

Role of Surgery in the treatment of Cervical Cancer Persistent to Chemoradiotherapy and its Importance in the Management of Adenocarcinomas: Experience with 100 Patients

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1. Abstract

1.1. Objective: To show the results of complementary and rescue surgeries in patients with Locally Advanced Cervical Cancer (LACC), Squamous Cell Carcinoma (SCC) and Adenocar-Cinoma (ADC), with confirmation or suspicion of tumor persistence to treatment with Chemo-Radio Therapy (CRT) with or without Intra-Cavitary Brachy Therapy (ICBT).

1.2. Material and Methods: Retrospective study of patients treated in the Oncology Service of the General Hospital of Mexico (GHM) in the period from 2008 to 2015, who had a diagnosis of Persistent Cervical Cancer (PCC) and were laparotomized in order to perform complementary or rescue surgeries.

1.3. Results: We performed 100 surgeries, 61 Complementary Hysterectomies (CH) with or without lymphadenectomy, 24 Pelvic Exenterations (PE) and 15 laparotomies because the neoplasm was unresectable. Major Complications (MC) occurred in 11/65 (16.9%)

patients treated with CRT and ICBT, and 1/20 (5.0%) of patients in the CRT group without ICBT ($p = 0.2290$). There was no postoperative mortality. Disease Free Survival (DFS) was 30.5 months in 66/90 (73.3%) of all patients; by surgery 51/56 (91.0%) CH and 15/19 (78.9%) PE; by histopatology, 35/56 (62.5%) with SCC and 31/34 (91.1%) with ADC ($p = 0.003$); and for stage **II** the main clinical stage with 58 patients: 22/36 (61.1%) for SCC and 20/22 (90.9%) for ADC ($p = 0.0145$).

1.4. Conclusions: Adjuvant surgery has a place in the management of LACC with tumor persistence or suspicion of this after conventional treatment with CRT. External Beam Radiation Therapy (EBRT) plus Chemo-Therapy (QT) plus surgery can be considered for the treatment of ADC from CS IB3.

2. Key words: Surgery Persistent; Cervical Cancer; Chemo-radio Therapy; Adenocarcinomas

Abbreviations: Cervical Cancer: CC; Locally Advanced Cervical Cancer: LACC; Gynecological Neoplasms: GN; Squamous Cell Carcinoma: SCC; Adenocarcinoma: ADC; Chemoradiotherapy: CRT; Intracavitary Brachytherapy: ICBT; Complementary Hysterectomies: CH; Pelvic Exenterations: PE; Major Complications: MC; Disease Free Survival: DFS; Clinical Stage: CS; External Beam Radiation Therapy: EBRT; Chemotherapy: CT; Whole Pelvic Radiotherapy: WPRT; Computed Tomography: CT; Positron Emission Tomography: PET; Oncology Unit: OU; General Hospital of Mexico: GHM

3. Introduction

Cervical Cancer (CC) is a health problem in developing countries due to its presentation in advanced stages and is the cause of the highest number of deaths from Gynecological Neoplasms (GN) [1,2,3]. The World Organization of Health (WHO) estimated in 2018 for Mexico an incidence of 105,051 new cases of cancer in women, of which 20,570 (19.5%) occurred in the genital tract, with CC being the first place for GN with 7,869 new cases and 4, 121 deaths [4].

In institutions of our country such as the National Cancer Institute and the GHM [5,6], the attention for CC is only surpassed by breast cancer. CC is predominantly diagnosed in advanced stages of the disease, for which the treatment of choice is the combination of EBRT for the pelvis with concomitant platinum agent-based chemotherapy (CT), continued with the application of ICBT for central injury [7,8].

Although CRT maintains its validity for the management of LACC, therapeutic schemes have been published that include adjuvant surgery for some of these patients [9-11]; This opens up the possibility of adapting

the established treatment in order to improve specific oncological results with conventional therapy.

In 2003, the Gynecologic Oncology Group (GOG) of the United States of America (USA) [12], published that patients with tumors limited to the cervix of 4-6 cm benefited from better local control of the disease when CH were added to the Whole Pelvic Radiotherapy (WPRT), which includes EBRT and ICBT. In 2010, Houvenaeghel et. al [13], published an experience with 35 patients with advanced lesions operated with CH or PE after receiving CRT. Locoregional control was obtained in 88.6% and a 10-year DFS of 66.4%, the authors conclude that adjuvant surgery reduces the risk of local recurrences and increases DFS.

