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TITLE: Brachytherapy and surgery versus surgery alone for IB2 (FIGO 2018) cervical cancers: A FRANCOGYN study

SHORTENED TITLE: Brachytherapy in early stage cervical cancer

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Keywords : brachytherapy, cervical cancer, IB2, surgery

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ABSTRACT

Objective: Evaluation of the management by first brachytherapy followed by radical hysterectomy (Wertheim type) compared to radical hysterectomy alone (Wertheim type) for the treatment of IB2 cervical cancer.

Methods: Data from women with histologically proven FIGO stage IB2 cervical cancer treated between April 1996 and December 2016 were retrospectively abstracted from twelve French institutions with prospectively maintained databases.

Results: Of the 211 patients with FIGO stage IB2 cervical cancer without lymph node involvement included, 136 had surgical treatment only and 75 had pelvic lymph node staging and brachytherapy followed by surgery. The surgery-only group had significantly more adjuvant treatment (29 vs. 3; $p = 0.0002$). A complete response was identified in 61 patients (81%) in the brachytherapy group. Postoperative complications were comparable (63,2% vs. 72%, $p=0,19$) and consisted mainly of urinary (36 vs. 27) and digestive (31 vs 22) complications and lymphoceles (4 vs. 1). Brachytherapy had

no benefit in terms of progression-free survival ($p=0.14$) or overall survival ($p=0.59$). However, for tumors of between 20 and 30 mm, preoperative brachytherapy improved recurrence-free survival ($p = 0.0095$) but not overall survival ($p = 0.41$). This difference was not observed for larger tumors in terms of either recurrence-free survival ($p = 0.55$) or overall survival ($p = 0.95$).

Conclusion: Our study found that preoperative brachytherapy had no benefit for stage IB2 cervical cancers in terms of recurrence-free survival or overall survival. For tumor sizes between 2 and 3 cm, brachytherapy improves progression-free survival mainly by reducing pelvic recurrences without improving overall survival.

Keywords: brachytherapy, cervical cancer, IB2, surgery

Introduction

The management of early-stage cervical cancer is currently an important issue in gynecological surgery and is currently debated (1,2,3). First, the precocity of cervical involvement is mainly based on tumor size and parametrial involvement. For this reason, the most recent FIGO classification subdivided the old IB1 stage into IB1 and IB2 (4). Tumor measurement is based mainly on clinical assessment, the tumor size on conization specimen, and pre-therapeutic magnetic resonance imaging (MRI). The second issue relates to the surgical approach. The LACC study published in 2018 compared the surgical approaches to treating and managing early-stage cervical cancers (IA1 to IB1) and found that laparotomy significantly improved overall survival and recurrence-free survival (5). Although this is the only prospective randomized study to report this result, it puts our practices into question. The third issue, which relates to a criticism levied against Ramirez et al.'s (5) study, concerns standardization of the surgical treatment of early-stage tumors (vaginal preparation) and also by brachytherapy before radical hysterectomy (6). The European society for medical oncology (ESMO) Clinical Practice Guidelines recommend preoperative brachytherapy for the treatment of early-stage cancers larger than 2 cm (IB2) (3). By contrast, the National Comprehensive Cancer Network guidelines recommend performing postoperative radiotherapy guided by various prognostic factors specific to the operative specimen without pre/postoperative brachytherapy (2). Although France has historically promoted brachytherapy, several centers in France do not use preoperative brachytherapy in this indication. This diversity led us to evaluate the management of IB2 cervical cancer by brachytherapy followed by radical hysterectomy (Wertheim type) compared to radical hysterectomy alone (Wertheim type)

Materials and Methods

Data from women with histologically proven FIGO stage IB2 cervical cancer treated between April 1996 and December 2016 were retrospectively abstracted from twelve institutions in France with prospectively maintained databases. All patients provided written consent to participate in the study, and the research protocol was approved by the Institutional Review Board of the Collège National des Gynécologues et Obstétriciens Français (CEROG 2016-GYN-). Patients were included if they were >18 years old and had a FIGO 2018 stage IB2 tumor and no clinical or imaging nodal involvement. The tumor size was defined by MRI and/or surgical specimen (where one

or more conization was performed). For patients who had brachytherapy, pelvic lymphadenectomy and/or pelvic sentinel lymph node dissection was performed to confirm no nodal involvement. Patients with nodal involvement were excluded and treated with concomitant radiotherapy and chemotherapy followed by brachytherapy. Surgery was performed 6–8 weeks after brachytherapy by laparotomy, laparoscopy or robot-assisted laparoscopy and consisted of type II or III radical hysterectomy according to the revised Querleu-Morrow classification, which removes the uterus and the surrounding parametrial tissue. No uterine manipulator was used and a protective closure of the colpotomy over the tumor was performed. Depending on age, some patients also underwent bilateral salpingo-oophorectomy. The exclusion criteria were previous pelvic radiotherapy, preoperative chemoradiotherapy, lymph node involvement detected during the primary lymphadenectomy in the brachytherapy group or during surgery in the surgery alone group, no surgical treatment after brachytherapy, or follow-up of less than 3 months after the end of the treatment.

