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Prognostic Factors and Morbidities After Completion Surgery in Patients Undergoing Initial Chemoradiation Therapy for Locally Advanced Cervical Cancer

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Learning Objectives

After completing this course, the reader will be able to:

1. Rate the prognostic factors for overall survival in patients undergoing completion surgery after initial chemoradiation therapy (CRT) for locally advanced cervical cancer.
2. In cervical cancer patients undergoing completion surgery, consider using laparoscopy to decrease the morbidity of the surgery.
3. In cervical cancer patients undergoing completion surgery, use PET-CT imaging to improve detection of para-aortic involvement.

Abstract

Purpose. **The aim of this study was to evaluate the prognostic factors and morbidities of patients undergoing completion surgery for locally advanced-stage cervical cancer after initial chemoradiation therapy (CRT).**

Patients and Methods. **Patients fulfilling the following inclusion criteria were studied: stage IB2–IVA cervical**

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carcinoma, tumor initially confined to the pelvic cavity on conventional imaging, pelvic external radiation therapy with delivery of 45 Gy to the pelvic cavity and concomitant chemotherapy (cisplatin, 40 mg/m^2 per week) followed by uterovaginal brachytherapy, and completion surgery after the end of radiation therapy including at least a hysterectomy.

Results. **One-hundred fifty patients treated in 1998–2007 fulfilled the inclusion criteria. Prognostic factors for overall survival in the multivariate analysis were the presence and level of nodal spread (positive pelvic nodes alone: hazard ratio [HR], 2.03; positive para-aortic nodes: HR, 5.46; $p < .001$) and the presence and size of residual disease (RD) in the cervix ($p = .02$). Thirty-seven (25%) patients had 55 postoperative complications. The risk for complications was higher with a radical hysterectomy ($p = .04$) and the presence of cervical RD ($p = .01$).**

Conclusion. **In this series, the presence and size of RD and histologic nodal involvement were the strongest prognostic factors. Such results suggest that the survival of patients treated using CRT for locally advanced cervical cancer could potentially be enhanced by improving the rate of complete response in the irradiated area (cervix or pelvic nodes) and by initially detecting patients with para-aortic spread so that treatment could be adapted in such patients. The morbidity of completion surgery is high in this context.** ***The Oncologist*** 2010;15:405–415

Introduction

Chemoradiation therapy (CRT) is considered the standard treatment for bulky cervical cancer (stage ≥IB2 according to the Fédération Internationale de Gynécologie et d'Obstetrique [FIGO] classification) by many American and European teams [1, 2]. In such patients, the role and modalities of completion surgery (after CRT) continue to be debated. In the literature, very few data are available on the results of completion surgery in patients treated with CRT [3–10]. Nevertheless, even if the therapeutic impact of completion hysterectomy continues to fuel debate, the analysis of prognostic factors (and mainly histologic factors) in hysterectomy and lymphadenectomy specimens could add interesting data in order to improve local and distant control for future patients undergoing CRT. This is the aim of this study. Morbidities of completion surgery in this context were also studied.

Patients and Methods

Patients treated at our institution from January 1998 to December 2007 fulfilling the following inclusion criteria were retrospectively reviewed and included in the present study.

Patients had to have a diagnosis of stage IB2–IVA cervical carcinoma according to the 1995 FIGO classification [11]). The pathologic subtypes included were squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, glassy cell carcinoma, and small cell carcinoma. Tumors had to be radiologically confined to the pelvic cavity (no para-aortic nodes >1 cm) on initial abdominopelvic magnetic resonance imaging (MRI) or CT scan and pelvic MRI.

Patients were treated with pelvic external radiation therapy delivering 45 Gy to the pelvic cavity and concurrent chemotherapy (cisplatin, 40 mg/m^2 per week). CRT was followed by uterovaginal brachytherapy performed at our institute. The brachytherapy dose was 15 Gy according to the International Commission on Radiation Units recommendations [12]. Since 2004, some patients were subjected to three-dimensional (3-D) MRI-guided brachytherapy according to the recommendations of the GEC-ESTRO group in order to deliver pulsed-dose-rate (PDR) brachytherapy [13]. Some patients with parametrial spread and/or bulky pelvic nodes on initial imaging received a pelvic lateral boost of 10–15 Gy.