Fanfani et. al [14], compared the results obtained with CRT plus ICBT vs. CRT plus CH in patients with stage III CC, reporting a significant increase in local recurrences in the first group ($p = 0.0210$), a lower number of deaths in patients operated ($p = 0.021$) and a 3-year DFS of 62.9% and 68.3%, respectively ($p = 0.0686$).

Failure to administer ICBT represents incomplete treatment for patients managing CRT scheme. This deficiency constitutes a reason to consider an increase in the 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, 14 received an EBRT overdose (7 recurrent and 6 died with tumor activity) and 5 CH class 1 or 3 [15] (all with DFS at 5 years), showing better oncological results in the surgical group.

In the first years of this century, the radiotherapy unit of our institute underwent a remodeling process during which it was not possible to administer ICBT in patients with CC who required WPRT, so some were channeled to other hospitals to complete their treatment and others who did not have this opportunity, should have been considered for complementary surgeries in order to conclude their treatment. In this setting, we publish our experience in 62 patients who underwent surgery, 56 CH with or without pelvic lymphadenectomy, 3 PE and 3 laparotomies for unresectable tumor. Only in 3/62 (4.8%) there was MC. There was no operational mortality. An average follow-up of 30 months without tumor activity was obtained in 76.2% of all cases. In subgroup analysis, this 30-month DFS period was obtained in 34/40 (85%) patients in the absent of residual disease vs. 8/13 (61.5%) patients in whom there was a report of tumor activity ($p = 0.03$). Likewise, 12/13 (92.3%) of patients in CS I; 27/33 (81.8%) CS II and 7/14 (50%) of stage III. It was concluded that surgery can be used as an alternative adjuvant treatment for patients with CC who require WPRT for its management and who for some reason cannot receive ICBT [16]. This publication shows the results of surgical treatment in 100 patients with LACC whose tumor persistence was documented by biopsy, or clinical suspicion and/or image of this after CRT; with a poor prognosis [17-19] either due to not having received ICBT or having received it incompletely.

4. Material and Methods

Retrospective study of patients treated in OU of GHM during the period from January 2008 to December 2015, with the diagnosis of LACC (SCC or ADC) and who received treatment with conventional or incomplete CRT with tumor persistence or suspicion of this by biopsy or imaging (Computed tomography or Positron Emission Tomography), and undergo laparotomies with the proposal to perform or not, depending on the findings, complementary or rescue surgery.

Patients were included with: 1) histopathological report of tumor persistence, 2) patients who did not receive or received ICBT incompletely, 3) patients with suspected clinical evidence or images of tumor activity with Computed Tomography (CT), and sometimes, Positron Emission Tomography (PET); for bulky tumors (5 cm or more), and 4) unfavorable pathologies (ADC) [17-19].

The cases were classified according to the current classification of the International Federation of Gynecology and Obstetrics (FIGO) [3] and the surgeries were performed between 6 and 10 weeks after the end of the treatment with ionizing radiation. According to the intraoperative findings and the criteria of the surgeon, the procedures consisted of: 1) HC: Class 1 or extrafascial, class 2 or with resection of the internal third of the parameter, and class 3 or radical with bilateral pelvic lymphadenectomy [15]; 2) Supra or infraelevatory PE: Anterior (with Bricker bypass), Posterior (with resection of the rectum plus definitive colostomy) or Total (with Bricker bypass or sigmoid ducts plus definitive colostomies); or 3) Laparotomy (unresectable tumors were considered to be those with a tumor fixed to the pelvic wall and / or the presence of metastatic paraaortic nodes).

Regarding morbidity, early surgical morbidity is considered to be the complications obtained during the first 30 days following surgery, and late complications, which are performed afterwards. As minor complications, surgical wound infections as well as wall abscesses, and as major complications anastomosis dehiscence, bladder dysfunction, and intestinal obstructions.