All enrolled women underwent a preoperative workup, which included medical history, physical examination, cervical biopsy, MRI, and, where required, positron emission tomography–computed tomography (PET-CT). The following clinical, surgical, and pathological data and details of adjuvant therapies were collected: the woman's age, body mass index, surgical procedure (type of hysterectomy and/or lymph node staging), brachytherapy side effects using Common Terminology Criteria for Adverse Events (v4), peri/postoperative complications assessed by Clavien Dindo classification (7), FIGO stage, final pathological analysis (histological type, tumor size, and lympho-vascular space invasion [LVSI] status), treatment modalities, and prognosis (first recurrence, death). All women were classified according to the 2018 FIGO classification (4).

For patients who underwent brachytherapy, vaginal molds were created, and brachytherapy was performed to deliver a dose of 60 Gy in 120 pulses (0.5 Gy/pulse) using a 192-iridium remote afterloading system. The target volume was defined based on the treatment technique. For two-dimensional treatments, the aim was to deliver 60 Gy at an isodose volume encompassing point A. For three-dimensional treatments, the CT and MRI findings were used to define the target volume, which consisted of the gross tumor volume plus the entire cervical tissue and adequate margins. The prescribed dose aimed to deliver at least 60 Gy to 90% of this volume. Dose constraints to organs at risk were defined as a dose of <85 Gy delivered to 2 cm³ of the bladder and a dose of <75 Gy delivered to 2 cm³ of the rectum and sigmoid colon. Small differences were noted regarding doses to be delivered on the surrounding tissues.

Patients were followed up with clinical examinations every 4–6 months for 5 years, then annually by their gynecologist. Suspected recurrences were confirmed by imaging (MRI, PET-CT, or CT) or clinical examination.

Operative times were not collected and were not studied since a comparison between the two groups was not possible, as lymphadenectomy was performed before brachytherapy in the brachytherapy group and during radical surgery in the surgery-only group. In both groups, complications collected peri- and postoperatively only

related to radical surgery. No quality of life scale was used as these data were not collected.

Quantitative variables were described by mean and standard deviation or by median and interquartile range. The normality of the distributions was verified graphically and by the Shapiro-Wilk test. Qualitative variables were described by frequency and percentage. When the numbers were sufficient, the qualitative variables were compared between groups using chi-square tests. If these tests were not valid (theoretical numbers <5), Fisher's exact tests were used. When the numbers were sufficient, quantitative variables were compared using Student's t-tests. In cases of non-normality of the data, non-parametric Wilcoxon tests were used. Overall survival and recurrence-free survival were estimated by the Kaplan-Meier method and compared between groups using Cox proportional hazards models. The significance level was set at 0.05. Analyses were performed using SAS software version 9.4 (SAS Institute, Cary NC, USA).

Results

In total, 211 patients with IB2 FIGO stage without lymph node involvement were included. Patient characteristics are reported in Table 1. Of all patients included, 136 received surgical treatment only and 75 had pelvic lymph node staging and brachytherapy followed by surgery. Median of follow-up was 5.1 years (between 4 and 10 years). No significant difference was observed between the two treatment groups regarding age (mean), BMI (mean), number of patients with BMI over 25 kg/m², or menopause. There was significantly more adjuvant treatment in the surgery alone group (29 vs. 3; $p = 0.0002$).

There was no difference in terms of surgical approach ($p = 0.06$). Due to the low number of perioperative complications, these were not compared statistically but were observed to have occurred in the same proportions in the two groups (Table 2). The histological subtypes were also comparable between the two groups ($p = 0.2$). There was no significant difference between the two groups with respect to mean tumor size (27 vs. 28 mm; $p = 0.27$) or number of patients with a tumor size greater than 30 mm (53 patients vs. 33 patients; $p = 0.57$) (Table 2).

The anatomopathological data concerning the two groups showed no significant difference in the length of the vaginal cuff (12.5 mm vs. 16.7 mm; $p = 0.09$), the healthy margin (129 vs 69; $p = 1$), parametrial invasion (8 vs 2), LVSI (36 vs 22; $p = 0.97$) or vaginal invasion (6 vs 2; $p = 0.71$). A complete response was identified in 61 patients (81%) in the brachytherapy group (Table 2).