The use of completion surgeries performed at our institution included at least a (radical) hysterectomy. During the study period, completion surgery after CRT was systematically used in patients with stage IB2–II cervical cancer (except for a few patients included in a randomized trial assessing the value of completion surgery). Surgery wasn't performed in patients with distant metastasis confirmed histologically. Surgery was conventionally performed 8–10 weeks after completion of brachytherapy. In 1996–2001, the type of radical hysterectomy performed was a Piver II or III procedure [14]. In order to decrease urinary tract morbidity, since 2001, a simple extrafascial hysterectomy was performed in patients who achieved a clinical and radiological complete response after brachytherapy.

During this pelvic surgery, nodal dissection could be added. Most of the patients had undergone complete para-aortic lymphadenectomy up to the left renal vessels. In terms of the surgical policy regarding pelvic nodes, all patients treated in 1998–2001 underwent a complete pelvic lymphadenectomy. Since 2001, in order to decrease the rate of postoperative morbidity related to this complete lymphadenectomy in a previously irradiated area (particularly the risk for permanent lymphedema), a selective lymphadenectomy was performed in patients with residual lymphadenomegaly detected during the surgical procedure.

Statistical Analysis

The statistical analysis was performed with SAS version 9.1 software (SAS Institute, Inc., Cary, NC). Association between factors was assessed by χ^2 tests or Fisher's exact tests. Postoperative complications were extracted from medical charts. We took into account all complications up to 90 days following surgery. The rate of lymphedema was studied without a time limit. Morbidities were classified according to the classification of Dindo et al. [15].

The median follow-up duration was estimated using Schemper's test [16]. Survival differences were compared using the log-rank test. To determine the independent prognostic significance of factors for survival, a multivariate analysis was conducted using the Cox proportional hazards regression method. Variables attaining significance at a p-value of .25 in the univariate analysis were retained for the multivariate analysis. Variables with a p-value $< .05$ in the multivariate analysis were considered significant prognostic factors for survival. The overall survival time was defined as the time between surgery and death from any cause, or the last follow-up for patients still alive. The event-free survival time was defined as the time between surgery and the first event (local or distant recurrence or death), or the last follow-up for patients free from recurrence.

Results

One hundred fifty patients fulfilled the inclusion criteria. The median age of the patients was 47 years (range, 19–77 years). The distribution of disease stages was as follows: stage IB2, $n = 48$ (32%); stage II, $n = 91$ (61%); stage III, $n = 10$ (7%), and stage IV, $n = 1$. The distribution of histologic subtypes was as follows: squamous cell carcinoma, $n = 108$ (72%); adenocarcinoma, $n = 26$ (17%); and other (and/or mixed) subtypes, $n = 16$ (11%).

Initial Imaging

At the pretherapeutic abdominopelvic MRI or CT scan, 49 patients were found to have enlarged pelvic lymph nodes. Six patients had enlarged para-aortic nodes, but all were <1 cm (five of them had suspicious nodes in the pelvic area). Twenty-four patients underwent initial positron emission tomography (PET)-CT imaging. Ten of those had pelvic node uptake and one also had uptake in the para-aortic area.

Treatment Modalities

All patients received CRT in the pelvic cavity (45 Gy) and brachytherapy. CRT modalities, including brachytherapy, are reported in Table 1.

Details concerning surgical treatments are given in Table 2. Among the 54 patients who underwent a pelvic lymph node resection, 34 had a complete lymphadenectomy and 20 had a selective adenectomy. All patients treated laparoscopically underwent an extrafascial hysterectomy (with para-aortic lymphadenectomy in 22 patients).

Table 1. Radiochemotherapy modalities ($n = 150$ patients)

Therapy	*n*	%
External radiation therapy (45 Gy)	150	100
Lateropelvic boost	38	25
Enlarged pelvic node	29	19
Parametrial spread	9	6
Para-aortic extended-field radiation therapy	3	2
Brachytherapy (15 Gy)	150	100
Once	136	91
Twice	14	9
LDR	136	91
PDR	14	9
Concurrent chemotherapy	72	68
Chemotherapy (cisplatin, 40 mg/m^2)	150	100

Abbreviations: LDR, low dose rate; PDR, pulsed dose rate.