The results obtained were subjected to statistical analysis using the Epi-Info v 7.2.2.6 program with a significance level of $p < 0.05$.

5. Results

During the 8 years analyzed, 100 surgical interventions were performed, including 61 CH (16 class 1, 26 class 2 and 19 class 3), 24 PE (13 in total, 9 anterior and 2 posterior) and 15 laparotomies (4 palliative surgeries: 2 ileal ducts and 2 colostomies). The clinicopathological characteristics of the 100 patients are shown in [Table 1] The average age was 47 years with limits of 28 years the youngest and 77 years the oldest. The ADC corresponded to 41% of the histologies and the predominant CS was II with 64 patients.

Table 1: Clinical-pathological aspects.

Variable	No. of patients	Percentage
Age in years*		
21 a 30	6	6.0
31 a 40	16	16.0
41 a 50	48	48.0
51 a 60	18	18.0
61 a 70	9	9.0
71 a 80	3	3.0
Total	100	100
Histological types		
SCC	58	58.0
ADC	42	42.0
Total	100	100
Clinical Stages**		
Stage I	8	8.0
Stage II	64	64.6
Stage III	25	25.2
Stage IVA	2	2.0
Total: ***	99	99.8

*Minor: 28 years. Major:77 years. Average: 47 years
 IB2:1; IB3:7; IIA2:2; IIB:62; IIIA:3; IIIB:19; IIICr:3. *
 1: Not classifiable (laparotomy outside the unit)

5.1. Residual Tumor

Of the patients who were operated for curative purposes, 41/85 (48.2%) had a complete response to radiotherapy in order of absence of tumor in the surgical samples. The highest figures without residual tumor were obtained with class 1 hysterectomies, and the lowest figures in PE. [Table 2]

Table 2: Complementary surgeries Pathology reports on 85 surgical specimens.

Surgeries	Pathology reports				Significance
	No residual tumor		Residual tumor		
	No.	%	No.	%	
Hysterectomies					
(a) Class 1	11/16	68.7	5/16	31.2	P=0.036
(b) Class 2	16/26	61.5	10/26	38.4	P=0.099
(c) Class 3	9/19	47.3	10/19	52.6	P=0.748
Exenterations	5/24	20.8	19/24	79.1	P=0.00006
Total:	41/85	48.2	44/85	51.7	P=0.6463

5.2. Surgical Morbidity

An evaluation of postoperative complications was made according to the type of surgery and the CRT received: Group 1: complete CRT (with WPRT) and group 2: incomplete CRT (EBRT without ICBT or incomplete). Postoperative complications were present in 11/65 (16.9%) of group 1 vs. 1/20 (5.0%) of group 2. (p = 0.2290). MC in group 1 with CH were present in 5/48 (10.4%) and with PE in 6/17 (35.2%) (p = 0.0388). [Table 3].

Table 3: Morbidity of surgeries with or without employment of brachytherapy.

Surgeries	Surgical morbidity*				Total:	
	(1) Without Brachytherapy		(2) With Brachytherapy			
	No.	%	No.	%	No.	%
(A)Hysterectomies	0/13	-	5/48	10.4	(a) 5/61	8.1
(B)Exenterations	1/7	14.2	6/17	35.2	(b) 7/24	29.1.0
Total:	1/20	5.0	11/65	16.9	12/85	14.1

*30 days after surgery

(A): (1) vs (2), p=0.5748 (B): (1) vs. (2), p=0.6245 (a) vs (b), p=0.0129 Total: (1) vs (2), p= 0.2786

5.2.1. Complementary hysterectomies: in group 1, early surgical complications were present in 7/61 (11.4%) patients vs. late in 2/61 (3.2%) cases. Two of the first were minor (3.2%), and 5 MC (8.1%); 4 resolved with surgery and 1 conservatively. Two patients (3.2%) presented late urinary tract dilatation and required the placement of double J catheters. There were no complications in 13 hysterectomies performed in patients who did not receive brachytherapy.

5.2.2. Pelvic exenterations: MC in this case occurred in 7/24 patients (29.1%). 6/17, (35.2%) in CS III with CRT and 1/7, (14.2%) in a patient with CS IIB who did not receive brachytherapy p=0.6245. Four were resolved with new surgeries and 3 with conservative management. There were 2 late complications with kidney failure in two patients (8.2%). Both were medically managed. There were no postoperative deaths in this series.

