



Early stage cervical cancer: Brachytherapy followed by type a hysterectomy versus type B radical hysterectomy alone, a retrospective evaluation

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Abstract

Background: Two options are possible for the management of early stage cervical cancer, without lymph node involvement: radical surgery or brachytherapy followed by surgery. The aim of this study was to compare overall survival (OS) and disease-free survival (DFS) of early stage cervical cancers managed by uterovaginal brachytherapy followed by extrafascial hysterectomy (group 1) or by radical hysterectomy alone (group 2). The secondary objectives were to compare the morbidity of these two different approaches and to evaluate the parametrial involvement rate in patients managed by radical hysterectomy.

Materials and methods: It is a retrospective and collaborative study between the Paoli Calmettes Institute (Marseille) and the Oscar Lambret Center (Lille) from 2001 to 2013, in patients with tumors FIGO stages IA1, IA2, IB1 and IIA less than 2 cm of diameter, without pelvic lymph node involvement.

Results: One hundred and fifty-one patients were included (74 in group 1 and 77 in group 2). The demographic characteristics of the two groups were comparable. OS and DFS were respectively 92.3% versus 100% ($p = 0.046$) and 92.3% and 98.7% ($p = 0.18$). Complication rates were 12.2% and 44.2%, respectively ($p < 0.0001$). In group 2, the parametrial invasion rate in this study was 1.30%.

Conclusion: In our study, the two strategies are comparable in terms of DFS. Complications seem more frequent in the group 2, but more severe in the group 1. Finally, the low rate of parametrial invasion in group 2 confirms the interest of a less radical surgical treatment in these stages with good prognosis.

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Keywords: Early stage cervical cancer; Radical surgery; Radiosurgical treatment; Overall and disease-free survival; Morbidity

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Introduction

Early stage cervical cancer is defined by a disease confined to the cervix and upper vagina (stage IA–IIA FIGO).¹ For early stage with clinically and radiological negative pelvic nodes, there is no standard management. In case of negative surgical pelvic staging the treatment can be²:

- For FIGO stage IA1 and IA2: surgery is the standard. Options consist of conisation or trachelectomy in case of fertility sparing surgery, or simple or radical hysterectomy
- For FIGO stage IB1: options consist of surgery (radical hysterectomy or conservative fertility-sparing surgery in case of excellent prognostic factors) or combined radio-surgery (preoperative brachytherapy followed later by extrafascial hysterectomy).

Radiation can be an option for medically inoperable patients or those who refuse surgery. All strategies are associated with similar cure rates in patients with early-stage uterine cervical carcinoma, but questions remain concerning the morbidity in relation with both treatment and the real interest of the parametrectomy in cases with good prognostics factors.

Landoni et al.³ determined in a randomized study that the 5-year survival rate for patients with tumor <4 cm was 87% when surgery was performed and 90% when radiotherapy was used.

Although radical hysterectomy has proven to offer excellent prognosis in terms of survival, the significant morbidity related with the procedure adversely affects the quality of life. Resbeut et al.⁴ demonstrated a high local control rates in early-stage cervix carcinoma with low-dose-rate brachytherapy and limited surgery, with lower morbidity rate. Besides, he also showed that limited vaginal hysterectomy after brachytherapy in patients without unfavorable prognostic factor could be promising.⁵ Furthermore, parametrial invasion is rare in patients with small tumors without lymphovascular space involvement and negative pelvic nodes. Trudel et al.⁶ showed that parametrial involvement rate in tumors <2 cm, without lymphovascular invasion, with negative lymph nodes and depth of invasion <10 mm is between 0 and 1.96%, suggesting that a simple hysterectomy may be adequate in these cases.

Furthermore, the factor that most reliably predicts parametrial invasion is the status of the lymph node. Benedetti-Panici et al.⁸ reported 69 patients with previously untreated stage IB1 IB2 IIA cervical cancer. All the patients underwent radical hysterectomy and pelvic lymphadenectomy. All patients with pelvic node metastasis showed parametrial invasion whereas only two patients had parametrial metastasis without pelvic lymph node involvement, indicating that the parametrium is the first site of extracervical involvement.

The aim of this study was to compare the overall survival and disease-free survival in patients with early stage cervical carcinoma without pelvic lymph node involvement, when treated by combined treatment associating an intracavitary brachytherapy followed by a simple hysterectomy (group 1) or by a radical hysterectomy alone (group 2). The secondary objective was to compare the morbidity of these managements and to evaluate the parametrial involvement rate in patients of group 2.

