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Impact of preoperative brachytherapy followed by radical hysterectomy in stage IB2 (FIGO 2018) cervical cancer: An analysis of SENTICOL I-II trials

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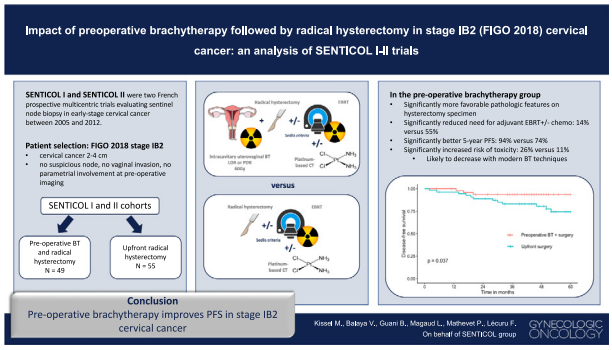
HIGHLIGHTS

- Pre-operative brachytherapy followed by radical hysterectomy was compared to upfront surgery for IB2 cervical cancer
- Pre-operative brachytherapy was significantly associated to better pathological features on hysterectomy specimens.
- Pre-operative brachytherapy was significantly associated to reduced rates of adjuvant treatments and better PFS.
- Pre-operative brachytherapy however led to increased toxicity, probably because of outdated brachytherapy techniques.

GRAPHICAL ABSTRACT



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ABSTRACT

Introduction. The goal of this study was to compare the outcomes of preoperative brachytherapy followed by radical surgery versus radical surgery alone in cervical cancer with tumor between 2 and 4 cm (FIGO 2018 IB2).

Material and methods. SENTICOL I and SENTICOL II were two French prospective multicentric trials evaluating sentinel node biopsy in early-stage cervical cancer between 2005 and 2012. Preoperative brachytherapy (low-dose rate or pulse-dose rate at the dose of 60Gy) could be performed 6 to 8 weeks prior to the radical hysterectomy, at the discretion of each center. SENTICOL I and SENTICOL II cohorts were retrospectively analysed to compare the outcomes of preoperative brachytherapy or upfront surgery in patients with IB2 cervical tumor.

Results. A total of 104 patients were included: 55 underwent upfront radical hysterectomy and 49 underwent preoperative brachytherapy followed by radical hysterectomy. Patients with preoperative brachytherapy were more likely to have no residual disease (71.4% vs. 25.5%, $p < 0.0001$) and to be defined as low risk according to Sedlis criteria (83.3% vs. 51.2%, $p < 0.0001$). Adjuvant treatments were required less frequently in case of preoperative brachytherapy (14.3% vs. 54.5%, $p < 0.0001$). Patients with preoperative brachytherapy experienced more postoperative complications grade ≥ 3 (24.5% vs. 9.1%, $p = 0.03$). Patients with preoperative brachytherapy had better 5-year disease-free survival compared to patients who underwent surgery alone, 93.6% and 74.4% respectively ($p = 0.04$).

Conclusion. Although preoperative brachytherapy was significantly associated with more severe postoperative complications, better pathologic features were obtained on surgical specimens and led to a better 5-year disease-free survival in IB2 cervical cancer.

1. Introduction

With >600,000 newly diagnosed cases and 340,000 deaths per year, cervical cancer is the fourth most frequent malignancy in women and the fourth major cause of cancer-related deaths in females [1]. The management of early-stage cervical cancer is mainly based on radical hysterectomy and lymph node staging by laparotomy [2]. According to Peters' criteria, adjuvant radiochemotherapy is required in case of positive margins, lymph node involvement or parametrial invasion and has been shown to increase relapse-free survival and overall survival [3]. Moreover, in case of a combination of minor Sedlis criteria described in the GOG92 study [4,5], namely the presence of emboli, deep invasion of the chorion, and tumor size, postoperative external beam radiotherapy (EBRT) is indicated to reduce the risk of relapse [4–6]. However, this radiosurgical association should be avoided due to its particularly high morbidity, especially in terms of urinary toxicity [4,7].