5.3. Results of the surgeries: Sixty six of 90 (73.3%) patients were followed up and evolved without tumor activity from 12 to 80 months with an average of 30.5 months. The figure includes patients in whom the surgical samples of hysterectomies and exenterations had no residual neoplasm 36/39 (92.3%) vs. tumor activity in 30/36 (83.3%) (p = 0.2352). Similarly, 35/56 (62.5%) was SCC and 31/34 (91.1%) ADC (p = 0.003). Ten patients (10%) abandoned their controls without tumor activity during the first months following their surgery and were not considered for the final results.

5.3.1. Complementary hysterectomies: The evolution without evidence of disease was presented in 51/56 (91.0%) patients. The figure includes 11/14 (78.5%) of class 1 hysterectomies, 24/25 (96%) class 2 and 16/17 (94.1%) class 3; 25/29 (86.2%) of the SCC vs. 26/27 (96.2%) of ADC (p = 0.1898) [Table 4].

Table 4: Complementary hysterectomies Treatment results.

Complementary hysterectomies	Evolution without disease*				Total:	
	(1) No residual tumor		(2) Residual tumor			
	No.	%	No.	%	No.	%
Class 1	9/11	81.8	2/3	66.6	(a) 11/14	78.5
Class 2	17/17	100	7/8	87.5	(b) 24/25	96.0
Class 3	7/7	100	9**/10	90.0	(c) 16/17	94.1
Total:	33/35	94.2	18/21	85.7	51/56	91.0

*30.5 months of average

**2 recurrence patients progressed without disease with additional therapy

Class1: (1) vs (2), p= >0.05. Class 2 (1) vs. (2), p=0.320. Class 3 (1) vs. (2), p= >0.05 (a) vs. (b), p=0.0893. (a) vs.(c), p= 0.2062. (b) vs. (c), p= 0.7811. Total. (1) vs. (2), p= 0.2804

5.3.2. Pelvic exenterations: a follow-up without evidence of disease was obtained in 15/19 (78.9%) patients. The figure includes 7/9 (77.7%) total PE vs. 8/8 (100%) anterior vs. 0/2 posterior ($p = 0.4705$). Likewise, 10/14 (71.4%) of SCC vs. 5/5 (100%) of ADV ($p = 0.5304$).

5.3.3. Laparotomies: 15/100 (15%) laparotomized patients were not candidates for surgeries with a curative purpose: 9/15 (60%) cases the tumor was fixed to the pelvic wall, in 5/15 (33.3 %) metastatic paraaortic nodes were present with or without a tumor fixed to the pelvic wall, and in 1/15 (6.6%), there was peritoneal carcinomatosis. In 11 patients (73.3%) a laparotomy with biopsy was performed, in 2 (13.3%) an ileal conduit and in two others (13.3%) a definitive colostomy.

Four of the 15 patients received palliative CT treatment, 3 with SCC evolved with progression of disease and death and 1 with ADC received 10 cycles of gemcitabine with stable 12-month disease and loss to follow-up.

5.3.4. Results by CS and the surgeries performed: They evolved without evidence of disease during the mentioned period 8/8 (100%) of stages I; 42/58 (72.4%) of II (1/2 CS IIA and 41/56, 73.2% CS IIB respectively); 15/21 (66.6%) of stages III (3/3 CS IIIA, 11/15 IIIB, 73.3% and 1/3 IIIC, 33.3% respectively); 1/2 (50%) of the stage IVA and 1/1 (100%) of the unclassifiable stage (laparotomized outside the OU of GHM). [Table 5]

Table 5: Evolution without disease by clinical stage and surgeries performed *

Clinical Stage	Surgeries						Total	
	Hysterectomies		Exenterations		Laparotomies		No.	%
	No.	%	No.	%	No.	%		
I	7/7	100	1/1	100	-	-	8/8	100
II	37/43	86.0	4/5	80.0	0/10	-	42/58	72.4
III	6/6	100	9/12	75.0	0/4	-	15/21	66.6
IVA	-	-	1/1	100	0/1	-	1/2	50.0
No Clasif**.	1/1	100	-	-	-	-	1/1	100
Total:	51/56	91.0	15/19	78.9	0/15	0	66/90	73.3