Histologic Results at the Time of Completion Surgery

Seventy-eight (52%) patients had histologic residual disease (RD) in the cervix. The sizes of the cervical RD were ≤ 1 cm in 38 cases (25%)—32 were <2 mm and six were 2–10 mm—and >1 cm in 34 patients (23%); size was missing in four cases. Involvement of the surgical margins was observed in nine pathological specimens (7%). Lymphatic node involvement was diagnosed in 28 cases (19%). Table 3 shows the association among nodal spread, surgical margin status, and the size of the RD.

Among six patients with enlarged (but <1 cm) para-aortic lymph nodes on initial conventional imaging (MRI or CT scan), four underwent a para-aortic lymphadenectomy and two had positive nodes.

Among the 29 patients with enlarged pelvic lymph nodes on initial imaging who received a lateropelvic boost (10–15 Gy), eight had nodal disease after a pelvic lymphadenectomy at the time of completion surgery. In the group of 19 patients with enlarged pelvic lymph nodes on initial imaging who did not receive a lateropelvic boost, five had involved nodes after the pelvic lymphadenectomy.

Complications

No major intraoperative morbidity (urinary tract, bowel, or vascular injuries) was observed. Thirty-seven patients

Table 2. Patient surgical and pathological characteristics

Characteristic	*n*	%
Pelvic surgery		
Extrafascial hysterectomy	106	71
Radical hysterectomy	44	29
Type II	16	55
Type III	13	45
Type of radicality not determined	15	–
Other procedures		
Bowel resection	1	<1
Appendectomy	1	<1
Omentectomy	2	1
Approach		
Laparotomy	124	83
Laparoscopy	26	17
Lymphadenectomy		
None	14	9
Pelvic	5	3
Para-aortic	82	55
Pelvic and Para-aortic	49	33
Histological residual disease (and size) in the cervix		
No	72	48
Millimetric (<2 mm)	32	21
≤1 cm	6	4
>1 cm	34	23
Residual disease but size undetermined	6	4
Lymphovascular space involvement on hysterectomy specimen	31	21
Location of extracervical (residual) disease		
Vagina	9	6
Parametria	7	5
Peritoneal carcinosis	1	1
Ovarian metastasis	3	2
Surgical margins in hysterectomy specimen		
Free of disease	141	93
Positive margins	9	7
Presence of histologically positive nodes		
Pelvic positive nodes	19	–[a]
Pelvic positive without para-aortic nodes	9	–[a]
Para-aortic nodes	19	14

[a]Rate not determined because pelvic lymphadenectomy was performed mainly in cases of suspicious lymph nodes during surgery.

(25%) had 55 postoperative complications. Details of these complications are shown in Table 4. The factors increasing the risk for postoperative complications were a radical hysterectomy, compared with an extrafascial hysterectomy (odds ratio, [OR], 2.4; $p = .04$), and the presence of cervical RD ≤1 cm (OR, 4.3) or >1 cm (OR, 2.5), compared with no RD ($p = .01$) (Table 5).

Recurrences

The median follow-up duration was 3.6 years (range, 0.2–10.6 years). Four patients were lost to follow-up postoperatively. During follow-up, 41 patients (27%) developed a recurrence. Thirty-seven patients died of recurrent disease. Table 6 shows the distribution of patients according to the location of the first recurrence, the nodal status, and the presence and size of RD in the cervix.

Among the 14 patients who received PDR brachytherapy, only one developed a pelvic recurrence. The overall survival rates at 1 year and 5 years were 91% (95% confidence interval [CI], 85%–95%) and 71% (95% CI, 61%–78%), respectively (Fig. 1). The event-free survival rates at 1 year and 5 years were 83% (95% CI, 77%–89%) and 66% (95% CI, 57%–75%), respectively.

Prognostic Factors

Overall survival was found to be associated with pathological response and lymph node involvement in the multivariate analysis. Patients with millimetric RD or RD ≤1 cm and patients with RD >1 cm had a higher risk for death than patients without RD (HR, 1.92 and 3.85, respectively; $p = .02$). Patients with positive pelvic nodes and positive para-aortic nodes had a higher risk for death than patients without nodal involvement (HR, 2.03 and 5.46, respectively; $p < .001$) (Table 7). Pathological response (HR, 2.18 for millimetric RD or RD ≤1 cm and 3.99 for RD >1 cm; $p = .008$) and lymph node involvement (HR, 1.76 for pelvic nodes and 4.81 for para-aortic nodes; $p < .001$) were associated with a higher risk for events. Overall survival curves according to the presence and size (if so) of RD are shown in Figure 1.