Brachytherapy (BT) plays an essential role in the therapeutic management of patients with cervical cancer and is the standard treatment after radiochemotherapy in locally advanced cervical cancers (LACC). According to the ESTRO guidelines and French guidelines, preoperative utero-vaginal BT followed by surgery 6–8 weeks later may be offered as an option in experienced centers in situations where the preoperative workup suggests the presence of a major criterion or a combination of minor criteria postoperatively with a low risk of lymph node involvement [8,9]. In fact, preoperative BT aims to decrease the tumor size and eradicate the presence of high-risk pathologic factors, thus reducing the need of adjuvant EBRT [10]. However, it remains unclear whether BT improves outcomes for these patients in the preoperative setting. Several retrospective data from expert BT centers supported that preoperative BT might be an efficient therapeutic option [9]. Modern brachytherapy techniques may reduce long-term toxicities; thus this strategy may be very competitive compared to upfront surgery +/− adjuvant EBRT in terms of morbidity.

Through an ancillary analysis of two prospective multicentric databases on sentinel lymph node (SLN) biopsy for cervical cancer (SENTICOL I and II), the goal of this study was to compare the outcomes of preoperative brachytherapy followed by radical surgery versus upfront radical surgery in cervical cancer with tumor between 2 and 4 cm in size.

2. Material and methods

2.1. Patient selection

Two French prospective multicentric database of patients with early-stage cervical cancer were retrospectively analysed (SENTICOL I

and SENTICOL II cohorts). Design of both studies have already been reported elsewhere [11,12]. Summarily, 145 patients from seven French gynecological oncology centers were enrolled in SENTICOL I between January 2005 and May 2007. This study assessed the diagnostic value of SLN biopsy compared to full pelvic lymphadenectomy for lymph node staging in early-stage cervical cancer [11]. In SENTICOL II, 267 patients were enrolled between January 2009 and July 2012 from 23 French gynecological oncology centers. This trial aimed to compare early and late complications between SLN biopsy alone and SLN biopsy associated with pelvic lymphadenectomy [12]. In both studies, all patients had early-stage cervical cancer with tumor size <4 cm, and no suspicious nodes neither parametrial involvement at preoperative workup (including MRI and physical exam for all patients). In the current study, patients with FIGO 2018 IB2 cervical tumor and who underwent radical hysterectomy with lymph node staging were included. Patients were excluded if tumor size was lower than 2 cm or if radical hysterectomy was not performed.

Approval to conduct this study was obtained from Paris Descartes *(Comité de Protection des Personnes "HEGP-Broussais", Ethical code: DRRC AOR 03063)* and Lyon's Hospital Ethical Committee *(Comité de Protection des Personnes "SUD-EST IV", Ethical code: 2008-A01369–46).* Patients included in both studies provided written informed consent stating the use of data for secondary analysis.

2.2. Data analysis

From both SENTICOL I and SENTICOL II database, demographic and clinical characteristics, surgical data, treatment type, and follow-up data were extracted and analysed.

Operative records were reviewed, and data about the type of surgical approach, the type of radical hysterectomy performed according to Querleu-Morrow classification and the type of lymph node staging (SLN biopsy only or additional pelvic lymphadenectomy), were collected. Minimally invasive approach was defined as surgery performed by laparoscopy or robotic-assisted laparoscopy.

Pathologic reports were reviewed and included tumor histology, tumor size, lymphovascular space invasion (LVSI), parametrial status, vaginal margin status, depth of stromal invasion, surgical margin status and node status. Preoperative tumor size was determined on pelvic magnetic resonance imaging (MRI) or on conization specimen then tumor size was macroscopically measured in surgical specimens. All pathology slides were analysed at the center where they were performed by experienced gynecologic pathologists.

Frozen section analysis of SLN was performed only on macroscopic suspicious nodes in 2 centers at the surgeon discretion and routinely in the others. SLNs were analysed after hematoxylin and eosin staining of 200-μm sections. Negative SLNs were then examined by immunohistochemistry with anti-cytokeratin AE1-AE3 antibodies. Isolated tumor cells (ITCs) were defined as <0.2 mm, micrometastases as between 0.2 and 2 mm, and macrometastases as >2 mm [13]. Node-negative patients were defined if bilateral SLN were free of disease or all non-SLNs were negative. The presence of LVSI was defined by the presence of tumor cells in the lumen of vessels or lymphatic channels. LVSI were categorized as absent, rare or numerous. Rare and numerous LVSI were considered LVSI +. Parametrial involvement was defined as any evidence of disease in the parametrial tissue: direct microscopic spread, positive parametrial nodes and lymphovascular space invasion, defined as tumor cells present within lymphovascular channels in the parametrium. According to the pathologic prognostic factors described by Sedlis et al., patients were categorized as having high-risk, intermediate-risk and low-risk disease [4,5]. The revised 2018 FIGO classification was used [14].