*30.5 months as average

**No classified

Regarding the relationship between CS and histopathology, the DFS range was obtained in 35/56 (62.5%) of the total SCC vs. 31/34 (91.1%) of ADC ($p = 0.003$). And in stage II, 22/36 (61.1%) of SCC and 20/22 (90.9%) of ADC ($p = 0.0145$). [Table 6]

Table 6: Results by clinical stage and Histological type

Clinical Stage	Evolution without evidence of disease *					
	(1) SCC		(2) ADC		Total	
	No.	%	No.	%	No.	%
Stage I	4/4	100	4/4	100	(a) 8/8	100
(A) Stage II	22/36	61.1	20/22	90.9	(b) 42/58	72.4
(B) Stage III	8/14	57.1	6/7	85.7	(c) 14/21	66.6
Stage IVA	0/1	-	1/1	100	1/2	50.0
No Classified	1/1	100	-	-	1/1	100
Total:	35/56	62.5	31/34	91.1	66/90	73.3

*30.5 months of average

Total:(1) vs. (2), $p=0.003$. (A): (1) vs (2), $p= 0.0145$ (B): (1) vs. (2), $p=0.5304$ (a) vs.(b), $p= 0.0903$

(a) vs.(c), $p= 0.0654$ (b) vs.(c), $p= 0.6215$.

5.3.4. Tumor recurrences: The number of recurrences was 11/85 (12.9%), this in a period of 5 to 23 months after surgery, with an average of 9.3 months. Its corresponded to 7/61 (11.4%) CH vs. 4/15 (16.6%) PE. In 5 cases (41.6%) the recurrences were local or locoregional, in 2 (18.1%) regional and distant (1 paraaortic lymph nodes and spleen) and in 4 (36.3%) several distant sites without locoregional activity: 3 to the mediastinum, 2 to the paraaortic lymph nodes, 2 to the lungs, 2 to the central nervous system, and 1 to the bone.

We performed additional therapeutic procedures in 2/11 (18.1%) patients and recovered without tumor activity, both stage **II B** ADCs who received CRT and class 3 hysterectomy; Case 1: the patient had been treated with incomplete CRT, had a residual tumor in the sample, the neoplasm recurred in the vaginal dome and was treated with adjuvant ICBT at 30 Gy with a DFS of 36 months; Case 2: the patient had a local residual tumor and a metastatic lymph node, 7 months later she had tumor recurrence in the vaginal dome and spleen (PET CT study report), she was treated with 4 cycles of paclitaxel plus vinorelbine and 5 cycles of gemcitabine with complete response, showed a 24-month follow-up without tumor activity.

6. Discussion

Although the role that complementary surgery in patients with LACC previously treated with CRT is considered controversial due to surgical morbidity, mortality and oncological results at 5 years compared to this conventional treatment scheme with CRT alone [11,12,14,20]; it is interesting to explore the role that complementary and rescue surgery can play in patients who received incomplete CRT or in patients who did receive it but who ended up with a confirmed or suspected residual tumor, and / or in patients with LACC whose response to CRT is poor [17-19]. In 15 of the 100 laparotomized patients, it was not possible to carry out a procedure with a curative purpose due to the presence of fixed lesions to the cut of the pelvis, and / or the presence of metastatic paraaortic nodes. Surely the number of unresectable neoplasms would have been lower if the Service had available PET CT studies that would have avoided laparotomies in extrapelvic neoplasms as they occurred on 6/15 (40.0%) of our cases. Unfortunately, the authors' Institution does not have these devices and this study must be subrogated to another Institution that is usually saturated with these requests.

Of the 85 surgeries performed for curative purposes, 44 (51.7%) had residual tumor and 41 (48.2%) did not ($p = 0.6463$). Twelve (14.1%) had postoperative complications, 11 belonging to the group of 65 patients previously treated with complete CRT (16.9%) vs. 1 of 20 (5.0%) of those in the incomplete CRT group ($p = 0.2290$). The number of complications included 5/61 (8.1%) in CH with complete CRT and 7/24 (29.1%) in PE, of which 6 had complete CRT and 1 incomplete.

