	183	2	124	
51 – 60	20	110	2	305	
61 – 70	21	29	4	246	
71 – 80	28	9	21	44	
Initial FIGO Clinical stage					0.002
I	25	31	5	110	
IIA	29	36	8	98	
IIB	23	177	2	305	
IIIA	15	9	9	29	
IIIB	16	139	1	114	
IVA	16	44	2	123	
Out-of service treatment	20	44	3	183	
Type of surgery					0.001
Anterior exenteration	23	236	1	305	
Total exenteration	18	234	2	246	
Posterior exenteration	11	10	2	27	
Parametria recurrence					P<.0001
No	27	266	2	183	
Yes	16	214	1	305	
Hydronephrosis					P<0001
No	21	444	2	305	
Yes	12	36	1	98	

Pelvic wall extent					P<0001
No	21	443	2	305	
Yes	11	37	1	98	
Bladder extent					0.002
No	21	416	2	305	
Yes	15	64	1	98	
Rectum extent					0.018
No	20	459			
Yes	11	21			
Uterine body extent					P<0001
No	20	454	2	305	
Yes	11	26	1	52	
Lymph node metastases					p<0001
No	22	395	2	305	
Yes	14	85	1	246	
Tumor recurrence					P<0001
< 12 months	17	400	1.6	142	
>12 months	38	80	6	305	

Table 6: Univariate analysis for overall survival in 480 pelvic exenterations.

Multivariate analysis for OS (Cox Regression) showed a positive impact on prognosis for APE (p<0.0001), but negative impacts for PPE (p<0001), parametrial invasion (p=0.003), pelvic wall invasion (p=0.053) and uterine body invasion (p<0.0001) (Table 7).

Variable	B	SE	Wald	Exp(B)	95.0% CI to Exp(B)	95.0% CI to Exp(B)	P Value
					Inferior	Superior	
Age group	0.007	0.044	0.023	1.007	0.924	1.097	0.879
Initial FIGO Clinical Stage	0.006	0.029	0.044	1.006	0.95	1.065	0.834
Type of surgery	0.329	0.091	12.943	1.389	1.161	1.662	P<0001
Parametria extent	0.324	0.111	8.543	1.382	1.113	1.718	0.003
Hydronephrosis	0.04	0.24	0.028	1.041	0.65	1.666	0.868
Pelvic wall extent	0.471	0.243	3.738	1.601	0.994	2.579	0.053
Bladder extent	0.146	0.151	0.938	1.158	0.861	1.556	0.333
Uterine body extent	0.765	0.214	12.718	2.148	1.411	3.271	P<0001
Lymph node metastases	0.126	0.136	0.867	1.135	0.87	1.48	0.352

The model included only those variables that showed significance in univariate analysis.

Table 7: Multivariate analysis for overall survival in 480 cases of pelvic exenteration (Cox Regression).

Recurrences: Information on tumor recurrence was documented for 91 patients. The recurrences occurred between 6 and 26 months (mean of 10.5 months) (Table 8). Of the 33 patients who developed distant metastases, 14 (42.4%) did not have locoregional recurrence. In 18/45 (40%) cases with local and locoregional recurrences, residual tumor was reported in the surgical specimens without additional treatment.

Location	No. of patients	Percent
Local	36	39.5
Regional	9	9.8
Locoregional	13	14.2
Distant *	33	36.2
Total:	91	99.7

*14 of these 33 patients (42.4%) did not have locoregional recurrences.

Table 8: Tumor recurrences in patients with pelvic exenterations.

Distant recurrences occurred in 1-4 anatomical locations, comprising: Lung: 13, (39.3%); Inguinal lymph nodes: 10, (30.3%); Retroperitoneum: 9 (27.2%); Mediastinum: 7, (21.2%); Bones: 4, (12.1%); Supraclavicular lymph nodes: 3, (9.0%); Central Nervous System: 3, (9.0%); Abdominal wall: 1, (3.0%)