Postoperative complications were also comparable (86 vs. 54; $p=0.19$) and mainly consisted of urinary and digestive complications (40 vs. 28) and lymphoceles (4 vs. 1) (Table 3). Likewise, the number of reoperations was comparable. Toxicities after

preoperative brachytherapy consisted of grade 1 or 2 urinary toxicity in five patients and grade 2 to 3 digestive toxicity in six patients.

The sites of recurrence were separated into pelvic recurrence and distant and/or lymph node recurrence. Significantly more pelvic recurrence was observed in the surgery group compared to the brachytherapy group ($p = 0.04$) (Table 3). However, there was no significant difference in instances of distant and/or lymph node recurrence ($p = 0.35$). Concerning survival data, brachytherapy did not have a significantly positive effect on recurrence-free survival (0.14) or overall survival ($p=0.59$) (Figures 1 and 2). However, for tumors between 20 and 30 mm, preoperative brachytherapy had a positive effect on recurrence-free survival ($p = 0.0095$) but not on overall survival ($p = 0.41$) (Figures 3a and 3b). This difference was not observed for tumors greater than 30 mm in terms of recurrence-free survival ($p = 0.55$) or overall survival ($p = 0.95$) (Figures 3c and 3d).

A subgroup study was performed to evaluate the population with a BMI greater than 25 kg/m². No significant difference was between these patients and those with a lower BMI ($p = 0.29$).

Discussion

Our study demonstrated no benefit from performing preoperative brachytherapy for stage IB2 cervical cancers in terms of recurrence-free survival or overall survival. For tumor sizes between 2 and 3 cm, brachytherapy improved progression-free survival by reducing pelvic recurrences but did not improve overall survival.

These results are based on fundamental data regarding tumor size, which is in line with the revision of the FIGO classification in 2018 (4). Furthermore, a study by Matsuo et al. showed that stage IB2 cervical cancer was independently associated with an almost two-fold increased risk of mortality compared to stage IB1 cervical cancer ([HR] 1.98, 95% [CI] 1.62–2.41, $p < 0.001$) (8). Therefore, good reliability of preoperative MRI, as well as pathological data on conization where applicable, is essential. Given this observation, several points concerning our results must be considered.

Brachytherapy is an effective modality for delivering radiation to cervical tumors and limiting the dose delivered to adjacent organs. Several retrospective series confirm the apparent effectiveness and safety of this treatment (6,9–13). Nevertheless, modification of the FIGO classification and the clear prognostic difference between the new different clinical stages make comparisons both more difficult and obsolete. To date, there is no published randomized trial evaluating the two management strategies, although there is one ongoing trial comparing preoperative brachytherapy and surgery with surgery alone (9). The preliminary results that have been published do not show a significant difference between the groups. However, the results should be interpreted

with caution since different tumor stages are included. Furthermore, Piver type III radical hysterectomy is no longer the recommended surgical technique in many centers, and the brachytherapy protocol, particularly high-dose brachytherapy, is not the most common treatment. In the absence of other randomized trials, our results can be compared with a recent study of a series of 80 patients who received preoperative brachytherapy as part of the management of stage IB to IIB cervical cancer (FIGO 2009). Brachytherapy treatment was found to have good tolerability. A tumor size greater than 3 cm and a BMI greater than 25 kg/m² were identified as predictors of poor response to brachytherapy. Our results, like those of Bataille et al., support the use of brachytherapy for tumor sizes between 2 and 3 cm. However, systematic management by radio-chemotherapy followed by brachytherapy, recommended by the authors, for tumor sizes greater than 3 cm should be tempered given the absence of randomized trials on this subject.

Given the current scientific context concerning the management of cervical cancer, the surgical route and, more generally, surgical techniques and surgical management must be considered. As the inclusion period for our study is long, consideration must be given to the fact that surgical modalities and the proportion of type B or C hysterectomies performed have changed over time. Moreover, on a more technical issue, vaginal preparation (Shauta) was probably not carried out in all the centers or during the entire period studied (14). This study also brings together a large number of French centers with different volumes of activity and surgical cultures. However, numerous criteria reflect the quality of care for these patients, such as the size of the vaginal cuff length and the rate of patients with healthy margins. In our study, most of the patients in the two treatment groups were operated on by laparoscopy (robot-assisted or otherwise). Ramirez et al. have shown that laparotomy is more positively associated with recurrence-free survival and overall survival compared to laparoscopy (robot-assisted or otherwise) and does not increase surgical morbidity or mortality (5). However, comparing this study with our study is difficult, as the two studies have different aims. The population is also difficult to compare, as 10% of the population in Ramirez et al.'s study had stage-IA cervical cancer. In addition, among the stage-IB1 cervical cancers (FIGO 2009) included, only 40% in each group measured more than 2 cm. Finally, no preoperative brachytherapy protocol was performed, as the study was conducted exclusively in the United States, where national protocols do not recommend such treatment in this indication (2). Despite the differences between the two studies, it is not illegitimate to presume that brachytherapy could have a place in the treatment algorithm, regardless of the surgical approach.