Discussion

Several teams consider CRT as a "neoadjuvant" therapy, adding a hysterectomy at the end of treatment [17]. A number of retrospective studies have been published concerning the results of this surgical procedure in this context. Those studies demonstrated that such surgery is "feasible" and "beneficial" in terms of removing RD [3–10, 17]. Nevertheless, those papers were unable to demonstrate any survival advantage in patients subjected to completion surgery because they all reported on their experience of patients treated surgically without comparing them with a control group of patients exclusively managed with CRT. Furthermore, in most of those papers, the CRT modalities were heterogeneous. This is why our study focused on a population

Table 3. Association between nodal status and status of surgical margins and the presence and size of cervical residual disease (RD) on the hysterectomy specimen (144 patients)

	Histologic RD on the cervix			
Histologic prognostic factor	**Absence, *n* (%)**	**RD ≤1 cm, *n* (%)**	**RD >1 cm, *n* (%)**	***p*-value**
Nodal status				
Negative nodes	65 (90%)	28 (74%)	25 (74%)	.05
Positive nodes	7 (10%)	10 (26%)	9 (26%)	
Negative nodes	65 (90%)	28 (74%)	25 (74%)	
Positive pelvic nodes alone	3 (4%)	2 (5%)	4 (12%)	.03
Positive para-aortic nodes with or without positive pelvic nodes	4 (5%)	8 (21%)	5 (15%)	
Margins status				
Positive margins	1[a]	1	7	.003
Negative margins	71	37	27	

[a]One patient without residual disease in the cervix but one single lymphovascular space involvement in the vagina.

Table 4. Postoperative complications of grade ≥2 according the Dindo et al. [15] classification

Characteristic	***n***	**%**
n of patients	37	25
n of deaths related to postoperative morbidity	2	1.3
Type of complication[a]		
Lymphedema	9	16
Lymphocyst	8	15
Abcess	5	9
Ureteral fistula	5	9
Bowel fistula	5	9
Peritonitis	3	5
Chylous ascites	3	5
Phlebitis	3	5
Bowel obstruction	2	4
Rupture of iliac vessels in large bowel[b]	2	4
Ureteral stenosis	2	4
Bladder retention	2	4
Wound dehiscence	2	4
Urinary incontinence	1	2
Unexplained epigastralgia	1	2
Bladder fistula	1	2
Vaginal vault dehiscence with abscess	1	2

[a]Several complications could be observed in the same patients.
[b]Both patients with rupture of iliac vessels in the large bowel were also included among the five patients with a bowel fistula.

of patients with very strict inclusion criteria concerning CRT in order to improve the reliability of the results observed.

Survival rates reported in the present series seem to be very close or similar to those reported by teams who manage patients exclusively with definitive CRT [1, 2, 18]. Nevertheless, the aim of this study was not to try to demonstrate the therapeutic value of completion surgery after CRT in locally advanced cervical cancer, because only a randomized trial could adequately explore this crucial question. A trial was opened in France 6 years ago (randomizing patients with a macroscopic and radiologic complete response after CRT between extrafascial hysterectomy and no hysterectomy), but it was closed because of insufficient accrual. Since the closure of that trial, at our institution, completion surgery is exclusively considered in the group of patients with persistent disease 8–10 weeks after brachytherapy. Our strategy is therefore to perform clinical and MRI evaluation to diagnose any RD. In cases of a clinical and radiological complete response, no surgery is performed. In cases of RD, a simple extrafascial hysterectomy (type A from Querleu and Morrow's classification [19]) is performed, or radical hysterectomy fitting the disease when possible.

Data concerning prognostic factors are important because histological results concerning the lymph nodes and cervix after CRT could help us to understand the natural history of treatment failure. We could then attempt to improve the modalities of CRT and local and distant control of disease for future patients.