Patients and methods

It is a retrospective study in two comprehensive cancer centers (Paoli Calmettes Institute, Marseille and Oscar Lambret Center, Lille). All the patients have been consent informed and therapeutics strategies were defined in our local tumor board.

Data were collected retrospectively, based on the following criteria: histologically confirmed carcinoma of the uterine cervix, FIGO stage IA1, IA2, IB1 or stage II, with largest dimension of less than 2 cm, treatment description with preoperative intracavitary uterovaginale brachytherapy followed by type A hysterectomy (Group 1) or radical hysterectomy (type B) alone (Group 2). These data were collected from 2001 to 2013. Informations concerning initial clinical examination and pelvic magnetic resonance imaging (MRI) have been reported. All patients underwent a conization before treatment to limit the risk of downstaging.

Lymph node staging was carried out radiologically or surgically. Some patients underwent a lymph node staging by resection of sentinel node dissection in the context of clinical research protocols (SENTICOL trial). In group 1, lymph node staging was realized before brachytherapy or after for eleven patients. In group 2, lymph node dissection was performed at the time of radical hysterectomy. All patients enrolled in our study had a negative pelvic lymph node staging; no treatment by external beam radiotherapy with concomitant chemotherapy has been necessary.

Preoperative uterovaginale brachytherapy was performed with a low-dose-rate ¹³⁷Cs application using a Delouche applicators and remote after loading with a Curietron. Treatments were planned on CT scan. The reference volume was that encompassed by the 60-Gy isodose⁹ prescribed at 0.5–0.8 Gy/h. Dosimetry was performed on CT scanner according to the guidelines in Report No. 38 of the International Commission on Radiation Units and Measurements.

The cervix dose, maximal and average rectal doses, maximal bladder dose, right and left point A doses, and volume of the reference isodose were reported. The maximal dose for the rectum and the bladder were respectively 65 Gy and 70 Gy.

In the Group 1, surgery was performed 6–8 weeks after brachytherapy: all the patients underwent an extra fascial hysterectomy (type A according to Querleu and Morrow classification). In the Group 2, proximal radical hysterectomies have been performed (type B according to Querleu and Morrow classification).¹⁰ As the classification of radical hysterectomy has changed in 2008, we reviewed all the operative reports in the two groups to establish a correlation between the older and the new surgical classification.

In the two groups, open surgery, conventional laparoscopy and robot assisted laparoscopy were used.

The follow-up has been realized 3 weeks after surgery, 4 months after brachytherapy, then every 4 months for the following 2 years, then every 6 months the next 3 years, then annually.

The demographic characteristics of patients were examined (age, body mass index, initial tumor histology, FIGO tumor stage), as well as descriptions of brachytherapy, surgery (type, conversion rate, intraoperative and early postoperative complications), final histological results (residual tumor size, number of lymph nodes removed) and follow-up (late postoperative complications, brachytherapy's complications, recurrence). Radiation's complications were graduated according to the Common Toxicity Criteria scale.¹¹ Surgical complications were graduated according to the Clavien and Dindo Classification.¹²

Recurrences were divided in local recurrence (central pelvic failures at the level in the vagina, lateral pelvic failures in the parametrium or the pelvic wall), lymph node recurrence (pelvic or latero-aortic) and metastatic disease.

Statistical analysis

The disease-free survival and overall survival were calculated from the date of diagnosis to the date on which the first recurrence (local or distant) was found, with censoring of other patients data at the time of the last

follow-up visit or death. Survival curves were drawn using Kaplan–Meier estimates. Curves were compared by the log-rank test. Survival rates and relative risks are presented with their 95% confidence interval (CI). Student T test has been used to analyze quantitative data.

Results

From 2001 to 2013, 151 patients with early stage cervical cancer, less than 2 cm with negative pelvic nodes were managed either by:

- intracavitary uterovaginale brachytherapy followed by extrafascial hysterectomy for 74 patients (group 1),
- or by radical hysterectomy alone for 77 patients (group 2).

The median patient age at diagnosis was 48.09 years [range 28–50] in group 1 and 45.86 years [range 28–74] in group 2.

Demographic characteristics reported in Table 1 were comparable in the two groups, except according to the body mass index ($p < 0.0001$).

Table 1
Demographics patients' characteristics, operative data, morbidity and definitive pathology.