Discussion

Surgical therapy is a well-established treatment for CC disease that is persistent or recurrent after RT. Surgery represents the last opportunity to achieve disease control, since patients left to the natural disease evolution will eventually succumb to the consequences of tumor spread [4,5,6,14,17]. Since up to 95% of CC patients present with advanced stages of disease, the failure rates after initial conventional treatment with RT are 23% for stage IIB, 42% for stage III, and 74% for stage IVA [18]. In this series presence of unresectable lesions was demonstrated in 45.3% of CC patients that were surgically explored. Currently, the main challenge with laparotomized patients is knowing if cases with a tumor fixed to the pelvic wall can be resected, since it may not be obvious whether the lesion is a tumor or fibrosis. Laparotomy can help to determine which patients may benefit from radical surgery [7,12,14]. Lopez et al [14] reported that intraoperative surgical evaluation is essential for the success of surgery and that the procedure is aborted in up to 30% of cases due to locally unresectable lesions or because of dissemination outside the pelvis. The reason for the high number of unresectable lesions in the present series was that many patients did not have extensive imaging studies prior to surgery, such as computed tomography. This resource started to be used routinely at the authors' institute from this century. More recently, when doubt exists about the use of laparotomy, patients are sent to other centers for Positron Emission Tomography (PET) in order to inform the course of action required [12,14]. Patients in the current series also did not undergo magnetic resonance studies because this resource is not available for CC patients in our Institute. Fewer surgeries for CC have been performed in recent years for the following reasons. Firstly, there are fewer cases and more oncology institutions [2]. Secondly, CT and PET enable better evaluation of tumor activity. Thirdly, fewer patients are being diagnosed with stage IVA disease. Finally, laparotomies are performed in patients who have suspected tumor persistence due to tumor size and pathologies that indicate a poor prognosis [19-22].

In the present study, APE and TPE were performed at almost identical frequency and urinary diversions were resolved using ileal conduits in 82.8% of cases. The latter procedure is the most common choice for patients who have previously been subjected to radiation [11,13,23,24]. PC occurred in 49.1% of cases, with 29.3% of these being considered as MC. The most serious MC was related to dehiscence of the anastomotic sutures. Some authors have reported that up to 70% of patients in their series experienced complications [8,10,20,23]. Teran-Moncayo et al from the National Cancer Institute previously reported that 65.3% of patients experienced complications in a study of 42 CC patients treated with PE in Mexico city [25]. The 30-day postoperative mortality rate in the present study was 9.6% for the overall cohort. However, it decreased from 15.7% (27/271) in the 1966-1979 period to just 1.9% (2/103) for the 2000-2018 period ($p < 0.0003$). We attribute the improvement in postoperative mortality to a number of factors, including the careful selection of candidates for these surgeries, the use of modern imaging procedures prior to surgery, having more experienced surgeons to perform the challenging procedures, and having modern anesthesia equipment and anesthesiologists dedicated exclusively to the care of cancer patients. In addition, new resources became available including an optimal choice of hemoderivatives for transfusion in patients who required them, dedicated intensive care rooms, more effective antibiotics, and patient discharge from the intensive care unit only after they had fully recovered from surgery. The operative mortality for PE procedures was initially 20% [4], but then decreased progressively from the 1970's with more recent reports now showing <5% mortality [8,10,11,12,26,27].

Recent publications on exenterations for gynecological cancer (GC) have reported a notable decrease in postoperative mortality. Bacalbasa et al reported an operative mortality of 3% for 100 cases of pelvic cancer, 56 of which were CC [10]. Kelly et al reported a mortality rate of 1.7% in a series of 523 cases, 108 of which were CC [27]. Finally, Matsuo et al reported a mortality rate of 1.9% following review of 2647 cases due to GC [8]. In this seriesThe Kaplan Meier Analysis showed a 5-year

follow-up without evidence of disease for DFS and OS, a median of 9 and 19 months respectively. When comparing for DFS the periods 1966-2006 vs 2008-2018, the figures (Log Rank Test) were 9 and 9 months p=0.964 and 19 and 20.0 months for OS, p=0.802. In the present series, 332/480 patients (69.1%) showed no disease recurrence after a follow-up period of one to 60 months. Furthermore, 208 patients (62.6%) stopped attending follow-up after surgery with no evidence of disease during the first 24 months after surgery. The average period of DFS was 24.2 months and for OS it was 34.4 months. Just over half (169/332, 50.9%) of patients had an OS of 25-60 months. Two-thirds of the patients from this study reside outside of Mexico city. Most of them lack social security and it is therefore difficult to obtain 5-year follow-up information. Multivariate analysis for overall survival (Cox Regression) revealed a positive influence on prognosis for APE ($p<0.0001$) and negative impacts for PPE ($p<0.0001$), parametrial invasion ($p=0.003$), pelvic wall invasion ($p=0.053$) and uterine body invasion ($p<0.0001$). The adverse results obtained in this series with the posterior exenteration in radiated patients have motivated us to no longer perform it. Parametrial involvement by tumor prevents giving satisfactory margins to these patients which favors tumor recurrence. Chiva et al [7] reported a 5-year OS of 42.8% following PE for 411 patients with CC that was persistent or recurrent after RT. The cases were collected internationally between 1995 and 2006. Maggioni et al [26] in 2009 reported a 5-year OS of 52% for 62 cases. Balcabasa et al [10] in 2019 reported a 63% survival rate after 2 years in 100 patients following PEs for recurrent pelvic cancer. This compares to the OS in our series of 50.9% after 24 months or more. The 5-year DFS rates for various PE series published in the first decade of this century range between 20% and 60% [7,13,24,27,28].