The first important prognostic factor in the multivariate analysis was the presence of RD in the cervix. The rate of RD we observed is very close to that of other different series, which was in the range of 20%–50% [17]. In theory, this could be a strong plea for completion surgery. Nevertheless, finding histologic RD and removing it does not necessarily imply a survival improvement. One half to two

Table 5. Risk factor for postoperative morbidity

	Univariate analysis		Multivariate analysis	
Variable	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
Pelvic surgery				
Extrafascial hysterectomy	1	.03	1	.04
Radical hysterectomy	2.3 (1.1–5.0)		2.4 (1.1–5.7)	
Laparotomy				
Laparoscopy	1	.43	–	–
Laparotomy	0.7 (0.3–1.7)		–	–
Residual cervical disease *(6 MD)*				
None	1	.001	1	.01
Millimetric and ≤1 cm	4.0 (1.6–10.3)		4.3 (1.7–11.1)	
>1 cm	3.0 (1.1–7.9)		2.5 (0.9–6.8)	
Histologically involved margins *(16 MD)*				
No	1	.82	–	–
Yes	0.8 (0.2–4.2)		–	–
Pelvic lymphadenectomy				
No	1	.07	*1*	*.36*
Yes	2.0 (1.0–4.3)		*1.5 (0.6–3.5)*	
Para-aortic lymphadenectomy				
No	1	.14	*1*	*.23*
Yes	3.1 (0.7–14.1)		*2.6 (0.5–12.9)*	
Pelvic lymph node status				
Negative	1	.02	*1*	*.11*
Positive	3.3 (1.2–8.9)		*2.5 (0.8–7.4)*	
Para-aortic lymph node status				
Negative	1	.07	*1*	*.21*
Positive	2.6 (0.9–6.7)		*2.0 (0.7–6.2)*	

Results in italics are results of the variable added to the final model (containing pelvic surgery and residual cervical disease).
Abbreviations: CI, confidence interval; MD, missing data; OR, odds ratio.

Table 6. Initial characteristics of recurrent patients according to site of first recurrent disease

	Histologic residual disease (RD) on the cervix (and size if so)				Histologic nodal status	
Location of first recurrence	**Absence (*n*)**	**RD ≤ 1 cm, *n***	**RD >1 cm, *n***	**Size undetermined, *n***	**Pelvic nodes involved alone, *n***	**Para-aortic nodes involved, *n***
Centro- (with or without latero-) pelvic alone ($n = 7$)	0	1	6	0	1	2
Lateropelvic alone (pelvic nodes) ($n = 5$)	3	1	0	1	2	1
Para-aortic nodes alone ($n = 3$)	1	1	0	1	0	3
Pelvic and/or para-aortic and distant ($n = 3$)	0	2	1	0	0	1
Distant without pelvic ($n = 23$)	5	8	8	2	1	7

thirds of the patients with RD had millimetric RD, and many of them would have had total surgical sterilization of the cervix if surgery had been performed later. In patients with larger RD (>1 cm in the current series or >2 cm in

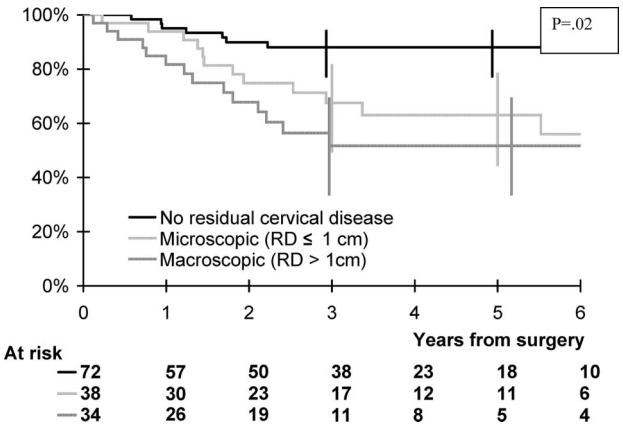

Figure 1. Overall survival according to the size of residual disease (RD) on the hysterectomy specimen.

other series [6, 10, 20]), surgery has a theoretical major therapeutic impact. But given the greater risk for extracervical disease (nodal spread or distant disease) in patients with RD, the real impact on survival of completion surgery in this subgroup remains unproven and is still debated [6, 20].

Given the frequency of histologic RD, the burning question is how to improve local control of the disease without significantly increasing morbidity (as we observed after completion surgery). The ideal solution is to improve the delivery of radiation therapy, particularly at the time of brachytherapy. The new modalities of this treatment (with 3-D MRI-guided procedures [13]) that are now becoming the new standard for this approach seem to clearly reduce the rate of local failure in this context [13, 21]. Fourteen patients received such treatment in this series and only one had (pelvic) failure.

