



Research Article

Complementary and Salvage Surgeries in the Treatment of Cervical Cancer Persistent Following Chemo Radiation. Experience with 105 Patients.

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Abstract

Objective: The purpose of this review is to show results of surgical treatment performed 6-12 weeks after chemo radiation, with or without brachytherapy, in patients with locally advanced cervical cancer with documented or suspected tumour.

Material and Methods: This was a retrospective study of patients with cervical cancer treated in the Oncology Service of Hospital General of Mexico during the period 2008-2018 who underwent surgery to perform complementary or salvage surgery due to actual or perceived tumour persistence.

Results: Patients had a median age of 46.5 years (range= 25-71) and underwent 105 surgeries which included 75 hysterectomies with or without lymphadenectomy (71.4%) and 30 pelvic exenterations (28.5%). Major complications occurred in 7/75 (9.3%) of hysterectomies and 9/30 (30.0%) exenterations. In this series, there was no postoperative mortality. In 105 hysterectomies and pelvic exenterations, the Kaplan Meier curves were generated for disease-free survival (DFS) and overall survival (OS) with a median follow-up of 20 months and 24.0 months respectively. Common variables for the 105 hysterectomies and exenterations demonstrated by univariate analysis for (DFS) and (OS) significant differences for age < 35 years ($p=0.031$ and $p=0.051$), adenocarcinoma ($p=0.023$ and $p=0.019$) and for the absence of lymph vascular infiltration on surgical specimens ($p=0.003$ and $p=0.001$). The multivariate analysis for DFS and OS only showed significant differences for the absence vs presence of lymph vascular invasion ($p=0.001$ and $p=0.002$). Seventy-five patients treated with hysterectomies had DFS with a mean of 29.4 months and OS of 32.4 months. In the multivariate analysis, Log Rank test showed significant differences for the DFS and OS in favour of class 3 hysterectomy ($p<0.0001$ and $p=0.003$) and DFS for the absence of lymph node metastases ($p=0.059$). In patients with exenterations, the multivariate analysis for OS demonstrated a significant difference with parametrial infiltration ($p=0.012$). In this series 13 of 105 (12.5%) patients developed recurrences with 53.8% % being distant.

Conclusions: Post chemo radiation surgery in patients with suspected or documented persistent cervical cancer showed better prognosis for adenocarcinoma as compared to squamous carcinoma and less morbidity in the absence of brachytherapy. The high number of distant metastases in patients with tumour recurrence suggests the importance of administering adjuvant chemotherapy to these at-risk patients.

Keywords: Complementary Salvage Surgeries; Persistent; Cervical Cancer; Chemo radiation

Abbreviations: RT: Pelvic radiation; EBRT: External Beam Radiotherapy; ICBT: Intracavitary Brachytherapy; CT: Chemotherapy; CCRT: Concurrent chemo radiation; EBRTCT: External beam radiotherapy/Chemotherapy; GHM: General Hospital of Mexico; DFS: Disease-free Survival; FIGO: International Federation of Gynaecology and Obstetrics; OS: Overall Survival; PET: Positron Emission Tomography; Gy: Radiation Treatment Unit; SCC: Squamous Cell Carcinoma; AC: Adenocarcinoma

Introduction

Cervical cancer is a serious health problem in developing countries due to its presentation in advanced stages and is the leading cause of death from gynaecological neoplasms [1-3]. The World Health Organization (WHO) estimated in 2020 there will be 105,963 new cases of cancer in women in Mexico, of which 20,691 (19.5%) appeared in the genital tract. Cervical cancer leads the list of gynaecologic cancers in terms of incidence and mortality, with 9,439 new cases (45.6%) and 4,395 deaths (49.6%) [4]. In Mexican institutions such as the National Cancer Institute

and the General Hospital of Mexico (GHM) [5,6], the number of affected patients with cervical cancer is only surpassed by those with breast cancer. Cervical cancer is predominantly diagnosed in advanced stages of the disease for which the treatment of choice is a combination of pelvic radiation with concomitant platinum agent-based chemotherapy followed by the application of Intracavitary Brachytherapy (ICBT) [7,8]. Although Chemo radiation (CCRT) maintains its validity for the management of locally advanced cervical cancer, therapeutic schemes have been published that include adjuvant surgery for some of these patients [12-14]. This increases the possibility of adapting the established treatments in order to improve specific oncologic results with conventional therapy. In 2003, the Gynaecologic Oncology Group of the United States of America [12] published data that patients with tumours of 4-6 cm limited to the cervix benefited from better local control of the disease when hysterectomy was added to the pelvic radiation (RT). In 2010, Houvenaeghel et al [13] published data on 35 patients with advanced lesions operated with hysterectomies or pelvic exenterations after receiving concurrent chemo radiotherapy (CCRT). Local regional control was obtained in 88.6% of patients with a 10-year disease-free survival (DFS) of 66.4%. The authors concluded that adjuvant surgery reduces the risk of local recurrences and increases DFS. Fanfani et al [14] compared the