Regarding PF in patients exenterated by CC, some studies emphasize that APE has a better prognosis than TPE, since rectal resection presupposes a greater tumor burden and is accompanied by greater operative morbidity and mortality [24]. In the present study, the univariate and multivariate analysis for OS showed a better prognosis for APE compared to TPE ($p<0.0001$). Fleish et al. [28] did not find significant differences in prognosis according to the type of exenteration performed in their study of 203 PE, of which 133 were due to CC. In the current study, age-related results were only statistically significant when the evolution of patients aged 21-30 years was compared with the rest of the study cohort. Some studies have reported that patients older than 60 years have an unfavorable prognosis for PE due to the greater number of comorbidities [28,29]. The mean patient age in our study was 45.8 years, with only 7.8% of patients aged over 60 years. Other recent publications of PE due to GC have reported the mean age of their study cohorts to be 60–63 years [15,18,19]. Here, univariate analyses for OS showed significant differences in prognosis for Stage I and II patients ($p=0.003$ and $p=0.002$, respectively) while some authors only refer to poor prognosis for stage IIIB and IVA patients [26,27]. In agreement with previous studies [15,17], univariate analysis for OS in our study showed a more favorable prognosis for surgeries performed 12 months after the diagnosis of tumor recurrence ($p<0.0001$). In a study of 37 PE of which 59.5% were due to CC, De Gregorio et al [15] reported a 5-year survival of 46.4% and that long evolution prior to PE was a favorable PF ($p = 0.020$). These investigators noted that the clinical stage or the histological type did not influence prognosis.

The variables associated with a negative influence on prognosis in our series were parametrial recurrence ($p<0.0001$), pelvic wall invasion ($p<0.0001$), hydronephrosis ($p<0.0001$), bladder invasion ($p=0.002$), uterine body invasion ($p<0.0001$), and lymph node metastases ($p<0.0001$). Having this information through prevous analyses [30] , for more than 12 years we had the idea of adding adjuvant therapy to patients at risk for tumor recurrence. Unfortunately, our government, which sponsors these treatments, only authorizes the use of chemotherapy, for concomitant management with radiotherapy as primary treatment for the advanced stages of this disease. In a study of 203 PE for advanced pelvic cancer of which 65% were due to CC, Fleisch et al [29] highlighted that adverse PFs were infiltration to the uterine corpus ($p = 0.01$) and infiltration to the PW ($p = 0.02$).

Shingleton et al [17] reported that favorable PFs in their study were tumor volume <3 cm, parametrial invasion that does not affect PW, and recurrences one year after finishing RT. These patients displayed a 5-year DFS of 58%. Patients with large tumors, fixed PW lesions, and a short disease-free period after RT showed a DFS rate of 42%. The diagnosis of lymph node metastasis (Stage IIIC) [3] is an adverse PF that has led some authors to give a controversial value to PE in the presence of such a diagnosis [28,29]. In our study, a report of lymph node metastases was adversely associated with prognosis in univariate analysis for OS ($p<0.0001$). The patient cohort reported here spans a period of 51 years and is limited to patients with advanced CC who were treated with RT as a base procedure, and in whom PE was the last opportunity to gain control of their disease. These challenging procedures remain relevant in our institution, even though they are being carried out less frequently.

Conclusions

Over the past 11 years, the number of PEs performed has decreased by 89.5% compared to those carried out in previous years. APE and TPE were performed with the same frequency over the past 5 decades. Almost half (49.1%) of our cases showed PC and these were considered MC in 29.4% of patients. The overall postoperative mortality was 9.5%, but this showed a decrease from 9.1% during the years 1966-1999 to just 1.9% for the years 2000 to 2018. No postoperative deaths were recorded over the past

11 years. In the present series, The Kaplan Meier curves showed for DFS and OS, in the 480 exenterations a median of 9 and 19 months respectively. 332/480 (69.1%) patients showed no disease at follow up. The median period of DFS in these 332 cases was 24.2 months and for OS it was 34.4 months. OS after 24 months was 50.9%. Of the patients who failed treatment, 42.4% showed distant metastases without tumor activity in the pelvic region. This suggests that adjuvant therapy will be suitable for patients who experience this type of disease evolution.

Author Contributions

BR, MM and SI developed the database and manuscript development. SA supported translation of the manuscript. BY performed radiotherapy treatment planning. MF performed statistical analysis. OJ performed several of the surgical procedures. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript

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