2.3. Treatment characteristics

Preoperative brachytherapy was left at the discretion of each center, for tumor size larger than 20 mm and/or positive lymphovascular space invasion (LVSI) on preoperative biopsy. Low-dose rate or pulse-dose rate brachytherapy was performed (depending on the era of inclusion) to reach a 60 Gy-dose to the CTV and was followed by radical hysterectomy 6 to 8 weeks later. Delineation of target volumes and organs at risk followed the GEC-ESTRO recommendations [15].

Detection of SLN was performed by using a combined labeling technique (radioactive tracer [99mTc] and patent blue). All patients included in the present study underwent type B or type C radical hysterectomy from the Querleu-Morrow classification. In SENTICOL I, patients underwent a systematic pelvic lymphadenectomy after SLN biopsy whereas, in SENTICOL II, patients underwent a SLN biopsy, and an additional pelvic lymphadenectomy was performed according to the randomization group. If no SLNs were detected on one hemipelvis, an homolateral hemipelvic lymphadenectomy was performed.

Adjuvant treatment was decided according to Sedlis criteria in tumor board. Concurrent chemoradiotherapy (CCR) was indicated for high-risk patients. Intermediate-risk patients received external beam radiation therapy (EBRT) or postoperative brachytherapy at the discretion of each inclusion center and depending on the patient's condition. No adjuvant treatment was required for low-risk patients.

2.4. Follow-up

Follow-up consisted in physical and pelvic examinations every 3 months for 2 years, every 6 months for 3 years, and yearly afterwards. Computed tomography (CT) scans, pelvic MRI, and/or positron emission tomography scans (PET-CT) were indicated if recurrences were suspected.

Intraoperative and postoperative complications were recorded according to time of onset: early complications were defined as occurring up to 30 days after surgery and late complications >30 days after surgery. Levels of morbidity were assessed according to the Clavien-Dindo classification for early-complications and according to the CTCAE classification V 4.03 for late complications [16]. A severe complication was defined as grade ≥ 3 in the Clavien-Dindo classification, requiring a radiologic or surgical operation, or as grade ≥ 3 in the CTCAE classification.

Disease-free survival (DFS) was defined as the interval in months between the date of surgery and the date of the first recurrence or the date of the last follow-up for patients who were still alive without any recurrence. Recurences were classified as centropelvic, nodal (pelvic or paraaortic nodes) or metastatic.

2.5. Statistical analysis

Qualitative variables were expressed as n (%) and were compared by applying chi-square test. Quantitative variables were expressed as mean [range] and were compared by applying the Student's *t*-test. DFS curve was built using Kaplan-Meier method, and the log-rank test was used for survival comparisons. A Cox proportional hazards regression model was applied to obtain hazard ratios (HRs) and a 95% confidence interval (CI). All statistical tests were two-sided and p values lower than 0.05 were retained as significance set. All statistical tests were carried out using R Studio and XLStat Biomed software (AddInsoft V19.4).

3. Results

3.1. Population characteristics

Among the 412 patients who were enrolled in SENTICOL I and SENTICOL II studies, 104 patients from 20 centers fulfilled the inclusion criteria and were included for analysis: 55 underwent upfront radical hysterectomy and 49 underwent preoperative brachytherapy followed by radical hysterectomy. The flow-chart is presented in Supplementary data.

The median age was 45 years [25-84]. Most patients had squamous cell carcinoma (76 patients, 73.1%) and were operated by minimally invasive approach (93 patients, 89.4%). The median interval from BT to surgery was 8 weeks [4.6 – 11.8]. Both groups were well-balanced in terms of age, body-mass index (BMI), histologic type, grade of differenciation and surgical procedure. Patients who underwent preoperative BT had significantly larger preoperative tumor size (28 mm vs 24.5 mm, p< 0.0001). The patient and surgical characteristics are presented in Table 1.