results obtained with CCRT vs. CCRT plus hysterectomies in patients with stage III CC and reported a significant increase in local recurrences in the first group ($p = 0.0210$), a lower number of deaths in patients undergoing surgery ($p = 0.021$) and a 3-year DFS of 62.9% and 68.3% respectively ($p = 0.0686$). Failure to administer intracavitary brachytherapy represents incomplete treatment for patients undergoing CCRT. This deficiency constitutes a reason to consider increasing the external beam radiotherapy (EBRT) dose or to evaluate complementary surgical treatment. Walji et al [8] evaluated both treatments in 19/208 patients in whom incomplete ICBT was administered. Fourteen received an EBRT overdose (7 recurrent and 6 died of tumour activity) and five underwent hysterectomies class 1 or 3, all of whom experienced DFS at 5 years [15]. Recently the radiotherapy unit of our institution underwent a remodelling process during which it was not possible to administer ICBT in patients with cervical cancer who required concurrent chemo radiotherapy (CCRT). Some were channelled to other hospitals to complete their treatment and other patients were considered for complementary surgeries to conclude their treatment. In this setting, we present our experience in 62 patients who underwent surgery which included 56 hysterectomies with or without pelvic lymphadenectomy, 3 exenterations and 3 laparotomies for unresectable tumours. In 3/62 (4.8%) patients, there was a major complication with no operative mortality. An average follow-up of 30 months without tumour recurrence was obtained in 76.2% of all cases. In a subgroup analysis, a 30-month DFS period was obtained in 34/40 (85%) patients vs. 8/13 (61.5%) patients in whom there was a report of tumour activity ($p = 0.03$). DFS was noted in 12/13 (92.3%) patients in clinical stage I, 27/33 (81.8%) in stage II and 7/14 (50%) in stage III. It was concluded that surgery can be used as an alternative adjuvant treatment for patients with cervical cancer who require CCRT for its management and who cannot receive ICBT [16]. The aim of this publication is to present the results of surgical treatment in 127 patients with locally advanced cervical cancer whose tumour persistence was documented by biopsy, incomplete chemo radiation treatment due to lack of brachytherapy, clinical suspicion and/or by imaging studies when these were available after CCRT or with histopathology of poor prognosis (advanced stage adenocarcinomas) [17-19].

Material and Methods

This is a retrospective study of patients treated in the Oncology Unit of GHM during the period from January 2008 to December 2018 with the diagnosis of locally advanced cervical cancer (either squamous cell carcinoma (SCC) or adenocarcinoma) who received treatment with conventional or incomplete CCRT: External Beam Radiation Therapy 50-54 Gy with linear accelerator: Intensity-modulated radiation therapy (IMRT) or volumetric arc therapy (VMAT) + chemotherapy with Cisplatin or carboplatin at

conventional doses. Intracavitary radiotherapy (brachytherapy 30 Gy) high 3D rate with Iridium 192 or low dose rate with Cesium 137, or Tele therapy 50-54 Gy plus Chemotherapy with Cisplatin or Carboplatin weekly. The patients were laparotomies 6-12 weeks after concomitant chemo radiation treatment was completed under the following criteria: 1. chemo radiation without brachytherapy, 2. the presence of residual tumour in the cervix and or vagina documented by biopsy, 3. residual tumour in parametria by imaging studies (CT and PET), when available, 4. a clinical suspicion of residual tumour in parametria made by the specialty's professors in the absence of imaging studies; 5. reports of adenocarcinomas in advanced stages in which a less favourable response to conventional treatment has been documented [17-19]. Surgeries were performed according to the following preoperative and trans operative findings [9-15]. Extra facial hysterectomy class 1, [9,12] on suspicion of residual tumour in the cervix and / or vagina for not having received brachytherapy; Class 2 hysterectomy, (Stage IB1:FIGO-2018, in treatment-virgin patients) [3]: central persistence < 2 cm with resection of the internal third of the parametrium without pelvic lymphadenectomy and no suspicion of lymph node metastases or lymphadenectomy with suspected lymph node activity; Class 3 hysterectomy, [9,10,14] advanced stage neoplasia with infiltrating central residual tumour of 3 or >4 cm. Pelvic exenteration for neoplasms with residual tumour in the parametrium or with inability to separate the vesicovaginal or rectovaginal septa in central neoplasms. Pelvic exenterations (PE) were divided as follows: anterior (with Bricker duct), posterior (with resection of the rectum plus definitive colostomy) or total (with Bricker duct or sigmoid duct plus definitive colostomies). The major surgical morbidity was considered to be the complications obtained during the first 30 days following surgery. This included anastomosis dehiscence, bladder dysfunction, pneumonia and intestinal obstruction. The variables analysed included age, type of surgery performed, history of having received chemo radiation (CCRT), clinical stage and pathology reports with or without local or regional residual disease in the surgical specimen (cervix, vagina, uterine body, parametrium), metastases to the adnexa and report of lymph node metastases. For pelvic exenterations, the following variables were also analysed: report of central residual tumour defined as tumour limited to the remains of the cervix and/or vagina, diagnosis of parametrial invasion with or without infiltration to the pelvic wall, histologic evidence of invasion of the bladder or rectum and report of hydronephrosis previously observed through preoperative imaging studies. For age, we selected the analysis of the groups 35 years old and under and 36 years old and greater because a previous publication on prognostic factors for pelvic exenterations for cervical cancer demonstrated that patients aged 35 years and younger had a better prognosis [20]. The clinical classification used was that of the International Federation of Gynaecology and Obstetrics (FIGO)

in its 2018 version [3] with consideration for stage I, IB2 and IB3 lesions, Stage II, IIA and IIB lesions and for stage III, IIIA and IIIB neoplasms. For the analysis of the variables, descriptive statistics were used with calculation of means and proportions for numerical and categorical variables. Survival analysis was performed using the Kaplan-Meier method. 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 overall survival (OS) with 95% confidence intervals being calculated for the odds ratio. All statistical analyses were performed with the SPSS 22.0 statistical program.

Results

During the 11 years analysed, 105 surgical interventions were performed which included 75 (71.4%) complementary or rescue hysterectomies (17 class 1, 46 class 2 and 12 class 3), 30 exenterations, (28.5%):13 total, 14 anterior and 3 posterior. The clinic pathologic characteristics of the 105 patients are shown in Table 1.

Variable	Mean o N	DE o %
Age (years)	46.5	9.8
Age group		
≤35 years	14	13.3
>35 years	91	86.7
Clinical stage		
I	17	16.2
IIA	2	1.9
IIB	60	57.1
IIIA	3	2.9
IIIB	20	19.0
IVA	2	1.9
Not Classified	1	1.0
Histologic type		
Squamous cell carcinoma	57	54.3
Adenocarcinoma	48	45.7
Previous treatment		
RT+CT (CCRT)	74	70.5
TLT+CT	31	29.5
Surgical specimen with nodes		

No	80	76.2
Yes	25	23.8
Number of nodes resected (n=63)	2.0	2.9
Lymph node metastasis		
No	101	96.2
Yes	4	3.8
Central tumor		
No	54	51.4
Yes	51	48.6
Histopathologic report of tumor in the surgical specimen		
No	46	43.8
Yes	59	56.1
Lymph vascular infiltration		
No	88	83.8
Yes	17	16.2
Parametrial infiltration		
No	102	97.1
Yes	3	2.9
Rectal invasion		
No	100	95.2
Yes	5	4.8
Invasion of the Uterine body		
No	103	98.1
Yes	2	1.9
Postoperative recurrence in months(n=35)	12.3	7.5

Table 1: General characteristics of 105 patients with cervical cancer following chemo radiotherapy.