The second major prognostic factor in the current series is histological nodal status. The rate of patients with positive para-aortic nodes was very high in the current series: 14% of patients had nodal involvement above the level of radiation therapy fields. In this series, among the 127 patients without enlarged para-aortic lymph nodes on conventional imaging who had undergone para-aortic lymphadenectomy, 17 (13%) had positive para-aortic nodes. Some of them could have experienced disease "progression" during CRT because this para-aortic spread may not have been present initially. However, most of them probably would have had such spread that was not visible during conventional imaging at the time of initial management.

This rate is high but is similar to that reported in a previous study [22]. Furthermore, the survival of patients with para-aortic nodal involvement at the time of completion surgery is very poor [22]. Lymphadenectomy at the time of completion surgery is probably pointless or of very limited value in terms of improving the survival of patients with para-aortic spread [22]. Thus, the next step is to improve the detection of para-aortic involvement. PET-CT imaging is a major asset in this context [23, 24]. Several excellent papers have clearly suggested longer survival in patients undergoing treatment based on PET-CT imaging [23, 24]. Over the last 3 years, this imaging modality has been systematically performed at our institution. However, although PET-CT imaging fails to exhibit uptake in the para-aortic area, we know that nearly 10% of patients have nodal involvement [25, 26]. This is the rationale behind the inclusion of laparoscopic para-aortic staging surgery in such patients to extend radiation fields in cases of positive para-aortic nodes [27, 28]. Even if the value of such management is still under debate [29], several papers suggest longer survival in patients undergoing surgical staging [30]. This surgery is now systematically performed at our institution in "operable" patients without uptake in the para-aortic area [25]. Such para-aortic lymphadenectomy is performed up to the level of the left vein [31]. The objective of this strategy is to extend the external radiation therapy field to the para-aortic region in cases of para-aortic node disease.

The most "problematic" result of the current analysis concerns the number of patients with positive residual nodes in an irradiated area (19 patients). Houvenaeghel et al. [32] and Ferrandina et al. [33] previously reported on residual pelvic lymph nodes after CRT, having observed 18% and 11% positive pelvic nodes, respectively. Such important data do not plead for us in favor of adding a pelvic lymphadenectomy at the time of completion surgery in this context because the lymphatic morbidity incurred by such a procedure is high in irradiated patients (lymphedema) and its usefulness in terms of optimizing survival is not proven.

However, this important observation raises the question of the optimization of pelvic nodal control in this context [34, 35]. The most appropriate procedure for optimizing complete nodal sterilization is the use of a lateropelvic boost of 10–15 Gy in patients exhibiting enlarged nodes on conventional imaging. Yet in this series of 29 patients who underwent lateropelvic boost, eight still had positive pelvic lymph nodes at the time of surgery, which means that the boost was probably not sufficient to completely sterilize bulky pelvic lymph nodes [34]. A new regimen of concurrent chemotherapy and/or image-guided intensity-modulated radiation therapy would probably increase the rate of complete sterilization [36]. In the present series, six patients had histologic nodal involvement, although no suspicious pelvic lymph nodes were observed on conventional imaging (and so no lateropelvic boost was performed). Furthermore, in the subgroup of five patients who had lateropelvic recurrence (considered pelvic nodal recurrence, Table 6),

Table 7. Prognostic factors for overall survival

Characteristic	*n* of deaths	3-Yr survival, % (SE)	Univariate analysis		Multivariate analysis[a]	
			HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
FIGO stage						
IB2	11	73 (7)	1[b]	.03	*1*[b]	*.36*
II	19	77 (5)	0.92 (0.44–1.94)		*0.65 (0.29–1.45)*	
III–IVA	7	40 (15)	3.07 (1.13–8.31)		*1.17 (0.40–3.44)*	
Histology						
Squamous	27	73 (5)	1[b]	.83	–	–
Nonsquamous	10	74 (8)	0.92 (0.45–1.92)		–	–
Pelvic surgery						
Extrafascial hysterectomy	20	81 (4)	1[a]	.01	*1*[b]	*.39*
Radical hysterectomy	17	54 (9)	2.26 (1.17–4.37)		*1.39 (0.66–2.93)*	
Laparotomy						
Laparoscopy	1	96 (4)	1[b]	.04	*1*[b]	*.12*
Laparotomy	36	68 (5)	8.40 (1.17–61.37)		*5.05 (0.67–38.00)*	
Pelvic lymphadenectomy						
No	20	77 (5)	1[b]	.48	–	–
Yes	17	67 (8)	1.27 (0.65–2.47)		–	–
Involved margin[c] (16 MD)						
No	29	75 (4)	1[b]	<.001	–	–
Yes	5	31 (18)	5.49 (2.09–14.39)		–	–
Residual cervical disease (6 MD)						
None	7	88 (4)	1[b]	.003	1[b]	.02
Millimetric and ≤1 cm	13	68 (9)	3.40 (1.34–8.64)		1.92 (0.69–5.32)	
>1 cm	14	52 (10)	4.91 (1.98–12.19)		3.85 (1.51–9.83)	
Nodal status[d]						
Negative nodes	19	83 (4)	1[b]	<.001	1[b]	<.001
Positive pelvic nodes alone	4	47 (19)	2.96 (1.01–8.69)		2.03 (0.67–6.16)	
Positive para-aortic nodes	14	29 (11)	6.24 (3.06–12.72)		5.46 (2.36–12.63)	