The last point that must be discussed relates to adjuvant treatments. One of the goals of preoperative brachytherapy is to reduce the need for adjuvant treatment with the aim of improving quality of life by reducing the side effects associated with more radical surgeries and postoperative treatments. This should be balanced against the fact that the patient must undergo two surgical procedures under general anesthesia: lymph node staging and radical surgery. Regarding preoperative brachytherapy, there is currently no recommendation for adjuvant therapy, even in the presence of pejorative prognostic factors in the final histology. In the surgery-only group in our series, 21% of the patients received adjuvant treatment. Although this result must be interpreted with

caution, no increase in the number of long-term complications was found in either treatment group. . Furthermore, modalities of treatments differed across the study period. Nonetheless, the question of adjuvant treatments remains unresolved. In the presence of a high-risk situation, such as parametrial invasion, an unhealthy margin, or lymph node invasion, consensus supports the use of radio-chemotherapy (15). The situation is more questionable in the intermediate-risk group, definitions of which are variable (16) but take into account the presence of lymphovascular space invasion, tumor size, and stromal invasion. The benefit of adjuvant radiotherapy in this situation was demonstrated in the GOG-92 study conducted 20 years ago (16). Cao et al. recently conducted a retrospective study, which, while respecting the criteria of GOG 92, found no benefit in additional treatment by radiotherapy with or without chemotherapy (17). An international phase III randomized trial (GOG-0263, NCT01101451) comparing adjuvant concurrent chemoradiotherapy in this sub-set of patients with radiation alone may instigate change in the adjuvant management of these patients the adjuvant management of these patients. Recently, several teams have expressed interest in the potential benefits of postoperative brachytherapy with or without radio-chemotherapy in this situation (18,19). A study by Bronsart et al. found that postoperative brachytherapy alone resulted in good tolerance. A tumor size greater than 3 cm seemed to be a factor in the failure of brachytherapy. The authors recommend the use of postoperative pelvic radiotherapy instead of brachytherapy in this situation. A study by Contreras et al. is less conclusive since the population was more heterogeneous; it was not limited to patients at intermediate risk, and brachytherapy was systematically associated with pelvic radiotherapy with or without chemotherapy. However, here too, the safety profile seemed satisfactory.

Conclusion

Preoperative brachytherapy for tumors between 2 and 3 cm is positively associated with progression-free survival, mainly through a reduction in pelvic recurrences, and has a satisfactory toxicity profile, but it provides no benefit in terms of overall survival. For tumors larger than 3 cm, the benefit of preoperative brachytherapy has not been demonstrated. The effectiveness of surgical treatment and/or radio-chemotherapy with brachytherapy in this situation should be assessed.

Authors contribution :

Othman Aissaoui : Main and corresponding author

Jérôme Phalipou : Study coordination

Abel Cordoba : Participation in data collection

Henri Azais : Participation in data collection

Lobna Ouldamer : Participation in data collection

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Table 1 Patients characteristics

	Surgery alone n=136	%	Brachytherapy and surgery n=75	%	Missing	p
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Age (mean)	50	36.7	47	62.6	0	0.13
BMI (mean)	26	19.1	24	32	19	0.09
BMI >25 kg/m ²	50	36.7	23	30.6	19	0.33
Menopausis	61	44.8	24	32	0	0.09
Adjuvant treatment	29	21.3	3	4	6	0.0002

Abbreviations, n, number ; BMI, Body mass index

Table 2 Surgical and pathological data

	Surgery alone n=136	%	Brachytherapy and surgery n=75	%	Missing	P value
Surgical route					0	0.06
Laparoscopy	100	73.5	47	62.6		
Laparotomy	19	13.9	11	14.6		
Robot-assisted laparoscopy	12	8.8	16	21.3		
Vaginal+ laparoscopy	5	3.6	1	1.3		

Histological subtypes					0	0.2
Squamous cell carcinoma	87	63.9	52	69.3		
Adenocarcinoma	38	27.9	14	2.8		
Adenosquamous carcinoma	4	2.9	3	4		
Mucosecretant	0	0	1	1.3		
Clear cell carcinoma	4	2.9	5	6.6		
Other	3	2.2	0	0		
Mean size (mm)	27	/	28	/	0	0.27
Size > 30 mm	53	38.9	33	44	0	0.57
No Margin invasion	129	94.8	69	92	2	1
Parametrial invasion	8	5.8	2	2.6	4	NA
Lymphovascular space invasion	36	26.4	22	29.3	13	0.97