3.2. Pathologic features

At final pathologic examination of surgical specimen, patients with preoperative BT had significantly smaller tumor size (2.0 ± 4.4 mm vs 17.4 ± 14.8 mm, $p < 0.0001$), smaller depth of stromal invasion (0.7 ± 1.9 vs 10.0 ± 10.1 mm, $p < 0.0001$), less vaginal invasion (2.0% vs 12.7%, $p = 0.04$) and less parametrial invasion (0.0% vs 9.1%, $p = 0.03$) (Table 2). The pathologic complete response rate was 71.4% (35 patients) after preoperative BT whereas it was 25.5% (14 patients) in upfront surgery group ($p < 0.0001$). In these 14 cases, cervical tumor was entirely removed during preoperative conization. According to Sedlis criteria, patients with preoperative BT were more likely to be defined as low risk (83.7% vs. 45.5%, $p < 0.0001$) (Table 2).

Table 1
Population characteristics.

Predictive variable	Upfront surgery N = 55		Preoperative Brachytherapy + Surgery N = 49		P
	n Median	[%] [range]	n Median	[%] [range]	
Age [years]					
Median	44	[27–82]	48	[25–84]	*0.99*
BMI [kg/m²]					
Median	23.1	[17.9–41.4]	23.1	[15.9–41.0]	*0.97*
Histology					
Squamous cell carcinoma	39	70.9	37	75.5	*0.82*
Adenocarcinoma	14	25.5	11	22.4	
Other type	2	3.6	1	2.0	
Grade of differenciation					
G1	20	46.5	10	28.6	*0.19*
G2	13	30.2	17	48.6	
G3	10	23.3	8	22.9	
Not specified	12		14		
Conization					
Yes	33	60.0	24	49.0	*0.26*
No	22	40.0	25	51.0	
Preoperative LVSI					
Yes	14	30.4	6	14.3	*0.07*
No	32	69.6	36	85.7	
Preoperative Tumor size					
Median	24.5	[20–35]	28	[20–40]	***<0.0001***
Surgical procedure					
Type of surgical approach					
Minimal Invasive Surgery	46	83.6	47	95.9	*0.68*
Laparotomy	4	7.3	2	4.1	
Type of radical hysterectomy					
Type B	43	82.7	41	87.2	*0.53*
Type C	9	17.3	6	12.8	
Not specified	3		2		
Type of Lymph node staging					
SLN biopsy alone	17	30.9	18	36.7	*0.53*
SLN biopsy + Pelvic lymphadenectomy	38	69.1	31	63.3	

Table 2
Pathologic features on final surgical specimen.

Predictive variable	Upfront surgery N = 55		Preoperative Brachytherapy + Surgery N = 49		P
	n Median	[%] [range]	n Median	[%] [range]	
Final pathologic examination					
Tumor size					
Mean ± SD	17.4 ± 14.8	[0–60]	2.0 ± 4.4	[0–16]	***<0.0001***
< 20 mm	27	49.1	48	98.0	***<0.0001***
≥ 20 mm	28	50.9	1	2.0	
Deep stromal invasion					
Mean ± SD	10.0 ± 10.1	[0–40]	0.7 ± 1.9	[0–8]	***<0.0001***
< 10 mm	25	45.5	48	98.0	***<0.0001***
≥ 10 mm	30	54.5	1	2.0	
Residual disease					
None	14	25.5	35	71.4	***<0.0001***
0–10 mm	5	9.1	10	20.4	
> 10 mm	36	65.5	4	8.2	
LVSI					
Yes	22	40.0	11	22.4	*0.05*
No	33	60.0	38	77.6	
Node status					
Negative	46	83.6	44	89.8	***0.01***
ITC	5	9.1	0	0.0	
Micrometastases	4	7.3	1	2.0	
Macrometastases	0	0.0	4	8.2	
Vaginal invasion					
Yes	7	12.7	1	2.0	***0.04***
No	48	87.3	48	98.0	
Parametrial invasion					
Yes	5	9.1	0	0.0	***0.03***
No	50	90.9	49	100.0	
Positive margin					
Yes	6	10.9	3	6.1	*0.39*
No	49	89.1	46	93.9	
Sedlis criteria					
Low risk	25	45.5	41	83.7	***<0.0001***
Intermediate risk	19	34.5	0	0.0	
High risk	11	20.0	8	16.3	

3.3. Functionnal outcomes

Intraoperative complications occurred in 6 patients: three had bladder injury, 2 ureteric injuries and one patient had uterine perforation due to cervical stenosis. There was no significant difference between both groups for intraoperative complications.