	Group 1: Uterovaginale brachytherapy and extrafascial hysterectomy	Group 2: Radical hysterectomy alone	Student T test (p)
Age (years) median (min, max)	48.09 (28–80)	45.86 (28–74)	p = 0.22
BMI			
<26	40.54% (n = 30)	63.64% (n = 49)	p < 0.0001
26–30	10.81% (n = 8)	11.68% (n = 9)	
>30	6.76% (n = 5)	15.58% (n = 12)	
FIGO stages			
IA1	1.35%	3.90%	p = 0.096
IA2	8.10%	13%	
IB1	86.48%	83.11%	
IIA	4.05%	0%	
Histology			
Adenocarcinoma	25.67%	31.17%	p = 0.46
Squamous cell carcinoma	70.27%	66.23%	
Mixed carcinoma	4.05%	1.30%	
Glass cell carcinoma	0%	1.30%	
Surgical approach			
Laparoscopy	83.78%	97.40%	p = 0.003
Open surgery	10.81%	0%	
Vaginal	1.35%	0%	
Conversion to open	2.70%	1%	
Complications			
Yes	12.16% (n = 9)	44.16% (n = 34)	p < 0.0001
No	62.16%	55.84%	
Grade (Clavien and Dindo classification)			
I	6.75% (n = 5)	38.96% (n = 30)	
II	1.35% (n = 1)	2.60% (n = 2)	
III	4.05% (n = 3)	2.60% (n = 2)	
Complete response rate			
Complete response	47.3% (n = 35)	NS	
Residual tumor <1 cm	14.86% (n = 11)	NS	
Residual tumor >1 cm	2.7% (n = 2)	NS	
Lympho vascular spaces involvement	0%	5.19%	p < 0.0001
Unknown	35.1% (n = 26)		
Parametrial invasion	0%	1.30%	p < 0.0001

Surgery

The median delay between first-line brachytherapy and extrafascial hysterectomy was 58.84 days [range 33–141].

In group 1, patients were managed laparoscopically in 83.78% of the cases versus 97.40% of the cases in the group 2 ($p = 0.0031$). The rate of conversion to open was respectively 2.70% and 1.30%. Despite conization and preoperative brachytherapy, residual tumor has been observed in 17.56% of the patients in the group 1. The rate of parametrial invasion in our study was 1.30% for patients of group 2. All patients, except two in the group 1, had pelvic lymphadenectomy, all but 1 had negative pelvic nodes (only one case of micro metastasis in the group 2, considered as negative pelvic node). Twelve patients (16, 22%) in the group 1 had a preoperative radiologic evaluation of lymph nodes; in particular those two who didn't had a lymphadenectomy, because of surgical difficulties. These two patients didn't have operative complications or radiation toxicity.

Survival and tumor recurrence

We observed five recurrences in the group 1 (6.76%): 3 metastatic diseases (bones and liver recurrence, and two peritoneal carcinosis recurrences), one pelvic node recurrence and one local recurrence (left pyramidalis muscle).

Two recurrences occurred in the group 2 (2.63%); one lymph node recurrence (renal pedicle) and one local recurrence in the pelvis (vagina).

The rate of deaths was 6.76% in the group 1, with two deaths due to new cancers (lung cancers).

We didn't observe death in relation with the cervical cancer in group 2.

The actuarial overall survival rate was 92.3% in the group 1 and 100% in the group 2 ($p = 0.046$) and disease-free survival rate was 92.3% and 98.7% respectively ($p = 0.18$) (Fig. 1).

Influence of treatment in complications

No deaths occurred as a result of the treatment procedures. There were no per-operative complications, except conversion to open.

We observed a highest complication rate in the group 2 (44.2% ($n = 34$) versus 12.2% ($n = 9$), $p < 0.0001$).

Grade I complications of Dindo and Clavien Classification were more frequent (Table 2).

In the group 1, grade 1 complications were lymphocele and dyspareunia. Eleven patients underwent extrafascial hysterectomy with pelvic lymphadenectomy after brachytherapy. None of them had operative complications or radiation toxicity.

In the group 2, there were especially lymphocele, legs lymphedema, legs sensorial neuropathy and dyspareunia.

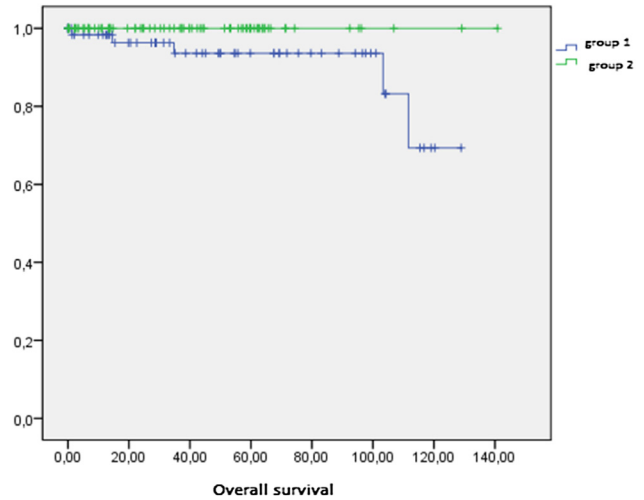


Figure 1. Overall survival.