Abbreviations, n, number

Table 3 Complications

	Surgery alone	%	Brachytherapy and surgery	%	Missing	p
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	n=136		n=75			
Complications after brachytherapy					0	NA
Urinary	NA		5	6.6		
Digestive	NA		6	8		
Perioperative	7	5.1	7	9.3	10	0.24
Hemorrhage	1	0.7	2	2.6		
Laparoconversion	1	0.7	1	1.3		
Ureteral injury	2	1.4	0	0		
Bladder injury	1	0.7	0	0		
Bowel injury	2	1.4	0	0		
Post-operative	86	63.2	54	72	16	0.19
Infection	8	5.8	2	2.6		
Urinary disorders	36	26.4	27	36		
Lymphocele	4	2.9	1	1.3		
Thrombosis	2	1.4	0	0		

Hemorrhage	3	2.2	0	0		
Scarring disorders	1 (0,7%)	0.7	1	1.3		
Paresthesia	1 (0,7%)	0.7	1	1.3		
Digestive disorders	31	22.7	22	29.3		
Reoperation	8	5.8	1	1.3	72	0.55

Na : Not applicable

Table 4 Recurrence pattern

	Surgery alone N=136	%	Brachytherapy and surgery N=75	%	p
Overall recurrence	25	18.3	11	14.6	0.4
Pelvic recurrence	10	7.3	2	2.6	0.04
Extra pelvic recurrence	15	11.0	9	12	0.35
Recurrence by tumor size					
2-3 cm	14	10.2	2	2.6	0.05
3-4 cm	11	8.0	9	12	0.48

Figure 1. Kaplan-Meyer analysis of 5-year progression-free survival for patients with early stage cervical treated by preoperative brachytherapy and surgery (red) vs surgery alone (blue)

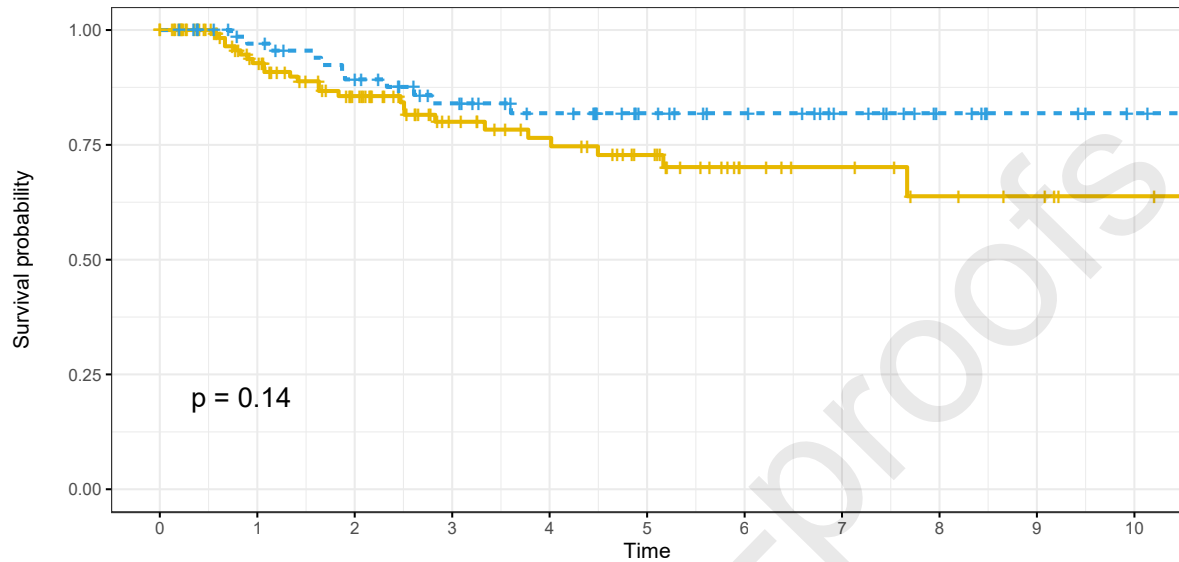


Figure 2. Kaplan-Meyer analysis of 5-year overall survival for patients with early stage cervical treated by preoperative brachytherapy and surgery (red) vs surgery alone (blue)