Residual Tumour

Forty-six of 105 (43.8%) patients who were operated upon for curative purposes had a complete response to radiotherapy without residual tumour in the surgical samples. The figures without residual tumour included 39/75 (52.0%) of the hysterectomies: 13/17 (72.4%) class 1, 22/46 class 2 (47.8%) and 4/12 (33.3%) class 3. For pelvic exenterations, the figures were 7 out of 30 patients (23.3%).

Surgical morbidity and mortality

An evaluation of postoperative complications was recorded according to the treatment prior to the surgery and the surgical procedures performed. For the patients who received concurrent chemo radiotherapy, the figures were 15/83 (18.0%) and 1/22 (4.5%) for those with chemo radiation without brachytherapy ($p = 0.2912$). Major complications were present in 7/75 (9.3%) hysterectomies and 9/30 (30.0%) exenterations. In this series, there was no postoperative mortality.

Complementary or salvage hysterectomies

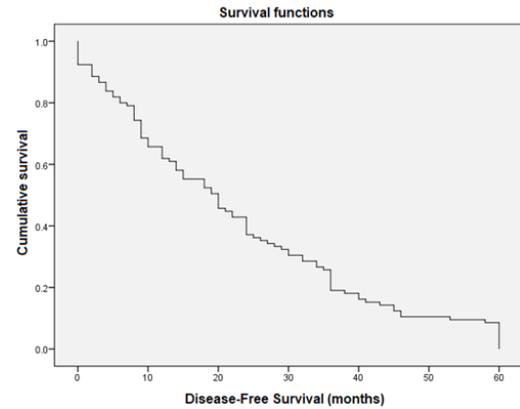
Seven of 75 patients (9.3%) who had received CCRT had major postoperative complications. Of these, 4/12 (33.3%) were present in class 3 hysterectomies (2 rectovaginal fistulas that required a definitive colostomy, 1 ureterovaginal fistula conservatively managed and 1 with bladder dysfunction which resolved with conservative therapy). In addition, 1 of 46 (2.3%) class II hysterectomies experienced an intestinal obstruction requiring surgery and 2/17 (11.7%) patients with class 1 hysterectomies developed rectovaginal and vesicovaginal fistula requiring a colostomy and ileal duct respectively.

Pelvic exenterations

Major complications occurred in 9/30 (30.0%) patients. Eight of 21 (38.0%) had previously received CCRT and 1/9 (11.1%) tele therapy plus CT. Findings included 5 ureterovaginal fistulas (2 resolved with surgical reoperations, 2 conservatively managed and 1 with nephrostomy), 1 rectovaginal fistula in one anterior exenteration that required a definitive colostomy, 1 dehiscence of the intestinal anastomosis managed conservatively, 1 intestinal obstruction surgically resolved and a medically resolved pneumonia.

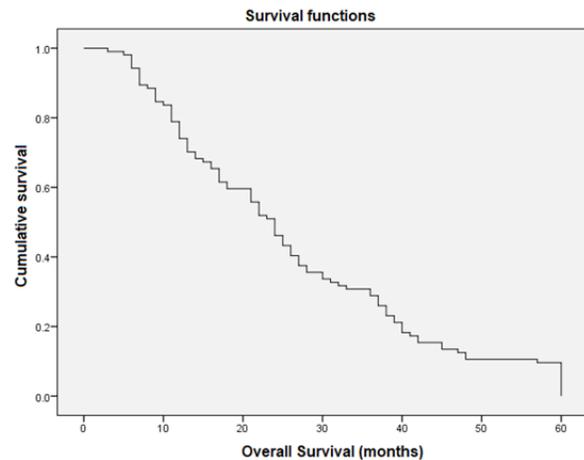
Results of surgical treatment

The Kaplan Meier curves for DFS and OS in the 105 hysterectomies and pelvic exenterations showed a median follow up of 20 months and 24.0 months respectively Figure 1.



Mean: 22.6 months (CI 95%: 19.2 – 26.0)

Median: 20.0 months (CI 95%: 14.5 – 25.4)



Mean: 26.3 months (CI 95%: 23.1 – 29.4)

Median: 24.0 months (CI 95%: 20.9 – 27.0)

Figure 1: Kaplan Meier curves for DFS and OS in 105 hysterectomies and pelvic exenterations.

Ninety-two patients (87.6%) had follow-up from 1 to 79 months without evidence of tumour activity at their last evaluation. At 60 months, the figures for DFS and OS were 8.6% and 9.6%, respectively. For DFS and OS, the univariate analysis showed significant differences in favour of age < 35 years (p=0.031 and p=0.051), adenocarcinoma (p=0.023 and p=0.019), and the absence of lymph vascular infiltration (p=0.003 and p=0.001). Tables 2A and 2B. The multivariate analysis for DFS and OS only demonstrated significant differences for the absence vs presence of lymph vascular invasion (p=0.001 and p=0.002) Tables 3A and 3B.

Variable	N	Media	DE	P Value
Age group				0.031
≤35 years	14	34.86	28.379	
>35 years	91	22.91	17.258	
Histologic type				0.023
Squamous carcinoma	57	20.58	18.902	
Adenocarcinoma	48	29.17	19.061	
Lymph vascular infiltration				0.003
No	88	26.9	19.7	
Yes	17	12.0	11.2	
Parametria infiltration				0.343
No	102	24.8	19.5	
Yes	3	14.0	8.6	
Lymph node metastasis				0.134

No	101	25.07	19.512	
Yes	4	10.25	5.500	
Previous treatment				0.080
CCRT	74	26.65	20.592	
TLT+CT	31	19.39	15.165	

Table 2A: Univariate analysis of disease-free survival (DFS) for different variables in 105 patients with cervical cancer.