Concerning grade III complications, we found 3 patients with grade III complications in the group 1 and 2 patients in the group 2 (4.05% versus 2.60%). In group 1, there was one case of ureteral stenosis treated by ureteral catheterization, one uretero-vaginal fistula treated by ureteral reimplantation, and one abscess of the abdominal wall treated by surgical drainage. All these patients underwent laparoscopic pelvic lymphadenectomy, followed by uterovaginal brachytherapy then laparoscopic extrafascial hysterectomy.

In the group 2, there was one ureteral stenosis treated by corticotherapy and one vaginal vault leakage managed by surgery. All these patients underwent laparoscopic radical hysterectomy and pelvic lymphadenectomy.

Table 2
Complications characteristics.

Clavien and Dindo classification	Group 1 (n = 74)	Group 2 (n = 77)
Grade I	n = 5 (6.75%)	n = 30 (38.96%)
Hematoma	1.35% (n = 1)	1.30% (n = 1)
Lymphocele	0%	5.19% (n = 4)
Lymphedema	4.05% (n = 3)	7.79% (n = 6)
Dyspareunia	1.35% (n = 1)	1.30% (n = 1)
Legs sensorial neuropathy	0%	10.39% (n = 8)
Bladder retention	0%	12.99% (n = 10)
Grade II	n = 1 (1.35%)	n = 2 (2.60%)
Irradiation injury (bladder/rectum)	1.35% (n = 1)	0%
Infected lymphocele	0%	1.30% (n = 1)
Ureteral stenosis (medical treatment)	0%	1.30% (n = 1)
Grade III	n = 3 (4.05%)	n = 2 (2.60%)
Umbilical hernia	0%	1.30% (n = 1)
Disunion of the vagina	0%	1.30% (n = 1)
Uretero-vaginal fistula	1.35% (n = 1)	0%
Ureteral stenosis (surgical treatment)	1.35% (n = 1)	0%
Abscess of abdominal wall	1.35% (n = 1)	0%

Concerning brachytherapy toxicity (Table 3), we found only grade 2 complications according to the CTC4 scale with one patient with radiation cystitis and proctitis relieved by medical treatment and one patient suffering dyspareunia.

Discussion

Survival

Data from literature demonstrate that surgery and radiotherapy are associated with similar cure rates in patients with early-stage uterine cervical carcinoma. In addition, after initial surgery such as a Piver class III hysterectomy, as many as two thirds of patients may require postoperative radiotherapy. In such cases, the survival rate is the same as when radiotherapy is used exclusively, but the expected complication rate is much higher, especially legs lymphedema rate of 9%.³

Resbeut et al. showed in his study that in low-stage uterine cervical carcinoma treated by combined brachytherapy and surgery, his results do not support the necessity of performing surgery more extensive than the Piver class I hysterectomy, with a high rate of disease control and lowest morbidity rate.⁴ He published a 5-year overall survival rate and disease-free survival rate of 96.9% and 91.2% respectively. In their study, Uzan et al.⁷ found an overall survival and free-disease survival rates of 95% and 94.3% in patients treated by brachytherapy uterovaginale followed by radical hysterectomy for a stage IB1 cervical cancer. They concluded that radical hysterectomy was feasible after uterovaginale brachytherapy without increasing morbidity rate. The ureteral postoperative morbidity rate was about 5%.

Our results are correlated to those of literature. We didn't observed any difference concerning DFS suggesting that the two treatments could be efficient in term of oncologic results.

Complications

A review of the literature about 6320 cases of radical hysterectomy with lymphadenectomy showed a mortality

Table 3
Brachytherapy toxicity (group 1) according to the CTC4 scale.