MC in patients treated with salvage surgeries due to persistent or recurrent CC after radiation consists of serious events that must be resolved judiciously since the life of these patients is at risk. Serious adverse events have been reported in 16-27% of patients treated with hysterectomies

after radiotherapy, the majority of class 3 hysterectomies [9,14,21]. In the series by Mazon et al., [21] with 54 cases, the figure was 25.9%, in the report by Mabuchi S et al. [9] with 31 patients, 27%, and in Fanfani et al. [14] they published with 73 patients the 16.4%.

For PE, the numbers of serious adverse events are even higher and generally reach 60% or more [20,22]. In the present series, 7/24 (29.1%) PE had MC, 6 of them with complete CRT and 1 with incomplete.

In this series they evolved without evidence of tumor activity from 12 to 80 months with an average of 30.5 months, 66 of 90 patients (73.3%) who had follow-up. The figure includes 36/39 (92.3%) patients undergoing CH and PE, that had surgical samples without residual tumor vs. 30/36 (83.3%) with it ($p = 0.2352$). Likewise, 51/56, (91%) of CH and 15 / 24 (78.9%) of PE.

The DFS for CS in the 90 patients who had follow-up was: 100% for stages **I**, 72.4% for stages **II**, 66.6% for **III** and 50% for **IVA**. By histological type, 35/56, (62.5%) for SCC and 31/34 (91.1%) for ADC ($p = 0.003$). By CS **II** and histopathology, there were results with statistical significance: 22/36, (61.1%) for SCC and 20/22 (90.9%) for ADC ($p = 0.0145$).

In the Mabuchi S. et al., series [9] with 30 radical hysterectomies due to persistent or recurrent CC, the 3-year survival rate was 53%. Fanfani F. et al., [14], compared the results obtained for stage **III** CC in 77 patients treated with CRT vs. 73 to whom radical hysterectomy was added to such 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 G. et al., [13] reported the results treated in 35 patients in stages **IB-IVA** treated with CRT plus surgery, 26 radical hysterectomies (21 with paraaortic lymphadenectomy) and 8 PE; in 17 patients (48.5%) there was a complete response and reported a 10-year DFS in 66.4% of the cases.

In this series, 11 of 85 patients (12.9%) had recurrence, and 4 (36.3%) of these had a report of absence of tumor activity in surgical samples. In 4 of these 11 patients (36.3%) the recurrences were distant in the absence of locoregional activity and in 2 of these 11 patients (18.1%) diagnosed with ADC they obtained control of their disease; one with local recurrence through ICBT application that she had not previously received, and the other with the combination of chemotherapy drugs.

7. Conclusions

In this series, 65 patients received complete CRT treatment and 11 of them (16.9%) had MC vs 1 of 20 (5%) treated with incomplete CRT ($p = 0.2290$). Five of 61 (8.1%) treated with CH and 7/24 (29.1%) with PE ($p = 0.0129$), vs. 1 out of 20 (5.0%) of those treated with incomplete CRT ($p = 0.2290$).

Sixty six of 90 patients (73.3%) who had follow up, evolved 30.5 months on average without tumor activity. The figure includes 51/56 (91.0%) CH

and 15/19 (78.9%) PE. Thirty-six of 39 (92.3%) in which the surgical samples did not have residual tumor vs. 30/36 (83.3%) of which they do ($p = 0.2352$).

By CS the results were 8/8 (100%) of stages I; 42/58 (72.4%) of stages II, 15/21 (66.6%) of stages III, and 1/2 (50%) of the stages of IVA.

By histological type, the follow-ups without tumor activity were: 35/56, (62.5%) in SCC and 31/34 (91.1%) in ADC ($p = 0.003$). For stage II, the most numerous with 58 patients the results were 22/36 (61.1%) for SCC and 20/22 (90.9%) for ADC ($p = 0.0145$).

Adjuvant surgery has a place in the management of LACC with tumor persistence or suspicion of this after conventional treatment with CRT. EBRT plus CT plus surgery can be considered for the treatment of ADC from CS IB3.

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