Early complications rates were similar between both groups but patients with preoperative BT had more grade ≥ 3 complications according to CTCAE classification (24.5% vs 9.1%, p = 0.03). Overall, 19 patients (18.3%) experienced at least one severe complication: 13 patients (26.5%) in preoperative BT group and 6 patients in upfront surgery group (10.9%) (p = 0.04). In preoperative BT group, there were more vaginal cuff dehiscences (12.2% vs 0.0%, $p = 0.009$) and more uro-vaginal fistulas (uretero-vaginal or vesico-vaginal) (12.2% vs 1.8%, $p = 0.04$).

Although no significant differences were found for overall urinary tract complications between both groups, patients with preoperative BT experienced more frequently postoperative stress urinary incontinence (12.2% vs 1.8%, $p = 0.04$). More lymphovascular complications were observed for patients with preoperative BT (40.8% vs 21.8% $p = 0.04$), especially more lymphocysts were reported (16.3% vs 1.6%, $p = 0.03$). Neurologic complications rates were comparable between both groups. Overall complications are summarized in Table 3.

3.4. Survival outcomes

Median follow-up was 49 months [5–127]. Patients with preoperative BT were less likely to require adjuvant treatment (14.3% vs 54.6%, p < 0.0001) (Table 4). During the follow-up, 15 patients experienced a

Table 3
Intraoperative and postoperative morbidity.

Predictive variable	Upfront surgery N = 55		Preoperative BT + Surgery N = 49		P
	n Median	[%] [range]	n Median	[%] [range]	
Intraoperative complications	**5**	**9.1**	**1**	**2.0**	***0.12***
Bladder	3	2.8	0	0.0	*0.24*
Ureter	2	1.9	0	0.0	*0.50*
Other	0	0.0	1	2.0	*0.47*
Clavien-Dindo Classification (< 30 days)					
None	31	56.4	31	63.3	*0.85*
Grade 1	4	7.3	2	4.1	
Grade 2	16	29.1	13	26.5	
≥Grade 3	4	7.3	3	6.1	
CTCAE classification (> 30 days)					
None	26	47.3	13	26.5	***0.03***
Grade 1	7	12.7	3	6.1	
Grade 2	17	30.9	21	42.9	
≥Grade 3	5	9.1	12	24.5	
≥1 Severe complication	**6**	**10.9**	**13**	**26.5**	***0.04***
Vaginal cuff dehiscence	0	0.0	6	12.2	***0.009***
Severe abdominal infection	0	0.0	2	4.1	*0.22*
Uro-vaginal fistula	1	1.8	6	12.2	***0.04***
Digestive fistula	0	0.0	1	2.0	*0.47*
Lymphocele drainage	1	1.8	1	2.0	*0.99*
Hydronephrosis	2	3.6	0	0.0	*0.50*
Hemorrhagic complications	1	1.8	0	0.0	*0.99*
Thromboembolic events	2	3.6	0	0.0	*0.50*
≥1 Urinary tract complication	**17**	**30.9**	**18**	**36.7**	***0.53***
Urinary infections (lower tract)	8	14.5	5	10.2	*0.50*
Urinary infections (upper tract)	1	1.8	1	2.0	*0.99*
Dysuria	3	5.5	3	6.1	*0.99*
Stress urinary incontinence	1	1.8	6	12.2	***0.04***
Urinary retention	4	7.3	2	4.1	*0.68*
Pollakiuria	0	0.0	2	4.1	*0.22*
≥1 Lymphovascular complication	**12**	**21.8**	**20**	**40.8**	***0.04***
Lower limb lymphedema	10	18.2	10	20.4	*0.77*
Lymphocyst	2	3.6	8	16.3	***0.03***
Pubic lymphedema	0	0.0	1	2.0	*0.47*
Inguinal lymphedema	0	0.0	2	4.1	*0.22*
≥1 Neurologic complication	**12**	**21.8**	**11**	**22.4**	*0.94*
Genito-femoral nerve	5	9.1	9	18.4	*0.17*
Obturator nerve	7	12.7	1	2.0	*0.09*
Lateral femoral cutaneous nerve	0	0.0	2	4.1	*0.22*

recurrence (14.4%): 5 centropelvic, 5 nodal and 5 distant metastases. Sites of recurrence were similar between both groups.