Variable	N	Mean	SD	P value
Age group				0.051
<35 years	14	37.07	28.824	
>35 years	91	26.24	17.276	
Histologic type				0.019
Squamous carcinoma	57	23.65	18.933	
Adenocarcinoma	48	32.48	19.007	
Lymph vascular infiltration				0.003
No	88	30.1	19.6	
Yes	17	15	11.5	
Previous treatment				0.112
RT+CT	74	29.64	20.651	
TLT+CT	31	23.03	15.276	

Survival analysis was performed using the Kaplan-Meier method. Differences between groups were assessed by using the log-rank test.

Table 2B: Univariate analysis of overall survival (OS) for different variables in 105 patients with cervical cancer.

Variable included in the model	B	SE	Wald	RM (IC 95%)	P value
Age group	0.448	0.314	2.033	1.56 (0.845 - 2.897)	0.154
Histological type	-0.309	0.204	2.302	0.734 (0.492 - 1.09)	0.129
Previous treatment	0.367	0.223	2.691	1.44 (0.931 - 2.23)	0.101
Lymph vascular infiltration	0.918	0.280	10.736	2.50 (1.44 - 4.33)	0.001

Only variables that were statistically significant in the univariate analysis were analysed in multivariate Cox regression models.

Table 3A: Multivariate analysis of disease-free survival (DFS) for different variables in 105 patients with cervical cancer (Cox Regression).

Variable included in the model	B	SE	Wald	OR (CI 95%)	P value
Age group	0.506	0.310	2.660	1.65 (0.903 - 3.04)	0.103
Histologic type	-0.313	0.203	2.377	0.731 (0.491 - 1.08)	0.123
Lymph vascular infiltration	0.853	0.278	9.433	2.34 (1.36 - 4.04)	0.002

Only variables that were statistically significant in the univariate analysis were analysed in multivariate Cox regression models.

Table 3B: Multivariate analysis of overall survival (OS) for different variables in 105 patients with cervical cancer (Cox regression models).

DFS and OS analysis for histopathologic reports: the presence or absence of tumour activity in these 105 patients showed no statistically significant differences. (P=0.428 and P=0.311).

Complementary or salvage hysterectomies

General characteristics of 75 patients undergoing hysterectomies are shown in Table 4.

Variable	Mean (SD) or Percentage (n)
Age (years)	46.3 (9.2)
Age Groups (years)	
35 years or minor	13.3 (10)
>35 years	86.7 (65)
Clinical Stage	
I	21.3 (16)
IIA	61.3 (46)
IIB	2.7 (2)
IIIA	12.0 (9)
IIIB	1.3 (1)
No classified	1.3 (1)
Histologic type	
Squamous carcinoma	45.3 (34)
Adenocarcinoma	54.7 (41)
Previous treatment	
Radiotherapy plus Chemotherapy (RT + CT)	70.7 (53)
Tele therapy plus Chemotherapy (TLT+CT)	29.3 (22)
Surgical specimen with nodes	
Yes	21.3 (16)
No	78.7 (59)
Number of lymph nodes resected	5.0 (1.6)
Lymph node metastasis	
Yes	4.0 (3)
No	96.0 (72)
Central tumour	
Yes	42.7 (32)
No	57.3 (43)
Tumour in the surgical specimen	
Yes	48.0 (36)
No	52.0 (39)
Lymph vascular infiltration	
Yes	4.0 (3)
No	96 (72)
Parametria infiltration	
Yes	1.3 (1)
No	98.7 (74)
Invasion to the uterine body	
Yes	1.3 (1)
No	98.7 (74)
Tumour persistence (months)	2.81 (0.99)
Postsurgical recurrence of the tumour (months)	12.5 (8.1)

Table 4: General characteristics of 75 patients undergoing hysterectomies.

Sixty-seven /75 patients (89.3.0%) had a follow-up of one to 60 months without evidence of disease. The mean DFS was 29.4 months and 33 (44.0%) patients had a follow-up of >25 months without evidence of disease. Figure 2.

The mean OS was 32.4 months and 38 (56.7%) patients had an OS of >25 months without evidence of disease. Figure 2.

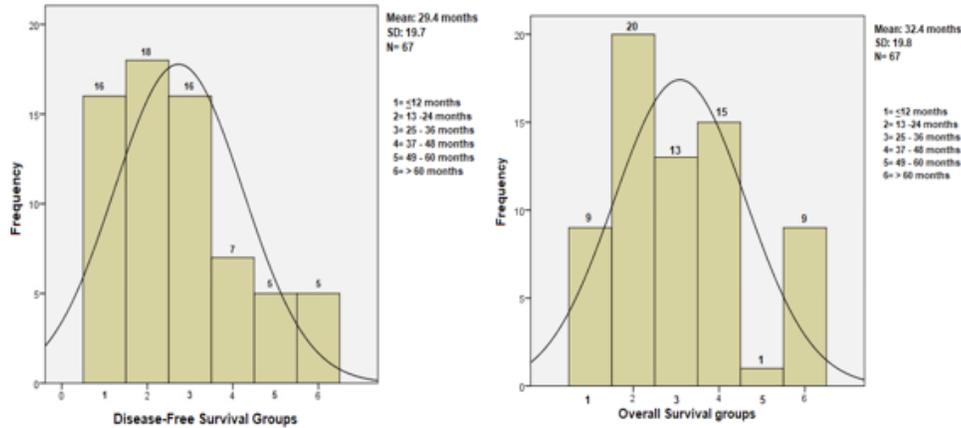


Figure 2: Disease-free survival and overall survival. 67 Hysterectomies, (29.4 and 32.4 months respectively).

For DFS, the univariate analysis had significant differences for patients aged 35 and under (p=0.004) and for class 3 hysterectomies (p=0.003) Table 5A.