[a]Italic results are results of the variable adding to final model (containing residual cervical disease and nodal status).
[b]Reference class.
[c]Not included in the multivariate analysis because of the association with residual cervical disease (correlation = −0.31).
[d]Lymph node status determined after histologic analysis of lymphadenectomy.
Abbreviations: CI, confidence interval; FIGO, Fédération Internationale de Gynécologie et d'Obstetrique; HR, hazard ratio; MD, missing data; SE, standard error.

two had positive lymph nodes after lymphadenectomy, and three other patients did not undergo lymphadenectomy. Three of these five patients had complete sterilization of the cervical tumor (suggesting the absence of disease progression during CRT), and those patients died of their lateropelvic recurrence. Those patients probably had initial spread in the pelvic lymph nodes that was misdiagnosed on conventional imaging. This observation is a strong argument in favor of using a lateropelvic boost in patients without enlarged lymph nodes on initial conventional imaging but exhibiting uptake in pelvic nodes during PET-CT imaging. This strategy is now used at our institution in this context.

The second results from the current series concern the morbidity of completion surgery in this context. We did not investigate the morbidity of combination CRT followed by completion surgery. If this had been the case, the interval of 3 months after the end of treatment would have clearly been too short to accurately evaluate this issue. In an excellent paper by Eifel et al. [37] published before the era of CRT, the rates of major morbidity at 3 and 5 years in a cohort of 1,784 patients treated for stage IB disease using radiation

therapy (with completion hysterectomy in 234) were 7.7% and 9.3%, respectively. After 5 years, there was a continuous risk of 0.34% per year for major morbidity, with a 14.4% rate of major complications at 20 years [37]. Thus, a longer follow-up would be required to evaluate the morbidity of the entire treatment. Furthermore, the morbidity of CRT itself is now relatively well evaluated [37, 38]. The aim of the study at a time when the usefulness of completion surgery is being questioned is to evaluate the morbidity directly related to the surgical procedure itself. This is why a period of 3 months after surgery seemed appropriate to answer to this question.

One of the major difficulties of studying morbidities in a retrospective study is the high risk of underreporting real morbidity rates. In the present series, we included morbidity ≥ 2 (i.e., morbidity requiring specific treatment) according to the Dindo et al. [15] classification. "Minor" morbidities (grade 1 in the Dindo et al. classification [15]) were not reported in this series because the analysis of such complications would probably not have been so accurate.

We also included lymphedema, which is rarely reported in different analyses of morbidity because it can really deeply impair the quality of life of patients and is mainly observed >3 months after surgery. It was included also because the risk for lymphedema exists in patients treated exclusively with radiation therapy, but it is low [37, 38]. However, this risk is clearly higher in patients subjected to combination surgery (particularly lymph node dissection) and radiation therapy [38]. In the randomized trial published by Landoni et al. [38], the rate of lymphedema was 0.6% in patients treated for early-stage cervical cancer using radiation therapy alone and 9% in patients treated with surgery and external radiation therapy. In the paper by Eifel et al. [37], among the seven patients who experienced "leg edema," six had undergone lymph node surgery combined with radiation therapy, and only one patient was treated with radiation therapy alone. In the series by Perez et al. [39] involving 811 patients treated with radiation therapy, only one case of leg edema was observed.

Even with the potential limit of underreporting in the current study, our series clearly demonstrates a very high morbidity rate after hysterectomy following CRT. Two patients died of postoperative complications and the rate of "major" digestive or urinary tract complications (fistula or stenosis) was close to 15%. Two patients developed major vascular complications.