Patients with preoperative brachytherapy had significantly better 5-year disease-free survival compared to patients who underwent surgery alone, 93.6% and 74.4% respectively (p = 0.04) (Fig. 1).

The cox regression analysis revealed that tumor size larger than 20 mm and the presence of residual disease larger than 10 mm were associated with increased risk of cervical cancer recurrence (HR = 3.04, 95%IC = [1.10–8.41], p = 0.03 and HR = 3.38, 95%IC = [1.06–10.74], $p = 0.04$ respectively) whereas preoperative brachytherapy was associated with a decreased risk of of cervical cancer recurrence (HR = 0.28, 95%IC = [0.08–0.98], $p = 0.049$) (Table 5). A stromal invasion deeper than 10 mm was borderline significant for recurrence (HR = 2.70, 95%IC = [0.98–7.46], $p = 0.05$). Multivariate cox regression analysis failed to identify independent factors associated with recurrence.

4. Discussion

Although preoperative brachytherapy was significantly associated with more severe postoperative complications, better pathologic features were obtained on surgical specimens and led to a better 5-year disease-free survival in IB2 cervical cancer.

This study based on prospective data showed that pre-operative BT provided a pathologic complete response rate of 71.4% which leads to a significant lower rate of adjuvant treatment in the pre-operative BT group of 14.3% versus 54.5% in the upfront surgery group. These results are concordant with those reported retrospective studies which ranged from 1% to 26% in BT studies versus 23% to 64% in upfront surgery studies [10]. This strategy, given the low rate of post-operative EBRT, may be particularly interesting for countries that lack external beam facilities but where uterovaginal brachytherapy could be given. Pre-operative brachytherapy in this setting may also be a cost-effective option, especially in low or middle-income countries.

Table 4
Adjuvant treatment and oncological outcomes.

Predictive variable	Upfront surgery N = 55		Preoperative Brachytherapy + Surgery N = 49		P
	n Median	[%] [range]	n Median	[%] [range]	
Adjuvant treatment					
None	25	45.5	42	85.7	***<0.0001***
Brachytherapy	11	20.0	0	0.0	
EBRT	9	16.4	0	0.0	
CCR	10	18.2	7	14.3	
5-year outcomes					
Recurrences					
Yes	12	21.8	3	6.1	***0.02***
No	43	78.2	46	93.9	
Site of recurrences					
Centro-Pelvic	4	7.3	1	2.0	*0.68*
Nodal	4	7.3	1	2.0	*0.68*
Distant metastases	4	7.3	1	2.0	*0.68*
Status					
Alive	50	90.9	46	93.9	*0.57*
Dead	5	9.1	3	6.1	

Concurrent radiochemotherapy was still necessary as an adjuvant treatment for 15% of the patients treated with preoperative BT in our study, mostly because of nodal involvement. Such situations may be rarer since the integration of systematic PET-CT as part of the initial work up for early-stage cervix cancer. However, false negative findings are quite frequent especially for low volume nodal disease. To avoid this pitfall, an alternative strategy would be to perform first surgical lymph node staging with SLN mapping, and if negative then to perform preoperative BT only. This strategy was used by Hannoun-Levi et al. and no local recurrence was reported with a median follow-up of 24 months [17]. However, it implies a two-steps surgical procedure, less convenient for the patient, and maybe with more adherences at the time of hysterectomy due to the upfront lymph node staging.