Variable	N	Media	DE	P value
Age Groups (years)				0.004
35 years or minor	10	44.0	27.5	
>35 years	65	25.1	16.8	
Type of surgery performed				0.003
Class 3 Radical Hysterectomy	12	36.7	23.1	
Class 2 Radical Hysterectomy	46	21.7	15.2	
Simple Hysterectomy	17	37.4	21.7	

Table 5A: Univariate analysis of disease-free survival for different variables in 75 patients undergoing hysterectomies.

In the univariate analysis for OS, the following variables were statistical significance: age equal to or less than 35 years (p=0.007) and class 3 hysterectomies (p=0.003) Table 5B.

Variable	N	Media	DE	P value
Age Groups (years)				0.007
35 years or minor	10	46.2	28.185	
>35 years	65	28.7	16.790	
Type of surgery performed				0.003
Class 3 Radical Hysterectomy	12	39.4	22.7	
Class 2 Radical Hysterectomy	46	25.1	15.3	

Simple Hysterectomy	17	41.2	21.4	
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Table 5B: Univariate analysis of Overall survival for different variables in 75 patients undergoing hysterectomies.

In multivariate analysis for DFS significant differences were found when comparing class 2 ($p<0.0001$) and class 3 ($p=0.001$) hysterectomies vs. class 1 hysterectomies Table 6A.

Variable included in the model	B	SE	Wald	OR (IC 95%)	P value
Type of surgery performed			14.778		0.001
Class 3 Radical hysterectomy	0.748	0.628	1.42	2.11 (0.617 - 7.2) 3	0.233
Class 2 Radical hysterectomy	1.43	0.378	14.29	4.18 (1.99 - 8.77)	$P<0.0001$
Surgical specimen with lymph nodes	-0.362	0.568	0.406	0.696 (0.229 - 2.12)	0.524
Lymph nodes metastasis	1.734	0.919	3.559	5.66 (0.935 - 34.33)	0.059

Table 6A: Multivariate analysis for disease-free survival in 75 patients undergoing hysterectomies (Cox Regression).

For the multivariate analysis for OS, statistical significance was noted for age equal to or less than 35 years, ($p=0.021$), class 2 hysterectomies ($p=0.002$) and class 3 ($p=0.008$) hysterectomies vs class 1 hysterectomies and the presence of lymph node metastases ($p=0.032$) Table 6B.

Variable included in the model	B	SE	Wald	OR (IC 95%)	P Value
Age group	1.076	0.465	5.348	2.933	0.021
Type of surgery performed			9.538		0.008
Class 3 Radical Hysterectomy	0.667	0.628	1.128	1.948	0.288
Class 2 Radical hysterectomy	1.002	0.325	9.498	2.724	0.002
Lymph nodes metastasis	1.736	0.810	4.600	5.676	0.032

Table 6B: Multivariate analysis for Overall survival in 75 patients undergoing hysterectomies (Cox Regression).

Differences between groups in 75 patients undergoing hysterectomies were assessed using the Log-Rank Test Figures 3 and 4.

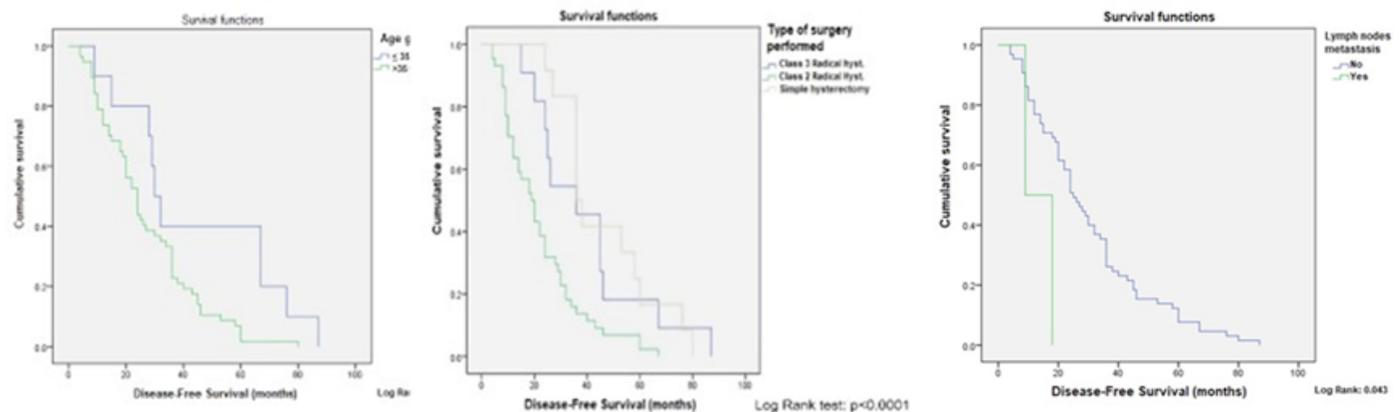


Figure 3. Disease- free survival. 75 Hysterectomies Log Rank Test.

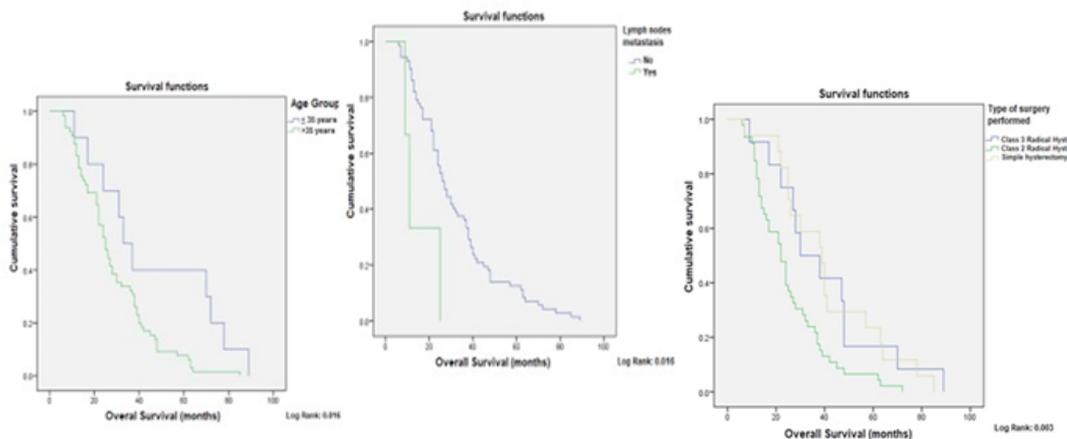


Figure 4 Overall Survival. 75 Hysterectomies Log Rank Test.