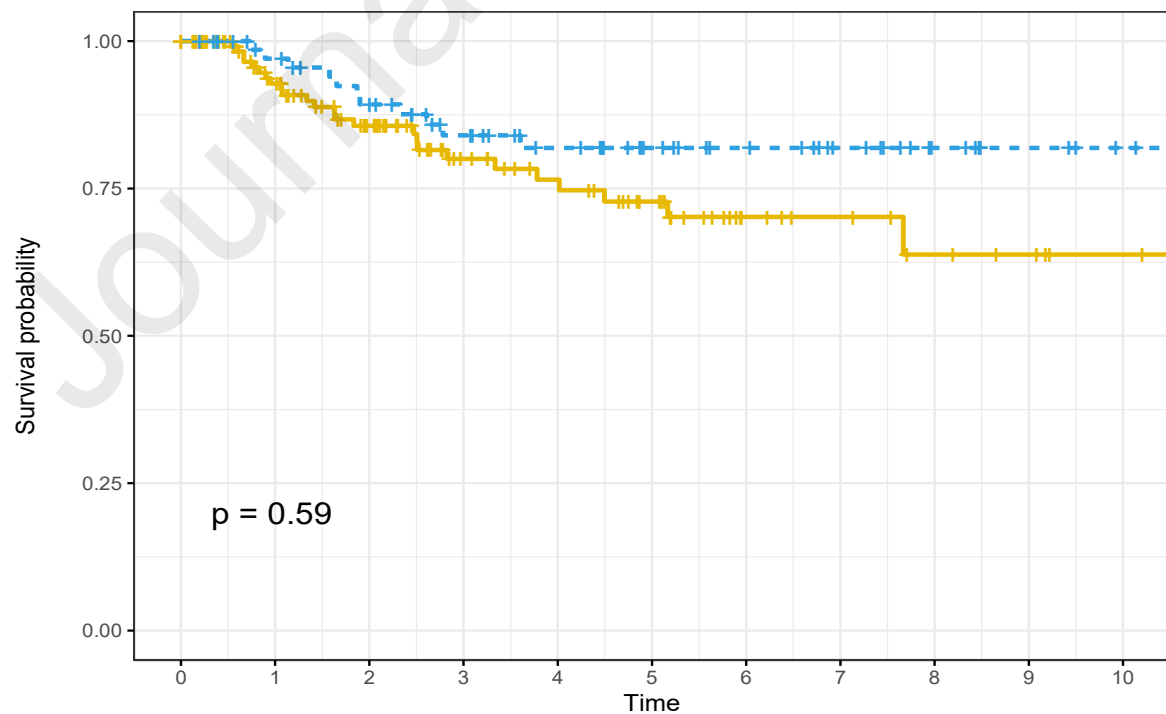
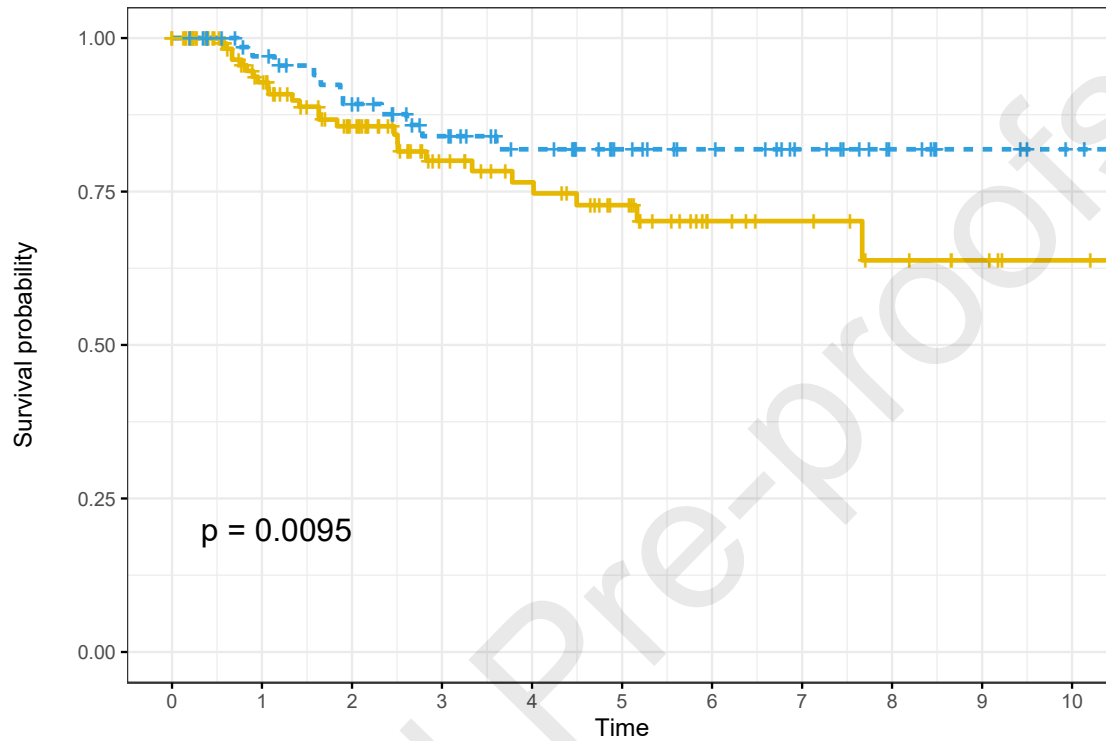
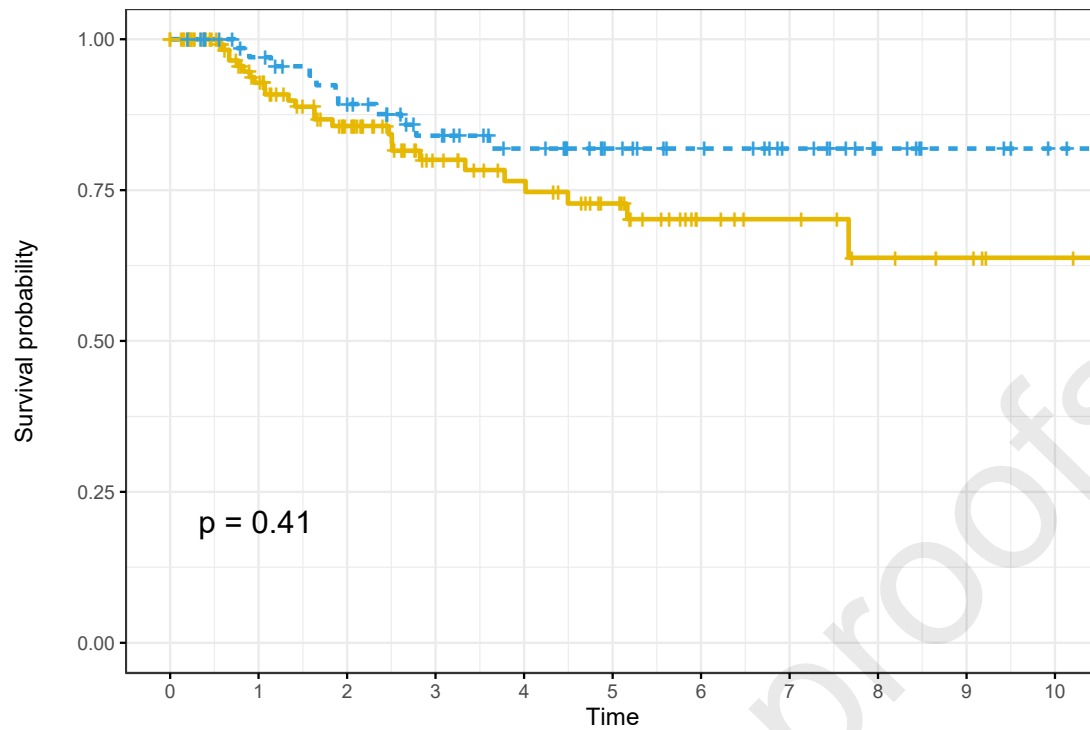