Three groups of complications were mainly observed: lymphadenectomy-related morbidities, urinary or digestive tract morbidities, and infectious morbidities (peritonitis or a deep abscess) treated using further surgery. The last two groups of complications were strongly correlated because peritonitis or a deep abscess often occurred secondary to a urinary or bowel fistula. In the paper by Eifel et al. [37], the risk for digestive or urinary tract fistula was double in patients who underwent a hysterectomy (and in that series only an extrafascial procedure was performed), compared with patients treated with radiation therapy alone (2.6% versus 5.3%; $p = .04$). Those complications were strongly correlated with the type of surgery used: the rate of ureteral stenosis or fistula or bowel fistula was greater in cases of more radical hysterectomy (with parametrial dissection). This phenomenon was previously reported at the time of pelvic surgery in patients treated with initial external radiation therapy [40]. We also observed a greater rate of morbidity in patients subjected to parametrial dissection in the present study. Such radical hysterectomies were statistically more frequently used in patients with RD in order to ensure clear surgical margins. These two factors (radical hysterectomy and RD) were correlated (Table 3). This result clearly suggests that systematic radical hysterectomy should be avoided in this context (if completion surgery is considered). This might have been feasible given the low risk for parametrial (7%) or vaginal (9%) involvement in our patients (Table 2).

Basically, if completion surgery is discussed (it has been proposed systematically by several teams) after CRT in patients devoid of macroscopic RD in the cervix, an extrafascial hysterectomy should be considered. A radical hysterectomy is more "logical" in patients with RD to guarantee free margins. However, such a basic proposal would also increase the morbidity of surgery, whereas the therapeutic value of completion surgery in patients with bulky RD (>1 cm or 2 cm according to the series) remains totally unproven because these poor responders also run a higher risk for extrapelvic disease (nodal involvement or distant metastasis) [6, 20]. This point also raises the important question of the evaluation of response (and thus, the potential presence of RD) at the end of CRT (should completion surgery be discussed). Response evaluation is based on a clinical examination and imaging (MRI) performed 6–8 weeks after brachytherapy, but the accuracy of such management is still debated [41]. Perhaps adding diffusion-weighted MRI or PET-CT imaging to predict potential RD could be helpful in this context [42, 43]. However, this last procedure should then be performed at least 3 months after brachytherapy, when the surgical procedure is more difficult (because adhesions and severe fibrosis are more frequent at that time).

A laparoscopic approach could also be a way to decrease the morbidity of the surgery. In the present series, a laparoscopic hysterectomy was used during the last 3 years

of the study in a selected group of patients devoid of clinical or radiological RD in the cervix, who had therefore undergone a "simple extrafascial hysterectomy." This is why we did not find any radical hysterectomies among these laparoscopically treated patients. Logically, no urinary or digestive tract morbidity was observed. Most of the morbidities in laparoscopically treated patients in our series were related to the use of a lymphadenectomy. The differences in the rates of lymphocysts and chylous ascites between the laparoscopic and laparotomic approach were almost of borderline statistical significance. We have no explanation for this higher rate of lymphatic morbidities in the laparoscopy group, but this explains why the use of a laparoscopic approach failed to reduce morbidity in our series. A recent interesting paper published on this topic compared a group of 46 patients undergoing radical hysterectomy by laparoscopy after CRT with a group of 56 patients undergoing similar surgery by a laparoscopic approach [8]. The rate of postoperative complications (particularly urinary fistula) was significantly lower in the laparoscopically treated patients without a higher rate of positive margins [8]. We were unable to conduct such a comparison in our study because no radical hysterectomy was performed laparoscopically.

The morbidity of completion surgery (based on hysterectomy with or without lymphadenectomy) was very high in this group of patients initially treated with CRT for locally advanced cervical cancer. Mortality was observed in 1.3% of cases, and the overall rate of urinary or bowel tract morbidity was close to 12%. The therapeutic value of completion surgery (which remains unproven today) should be weighed against the high morbidity rate in this context. Perhaps a laparoscopic approach could reduce the overall morbidity of completion surgery. Nevertheless, because the therapeutic value of this surgery has not been demonstrated, using an approach that could reduce surgery-related morbidity is not a proof of the usefulness of such surgery in terms of improving survival. Finally, the only certainty about completion surgery after CRT is that it gives rise to a high incidence of morbidity.

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