Pelvic exenterations

General characteristics of 30 patients undergoing pelvic exenterations are shown in Table 7.

Variable	Mean (SD) or Percentage (n)
Age (years)	46.9 (11.3)
Age Groups (years)	
35 years or minor	13.3 (4)
>35 years	86.7 (26)
Clinical Stage	
I	3.3 (1)
IIA	6.7 (2)
IIB	46.7 (14)
IIIA	3.3 (1)
IIIB	36.7 (11)
IVA	3.3 (1)
Histologic type	
Squamous carcinoma	76.7 (23)
Adenocarcinoma	23.3 (7)
Previous treatment	
Radiotherapy plus Chemotherapy (RT + CT)	70.0 (21)
Tele therapy plus Chemotherapy (TLT+CT)	30.0 (9)
Type of surgery performed	
Anterior Exoneration	46.7 (14)
Total Exoneration	43.3 (13)

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Posterior Exoneration	10.0 (3)
Surgical specimen with nodes	
No	70.0 (21)
Yes	30.0 (9)
Number of lymph nodes resected	1.5 (3.1)
Lymph node metastasis	
No	96.7
Yes	3.3
Central tumor	
No	36.7 (11)
Yes	63.3 (19)
Residual tumor in the surgical specimen	
No	23.3 (7)
Yes	76.7 (23)
Parametria infiltration	
No	53.3 (16)
Yes	46.7 (14)
Hydronephrosis	
No	93.3 (28)
Yes	6.7 (2)
Bladder invasion	
No	86.7 (26)
Yes	13.3 (4)
Invasion to the uterine body	
No	96.7 (29)
Yes	3.3 (1)
Invasion of the rectum	
No	83.3 (25)
Yes	16.7 (5)
Tumor persistence (months)	2.6 (1.1)
Postsurgical recurrence of the tumor (months)	12.2 (7.4)
Disease-free survival (months)	18.7 (18.0) Minimum: 2 Maximum: 79

Table 7: General characteristics of 30 patients undergoing pelvic exonerations.

Twenty-five of the 30 patients (83.3%) had a follow-up of 1 to 79 months without evidence of disease with a mean DFS of 18.7 months and OS of 20.2 months Figure 5.

In this series 7/25 (28.0%) patients had a disease-free follow-up of >25 months. The remainder ceased follow-up without evidence of disease during the course of the first 2 years.

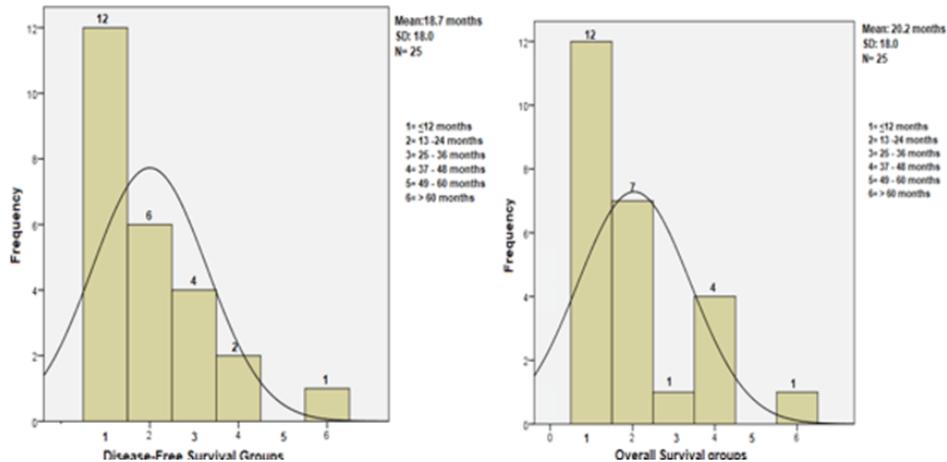


Figure 5: Disease-free survival and Overall survival 25 pelvic exonerations (18.7 and 20.2 months respectively).

The univariate analysis for DFS showed variables with statistical significance for prognosis: absence of residual tumour in the surgical specimen (p=0.034) and the report of central tumour (p=0.024) and parametria infiltration (p=0.007). Table 8A In the Univariate analysis of OS, only parametria infiltration influenced prognosis (p=0.030) Table 8B.

Variable	N	Media	DE	P value
Residual tumor in the surgical specimen				0.034
No	5	33.8	27.7	
Yes	20	14.9	13.2	
Central tumor				0.029
No	11	6.3	10.7	
Yes	19	20.9	19.2	
Parametria infiltration				0.007
No	16	23.5	19.9	
Yes	14	6.5	9.6	
Yes	8	18	12.8	

Table 8A: Univariate analysis of disease-free survival for different variables in 30 patients undergoing pelvic exonerations for cervical cancer.

Variable	N	Media	DE	P Value
Histologic type				0.080
Squamous carcinoma	23	16.2	11.9	
Adenocarcinoma	7	29.0	26.5	
Parametria infiltration				0.030
No	16	25.37	19.490	
Yes	14	12.21	9.839	
Invasion of the rectum				0.061
No	25	21.80	17.371	
Yes	5	6.40	2.191	

Table 8B: Univariate analysis of Overall survival for different variables in 30 patients undergoing pelvic exoneration for cervical cancer.

In the multivariate analysis for DFS, no statistically significant differences were found. Table 9A In the multivariate analysis for OS, only the invasion of the rectum showed significant differences, (p=0.006) Table 9B.