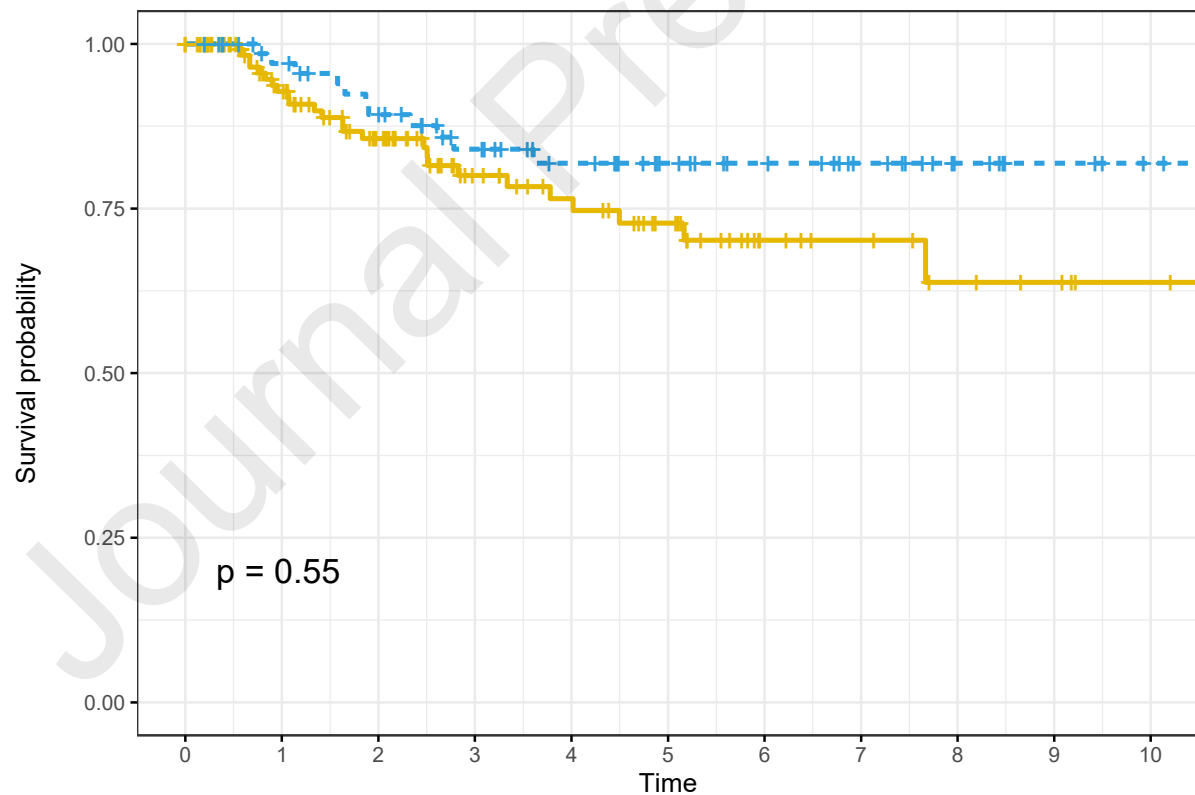
Figure 3 Kaplan-Meier analysis of 5 year progression-free survival and overall survival based on tumor size for patients with early stage cervical treated by preoperative brachytherapy and surgery (red) vs surgery alone (blue)