In the upfront surgery group in SENTICOL, 20% of patients had vaginal brachytherapy as sole adjuvant treatment. This attitude, rather popular in France, is hypothesized to give good results in terms of

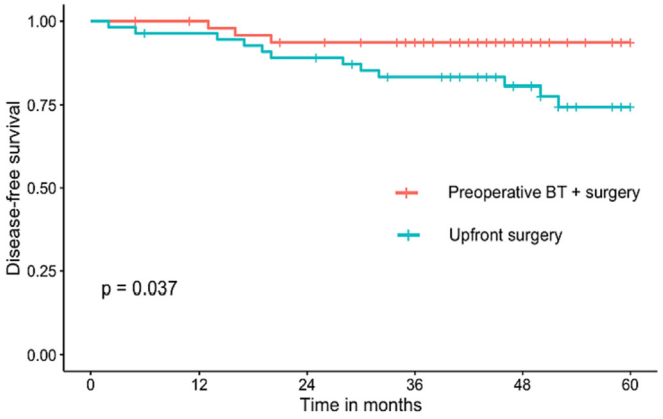

Fig. 1. Kaplan-Meier 5-year disease-free survival curves of preoperative BT with surgery and upfront surgery groups.

Table 5
Cox proportional Hazards models of Disease-free survival.

Risk-factors	Reference	Hazard ratio	95% CI	*p*
Preoperative brachytherapy	**No**	**0.28**	**0.08–0.98**	***0.049***
Node status	Negative	2.24	0.71–7.05	*0.17*
Tumor size (final pathology)	**< 20 mm**	**3.04**	**1.10–8.41**	***0.03***
Deep stromal invasion	< 10 mm	2.70	0.98–7.46	*0.05*
LVSI	No	2.43	0.88–6.71	*0.09*
Vaginal invasion	No	1.80	0.40–8.00	*0.44*
Parametrial invasion	No	2.78	0.63–12.40	*0.18*
Residual disease				
0–10 mm	None	1.26	0.14–11.24	*0.84*
> 10 mm	**None**	**3.38**	**1.06–10.75**	***0.04***
Pathologic risk level				
Intermediate	Low	3.02	0.92–9.92	*0.07*
High	Low	2.15	0.61–7.62	*0.24*
Adjuvant treatment				
Brachytherapy	None	2.09	0.40–10.82	*0.38*
EBRT	None	**5.67**	**1.52–21.14**	***0.01***
CCR	None	3.13	0.84–11.68	*0.09*

relapse prevention with limited toxicity compared to EBRT. However, this adjuvant treatment has never been studied in a prospective study and even retrospective studies are scarce at best. Furthermore, pre-operative BT in our study was significantly and positively associated with PFS in cervix cancer with a large difference in 5-year PFS (15% absolute difference). The results in terms of 5-year PFS is consistent with modern series such as the one reported by Gauci et al. [18], with only 5% of local relapses at 5 years. A significant gain in PFS with pre-operative brachytherapy has also been reported in a retrospective study by Zhang et al. [19]. With a median follow-up of 30 months, the 3- and 5-year locoregional control rates were 83% and 78% in preoperative BT group, while that of surgery alone group were 62% and 53%, respectively ($p < 0.05$), However, there was no significant difference in OS. Our series also found no gain in terms of overall survival but the study was not powered to detect any difference in OS in this unplanned analysis.

The rate of positive margins was not decreased by preoperative BT in this cohort, contrarily to Vízkeleti et al.'s study [20]. However, parametrial invasion was significantly reduced by pre-operative BT (9% versus 0%). Parametrial spread reported by other authors was similar and ranged from 0.5% to 4.3% [21–24]. Contrarily to Gauci et al. that found no clinical or surgical factors predictive of relapse in univariate or multivariate analysis, residual tumor size was a prognostic factor in SENTICOL. Of note, adenocarcinoma histology sub-type was considered the only independent prognostic factor for residual tumor in Gauci et al.'s study ($p = 0.04$).