	Brachytherapy toxicity: group 1, n = 7 (9.46%)				
	CTC4 scale				
	Grade				
	0	1	2	3	4
Pain: dyspareunia			n = 1 (14.3%)		
Lymphatics			n = 3 (42.8%)		
Ureteral obstruction				n = 1 (14.3%)	
Uretero-vaginal stenosis				n = 1 (14.3%)	
Proctitis			n = 1 (14.3%)		

rate lower than 0.6%, basically because of bleeding, severe sepsis and thromboembolic complications.¹³ Late complications were especially urinary complications, with fistula. Their frequency varies to less than 1%–5% with parametrial dissection. Apart from ureteral stenosis, bladder's dysfunction rate varies to 1%–33%, in relation with the extent of parametrial dissection. Bowel complications are exceptional.¹⁴ Lymphocele frequency is associated with the extent of the lymphadenectomy but in 80% of cases, lymphoceles are asymptomatics.^{15,16}

Parametrial dissection increases the risk of morbidity, especially ureteral stenosis, ureteral fistula (4%), bladder retention more or less persistent (3–5%), and urinary tract infection (8%)¹⁷ whatever surgical way (laparoscopy or open). In Bergmark et al. study,¹⁸ patients treated by radical hysterectomy had greater risk of incomplete miction, and greater risk of dysuria, comparing with patients treated by extrafascial hysterectomy. Chen et al.¹⁹ have noticed an increased rate of urinary incontinence of 9.4% and abnormalities of urodynamic evaluation at 6 months in 53% patients.²⁰

In our study, there were more grade 1 complications in the group 2 and a trend of more grade 3 complications in the group 1; but our study is retrospective and we can hypothesize that all grade 1 complications and particularly lymphatics complications has not been informed in patients charts. Concerning grade 3 complications, the difference between the two groups is not significative according to the small number of patients involved, but the severity of these complications must be emphasized. This underlines the necessity of the patient's follow-up, concerning postoperative morbidity evaluation in relation to our practice. And even if brachytherapy's morbidity has been described and seems to be low, especially with new technical irradiation protocol,^{21–27} we can hypothesize that the highest grade 3 complications rate in the group 1, particularly concerning ureteral injuries, may be in relation with the radio surgical association.

Interest of parametrectomy

In the 1990s, the concept of modified radical hysterectomy was accepted to reduce the radicality of parametrium's resection.¹⁴ The aim was to reduce long-term morbidity which is associated with the radical resection of the parametria, where potential injury to the innervation of the rectum and bladder can occur. Extension and utility of the parametrectomy in early stage cervical cancer have been debated in the literature.²² Uzan et al.⁷ had meanwhile shown that the interest of a dissection of the parametria could remain questionable in patients with stage IB1 cervical cancer after a preoperative brachytherapy, as this dissection increases the rate of urinary tract disease, mainly ureteral morbidity or bladder retention.

Several studies have confirmed a correlation between tumor size or infiltration of the stroma and positive lymph

nodes with involvement of the parametria.²³ Grisaru et al.²⁴ showed in their study that parametrial invasion was not a prognostic factor. Pluta et al.²⁵ showed a risk of parametrial involvement lower than 1% in cervical cancer IA2 and IB1 when tumor size was less than 20 mm in diameter and when invasion was less than 10 mm, with negative pelvic lymph nodes. For them, the most important prognostic factor was positive pelvic lymph nodes, with a risk of parametrial involvement of 28%. According to Sartori et al.,²⁶ overall survival rate and free disease survival rate were the same although there was parametrial involvement or not. Covens et al.²⁷ have defined a low risk group (diameter less than 2 cm, negative pelvic lymph nodes, depth of invasion less than 10 mm) in which the benefit of radical hysterectomy compared to extrafascial hysterectomy in term of overall survival rate was only to 0.2%, because microscopic disease of the parametrium is supported by postoperative treatments.

In our study, we observed 1.3% of parametrial invasion in the group 2. This result confirms literature's rate and constitutes a new argument for type A hysterectomy in early stage cervical cancer of less than 2 cm with negative pelvic lymph node to reduce surgical morbidity.

Conclusion

Early stage cervical cancer have good prognosis but there is no gold standard treatment in these cases. In our study, the surgical treatment alone with radical hysterectomy seems to have a better overall survival and a complications rate significantly more important than in the radio surgical group, however we do not observe any difference concerning the DFS.

Grade 3 complications in relation with the radiosurgical association, and particularly ureteral morbidity must be explored in largest studies.

In selected patients, lack of preoperative brachytherapy or parametrectomy could reduce the rate of treatment morbidity.

Moreover, the parametrial invasion rate in the group 2 constitutes a new argument to limit parametrial dissection in such indication, with probably the same therapeutic role control and a lowest complications rate.

Prospective studies (as SHAPE trial) are needed to compare and to evaluate prospectively oncologic outcomes and early and late complications between both strategies.

Conflicts of interest statement

The authors declare that there are no conflicts of interest.

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