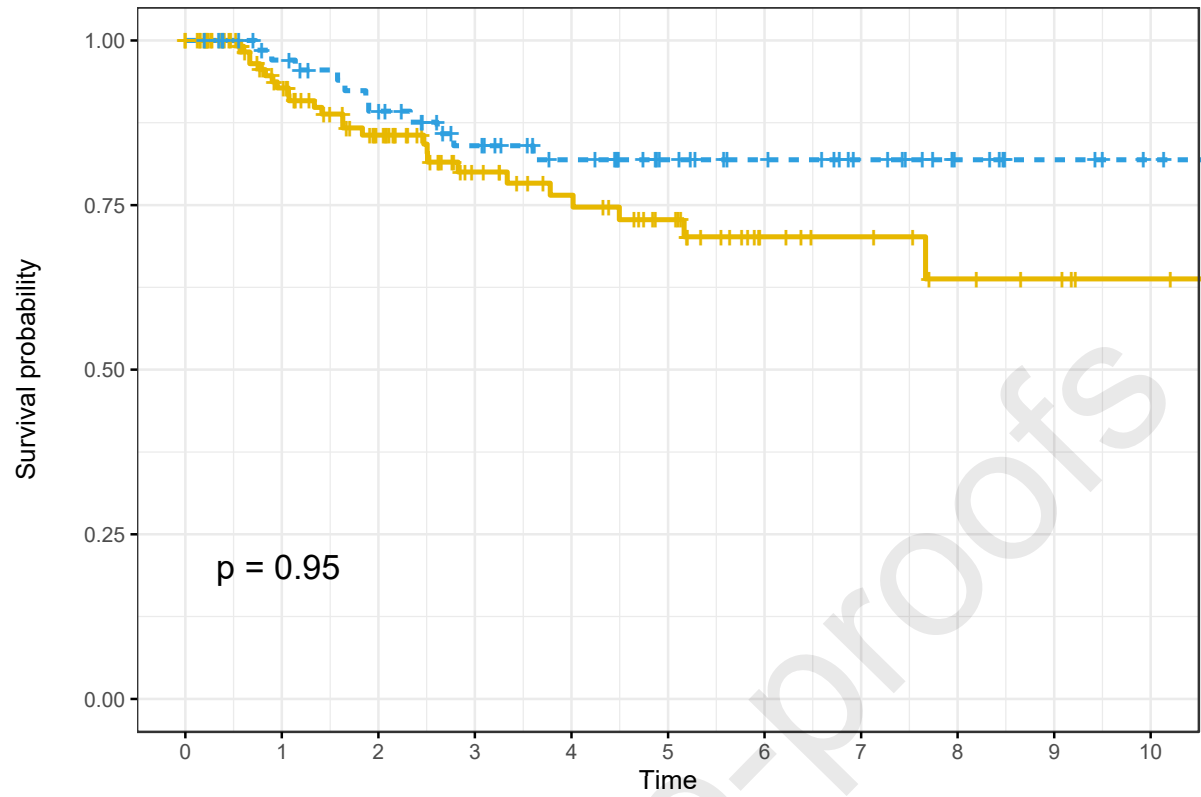
A. Kaplan Meyer analysis of 5 year progression-free survival for tumor between 2 and 3 cm.



B. Kaplan Meyer analysis of 5 year overall survival for tumor between 2 and 3 cm.



C. Kaplan Meyer analysis of 5 year progression-free survival for tumor greater than 3 cm.



D. Kaplan Meyer analysis of 5 year overall survival for tumor greater than 3 cm.