The high rate of urinary toxicity with pre-operative BT (mainly fistula and stress incontinence) in SENTICOL is of concern. Indeed, 12% of patients in the preoperative BT group presented with severe urinary toxicity, while “only” 6% of severe toxicity was reported in a surgery + adjuvant EBRT strategy in a randomized trial [4]. The rather high toxicity in SENTICOL may be attributed to the BT and the surgical techniques. Given the era of inclusion in this study (2005 to 2007 in SENTICOL-1 and 2009 to 2012 in SENTICOL-2), brachytherapy techniques are outdated compared with modern 3D MRI-based brachytherapy. Indeed, stepping source technology in pulse-dose rate or high-dose rate BT has allowed for dose optimization, thus further conformation to tumor volume and reduced exposition of OAR [25]. Furthermore, the advent of image guided brachytherapy and especially with MRI has been shown to increase local control and decrease toxicity [26]. Modern series of pre-operative brachytherapy report much less toxicity [18,21,27,28]. For instance, in a series using MR-guided pulse-dose rate pre-operative BT, Grade 3–4 urinary toxicity was only 1.3%. Preoperative BT series usually report less grade 2+ toxicities compared to hysterectomy with adjuvant EBRT studies (10% vs. 59% respectively) [18]. Moreover, one has to remember that contrarily to definitive uterovaginal BT after EBRT for LACC, dose escalation is not an end in itself and stringent constraints to OAR should be fulfilled to facilitate the ulterior surgery. Dose-volume histogram (DVH) parameters for modern pre-operative brachytherapy are of interest but more solid data is needed to refine modern dose constraints [25]. In a retrospective study, the only correlation that could be found between dose/volume parameters and toxicity was between the TRAK and the probability of vaginal toxicity ($p = 0.002$) but no correlation between DVH parameters and bladder or rectal toxicity could be shown [27], contrarily to LACC where BT is used after EBRT [29–31].

The other advantage of pre-operative BT is that is allows for a more limited surgery. Minimally invasive surgery decreases postoperative morbidity after radical hysterectomy for early-stage cervical cancer. However, a randomized trial and large retrospective data question its safety after observing lower rates of survival than open surgery [1,2]. The causes of this higher recurrence rate are not definitely established but may result from cancer exposure to the peritoneum during vaginal section and cancerous cells' spillage enhanced by pneumoperitoneum or a uterine manipulator. Hence, pre-operative brachytherapy may be the only remaining setting in which minimally invasive surgery can be safely offered. Resbeut et al. also retrospectively evaluated the survival data, rates and patterns of complications and recurrences for patients who had early cervical carcinoma and underwent preoperative brachytherapy and subsequent surgery [32]. A less extensive procedure appeared to be an adequate choice after primary brachytherapy. The tumor control-rate was similar after preoperative uterovaginal brachytherapy and modified radical hysterectomy with bilateral pelvic lymphadenectomy or after primary radical abdominal hysterectomy with bilateral pelvic lymphadenectomy. The morbidity rate was lower in the group of patients treated by preoperative uterovaginal BT followed by radical hysterectomy. The type of surgical procedure is guided by the evaluation of prognostic factors that ultimately correspond to the Sedlis criteria used for the decision of adjuvant treatment. Indeed, for low-risk tumors (<2 cm, no emboli, invasion of the inner third of the stroma), a type B1 (possibly A) hysterectomy according to Querleu-Morlow is recommended. For high-risk tumors (>2 cm with emboli), a C1 or C2 hysterectomy is recommended. For intermediate tumors, a B2 or C1 hysterectomy is recommended [8]. Preoperative brachytherapy would thus allow for a less extensive and therefore less toxic procedure [33].

One should not forget that EBRT + BT in this setting is also an option, with a Level 1 evidence thanks to a large randomized trial with very-long follow-up [7]. Given the relatively favorable toxicity profile of this option, it should be considered in inoperable patients or for women refusing surgery.

No randomized trial to date has compared results between primary surgery and preoperative uterovaginal BT followed by surgery but a Hungarian randomized study is underway [20]. However, the dose in this trial is particularly low (2x8Gy HDR i.e., 24Gy EQD210 vs 60Gy in our study), which may explain the low rate of complete pathological response reported in the preliminary publication of the study (26% versus 71% in SENTICOL).

The strength of this study is of course the prospective collection of data in a multicentric setting but its weaknesses are the relatively low numbers and the lack of technical data regarding brachytherapy that hinders the toxicity analysis.

5. Conclusion

Although preoperative brachytherapy was significantly associated with more severe postoperative complications, better pathologic features were obtained on surgical specimens and led to less adjuvant treatments and a better 5-year disease-free survival in IB2 cervical cancer.

Author contribution

M. KISSEL and V. BALAYA: Conceptualization, Methodology, Formal analysis and investigation, Writing - original draft preparation; B.

GUANI, L. MAGAUD, P. MATHEVET: Writing - review and editing; F. LECURU: Conceptualization, Writing - review and editing, Supervision.

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Appendix A. Supplementary data

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