Variable included in the model	B	SE	Wald	OR (IC 95%)	P value
Histologic type	0.009	0.544	0.000	1.009 (0.347-2.93)	0.987
Central tumor	0.213	0.696	0.094	1.238 (0.316-4.84)	0.759
Parametric infiltration	1.116	0.685	2.657	3.054 (0.798-11.6)	0.103
Residual tumor in the surgical specimen	0.416	0.627	0.441	1.516 (0.444-5.18)	0.507

Table 9A: Multivariate analysis for disease-free survival in 30 patients undergoing pelvic exonerations for cervical cancer (Cox Regression).

Variable included in the model	B	SE	Wald	OR (IC 95%)	P Value
Histologic type	-0.113	0.521	0.047	0.893 (0.322 - 2.47)	0.828
Parametric infiltration	0.717	0.455	2.486	2.048 (0.840 – 4.99)	0.115
Invasion of the rectum	1.752	0.643	7.422	5.769 (1.63 – 20.35)	0.006

Table 9B: Multivariate analysis for Overall survival in 30 patients undergoing pelvic exoneration for cervical cancer (Cox Regression).

Differences between groups were assessed using the Log-Rank Test Figure 6.

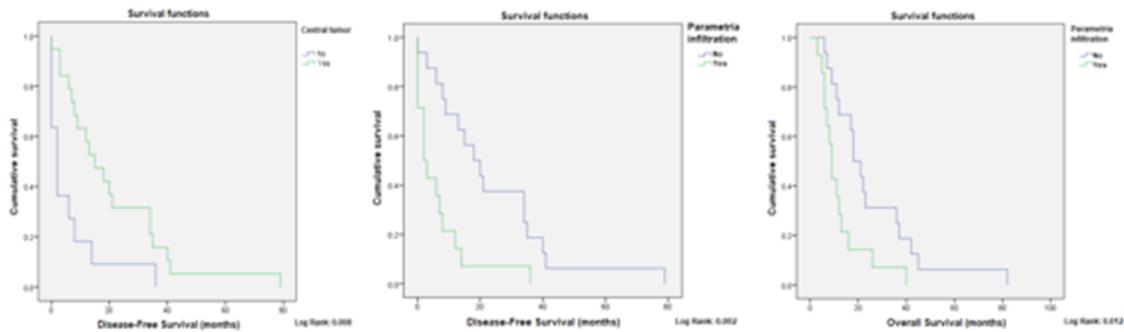


Figure 6: Disease-free survival and Overall survival 30 pelvic exenterations. (Log Rank Test).

Tumour recurrences

The number of recurrences was 13/105 (12.3%) during the period of 5 to 29 months after surgery with an average of 12.3 months. This corresponded to 9/75 (12.0%) hysterectomies and 4/30 (13.3%) exenterations. Ten out of 74 (13.5%) patients had a previous history of radiotherapy plus concomitant chemotherapy and 3/31(9.6%) had tele therapy plus chemotherapy. Five out of 105 patients (4.7%) with radical surgery with no residual tumour in the surgical specimens developed tumour recurrences. The includes 3/75 (4.0%) of the hysterectomies and 2/30 (6.6%) exenterations. In 6/13 cases (46.1%), the recurrences were local or loco regional and distant in 7 (53.8%). In 3 cases (23.0%), the dissemination was regional and distant and the remaining 4 (30.7%) had several distant sites without loco regional activity. We performed additional therapeutic procedures in two patients, both stage IIB adenocarcinoma who received CCRT and class 3 hysterectomy. Case 1: the patient had been treated with incomplete CCRT, had residual tumour in the sample with the neoplasm recurring in the vaginal dome and required treatment with adjuvant ICBT at 30 Gy with a DFS of 36 months. Case 2: the patient had a local residual tumour and a metastatic lymph node and 7 months later had tumour recurrence in the vaginal dome and spleen requiring treatment with 4 cycles of paclitaxel plus vinorelbine and 5 cycles of gemcitabine with complete response demonstrating 24-month follow-up without tumour activity.

Discussion

The role that complementary surgery in patients with local advanced cervical cancer previously treated with CCRT is considered controversial due to surgical morbidity, mortality and oncologic results at 5 years compared to conventional treatment scheme with CCRT alone [11,12,14,21]. Working in an institution without optimal resources for the diagnosis and conventional treatment of advanced CC and the fact that the patients are admitted with advanced neoplasms, lack social security and live

far from Mexico City, makes it very difficult to keep them under surveillance. Therefore, our Service decided to implement the treatment plan shown here for patients who received incomplete CCRT [8] or in patients who did receive it but who ended up with a confirmed or suspected residual tumour and/or in patients with local advanced cervical cancer whose response to CCRT is poor [17-19]. Performing surgery a few weeks after the end of conventional treatment offers the advantage of avoiding radiation-induced fibrosis in the pelvic tissues, which will hinder surgical dissection due to inflammation and adhesion formation resulting in an increased risk of morbidity [11]. Of the 105 surgeries performed for curative purposes, 59 (56.1%) had residual tumour with the majority beginning in complementary class 1 hysterectomies (13/17, 72.4%) who did not receive brachytherapy. Sixteen (15.2%) experienced postoperative complications, 13 belonging to the group of 83 patients previously treated with complete CCRT (15.6%) vs. 1 of 22 (4.5%) of those in the incomplete CCRT group. (p = 0.2912) The number of complications included 7/75 (9.3%) in hysterectomies with complete CCRT and 9/30 (30.0%) in exenterations of which 8/21(38.0) had complete CCRT and 1/9 (11.1%) incomplete. The lower number of complications observed in this series in patients without brachytherapy is attributed to the fact that the increased dose of radiation received in the pelvis favors the inflammation and fibrosis processes described, with a higher risk of morbidity during surgical dissection [11]. Major complications in patients treated with salvage surgeries due to persistent or recurrent CC after radiation consists of serious events that must be resolved judiciously. Serious adverse events have been reported in 16-27% of patients treated with hysterectomies after radiotherapy, the majority being class 3 hysterectomies [9,14,22]. In the series by Mazon et al [22] with 54 cases, the figure was 25.9%; the report by Mabuchi S et al [9] with 31 patients 27%; and in Fanfani et al [14] with 73 patients, the figure was 16.4%. For PE, the numbers of serious adverse events are higher and generally reach 60% or more [20]. In the present series, 9/30 (30.0%) exenterations had major complications, 6

of them with complete CCRT and 1 with incomplete CCRT. The analysis of the 105 patients with common variables and surgeries for curative purposes showed a median OS of 24 months. For DFS and OS, univariate analysis and multivariate analysis of OS showed significant differences in favour of age < 35 years ($p=0.031$, $p=0.051$ and $p=0.007$) adenocarcinoma vs squamous carcinoma ($p=0.023$ and $p=0.019$) and for the absence of lymph vascular infiltration ($p=0.003$ and $p=0.001$). The multivariate analysis for DFS and OS only showed significant differences for the absence vs presence of lymph vascular invasion. ($p=0.001$ and $p<0.0001$). For age, we selected the analysis of the groups 35 years old and under and 36 years old and greater because a previous publication on prognostic factors for pelvic exenteration for cervical cancer demonstrated that patients aged 35 years and younger had a better prognosis [20]. The differences in prognosis observed in the univariate analyses in favour of adenocarcinoma in which conventional therapy does not offer the desired results [17-19] suggests that the treatment modality employed by the authors could be useful in the treatment of advanced lesions of this histologic variety, although it will be necessary to have more data accumulated. Lymph vascular infiltration negatively influenced the prognosis of the 105 patients in the multivariate analyses for DFS and OS ($p=0.001$ and $p=0.003$) and has been previously reported [23,24]. For hysterectomies, the OS was 32.4 months and 38 (56.7%) patients were free of disease 25 months and greater during follow-up. The following variables were found with statistical significance in univariate analysis: age equal to or less than 35 years ($p=0.004$ and $p=0.007$) and class 3 hysterectomies ($p=0.003$ and $p=0.003$). For the multivariate analysis, statistical significance was found for age equal to or less than 35 years ($p=0.004$ and $p=0.021$) and class 3 hysterectomies ($p<0.001$ and $p=0.003$) suggesting the need for more radical surgical treatment of these patients when hysterectomies are indicated. Mabuchi et al reported [9] 30 radical hysterectomies due to persistent or recurrent CC with the 3-year survival rate being 53%. Fanfani et al [14] compared the results obtained for stage III CC in 77 patients treated with CCRT vs. 73 to whom radical hysterectomy was added to the management without ICBT. The 3-year DFS range was 62.9% for the first group and 68.3% for the second ($p = 0.0686$). Houvenaeghel et al [13] reported the results in 35 patients in stages IB-IVA treated with CCRT plus surgery with 26 radical hysterectomies (21 with Para aortic lymphadenectomy) and 8 pelvic exonerations. In 17 patients (48.5%), there was a complete response with a reported 10-year DFS of 66.4% of the cases in the presence of lymph node metastases ($p=0.032$). Also noteworthy is the absence in this series of differences for DFS ($p=0.080$) and OS ($p=0.112$) when comparing the results obtained with the use of CCRT vs tele therapy plus chemotherapy. The latter scheme was accompanied by less surgical morbidity (1/22, 4.5%, vs 13/83, 15.6%) which suggests its safe to use in patients who are unable

to complete their treatment regimen [8,14]. The results obtained with pelvic exonerations showed failure of surgical treatment in 5/30 (16.6%) patients. DFS and OS for the 25 patients were 18.7 and 20.2 months respectively. The univariate analysis for DFS showed variables with statistical significance for prognosis being the absence of residual tumour in the surgical specimen ($p=0.034$), the report of central tumour ($p=0.024$) and parametrial infiltration ($p=0.007$). For multivariate analysis, parametrial infiltration ($p=0.008$ and $p=0.012$), for DFS central tumour ($p=0.008$) and rectal invasion for OS ($p=0.006$) were statistically significant. These results are consistent with those reported in the literature. [25,26]. regarding the benefit of adjuvant hysterectomy after concurrent chemo radiation for locally-advanced cervical cancer is controversial; the met analysis recently published by Weijia Lu et al [27]. Indicated that the recurrence rate may be higher in patients undergoing CCRT without hysterectomy. In this series, 13/105 (12.3%) patients had recurrences and in 7 (53.8%) cases the recurrences were distant, 4 of them without loco regional tumour activity. Eleven patients died with tumour activity and 2 (15.3%) patients diagnosed with adenocarcinoma obtained control of their disease for 36 and 24 months, one with local recurrence through ICBT application that she had not previously received and the other with the combination of chemotherapy agents. The observation that 53.8% of recurrences in this series were distant suggests consideration of chemotherapy for patients with lesions at risk for recurrence with reported parametrial, bladder and/or rectal invasion, lymph vascular infiltration and lymph node metastases.

Conclusions

In this series, 83 patients received complete CCRT treatment with 13 (15.6%) having MC vs 1 of 22 (4.5%) treated with incomplete CCRT. The Kaplan Meier curves showed DFS and OS in the 105 hysterectomies and pelvic exenterations with a median follow up of 20 months and 24.0 months respectively. For complementary or salvage hysterectomies, the mean OS was 32.4 months. For pelvic exonerations, OS was 20.2 months. The analysis of the 105 cases treated with radical surgery demonstrated by univariate analysis statistical significance in favour of age < 35 years and the absence of lymph vascular infiltration. The multivariate analysis for DFS and OS only showed significant differences for the absence vs presence of lymph vascular invasion. In hysterectomies, the multivariate analysis for OS showed the following variables with statistical significance: age equal to or less than 35 years, class 3 hysterectomies and the presence of lymph node metastases. In pelvic exonerations, the univariate analysis for DFS showed variables with statistical significance for prognosis being the absence of residual tumour in the surgical specimen, the report of central tumour and parametrial infiltration. The results obtained in this series with adjuvant or rescue surgeries suggest

that it could be used in patients with advanced adenocarcinoma in which the conventional treatment offers less favourable results than those obtained with squamous carcinoma. In this series, 53.8% of tumour recurrences were detected at distant sites with or without tumour in the pelvis, which suggests the benefits of using adjuvant chemotherapy in patients at risk for recurrence.

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