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Quelle est la place de la curiethérapie préopératoire suivie d'une hystérectomie par voie mini invasive dans la prise en charge des cancers du col de stade précoce ?

Clémence Beyer

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UNIVERSITÉ GRENOBLE ALPES
UFR DE MÉDECINE DE GRENOBLE

Année : 2020

**Is there a place for preoperative brachytherapy followed by
Laparoscopic Hysterectomy
in less than IB3 cervical cancer after LACC trial?
Oncological Outcomes of a retrospective study**

THÈSE
PRÉSENTÉE POUR L'OBTENTION DU TITRE DE DOCTEUR EN MÉDECINE

DIPLÔME D'ÉTAT

Mlle Clémence BEYER [Données à caractère personnel]

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**Is there a place for preoperative brachytherapy
followed by Laparoscopic Hysterectomy
in less than IB3 cervical cancer after LACC trial?
Oncological Outcomes of a retrospective study**

RESUME

OBJECTIFS

L'objectif de cette étude est d'évaluer les résultats oncologiques et chirurgicaux d'une stratégie thérapeutique consistant en une curiethérapie préopératoire suivie d'une hystérectomie abdominale ou laparoscopique de type A, comme alternative à la chirurgie première dans le traitement des cancers du col de stade précoce (Stade FIGO < IB3).

MATÉRIEL ET MÉTHODES

Il s'agit d'une étude rétrospective menée à l'Institut Paoli Calmettes, centre anticancéreux (Marseille, France) entre 2001 et 2012, concernant des patientes prises en charge pour un cancer du col de l'utérus de stade précoce (taille de la tumeur < 4 cm, stade FIGO IA1, IA2, IB1 et IB2 - FIGO 2018) par une approche radiochirurgicale.

Une curiethérapie préopératoire à faible débit de dose a été réalisée chez des patientes N0 (chirurgicale et radiologique), suivie 6 à 8 semaines plus tard d'une hystérectomie de type A par voie mini-invasive ou par laparotomie.

Les patientes présentant des métastases ganglionnaires pelviennes ou ayant bénéficié d'un traitement adjuvant ont été exclues.

Le critère d'évaluation principal était la survie sans progression (SSP) et les critères d'évaluation secondaires étaient la morbidité de la chirurgie et celle de la curiethérapie.

RÉSULTATS

Au total, 138 patientes ont été incluses. L'analyse histologique a montré une réponse complète chez 68 patients (49,3 %) et une tumeur résiduelle < 1 cm chez 36 patients (26 %).

Avec un suivi médian de 132 mois (60 - 204 mois), la SSP était de 93,5 % et il y a eu 9 récurrences - 6 métastatiques et 3 récurrences loco régionales (2 ganglionnaires pelviennes et 1 dans le muscle pyramidal gauche)-.

En analyse univariée, un délai de plus de 52 jours entre la fin de la curiethérapie et la chirurgie était associé à une SSP significativement plus faible ($p = 0,004$, OR = 8,5, IC95 {1,5 ; 48,7}), et une réponse pathologique complète était associée à une meilleure SSP ($p = 0,03$, OR = 6,1, IC95 {1,8 ; 55,3 }).

Nous avons rapporté un taux global de complications tardives de la curiethérapie (glossaire Chassagne) de 17,3 % (n= 24) et un taux global de lésions urinaires chirurgicales de 6,5 % (n = 9), avec seulement 2 patientes (1,5 %) présentant des complications de grade 3 (classification Clavien et Dindo).

CONCLUSION

Avec un suivi médian de 132 mois, une stratégie thérapeutique radio chirurgicale des cancers du col de l'utérus à un stade précoce (inférieur à IB3 FIGO 2018) incluant une curiethérapie endocavitaire préopératoire suivie d'une hystérectomie totale par voie laparoscopique de type A semble offrir un taux de récurrence raisonnable par rapport aux résultats de l'essai LACC (Laparoscopic approach to cervical cancer). Cette stratégie peut être une alternative à l'hystérectomie radicale initiale chez certaines patientes afin de maintenir une approche minimale invasive.

MOTS CLES : cancer du col, stade précoce, curiethérapie préopératoire, hystérectomie type A, chirurgie mini-invasive

ABSTRACT

OBJECTIVES

The aim of this study is to report the oncological and surgical outcomes concerning the combination of a preoperative brachytherapy followed by Type A laparoscopic or abdominal hysterectomy as an alternative to upfront surgery in early stage cervical cancer (<FIGO IB3).

MATERIAL AND METHODS

This is a retrospective study conducted at Paoli Calmettes Institute, comprehensive cancer center (Marseille, France) between 2001 and 2012, concerning patients managed for early stage cervical cancer (tumor size < 4 cm, FIGO stage IA1, IA2, IB1 et IB2 - FIGO 2018) by a radiosurgical approach.

A preoperative low dose rate brachytherapy was performed in pN0 patients (surgical and radiological staging), followed 6-8 weeks later by a type A hysterectomy by laparoscopic or open surgical approach.

Patients with pelvic lymph node metastases or adjuvant treatment were excluded.

The primary endpoint was the Disease Free Survival (DFS) and the secondary endpoint was the surgical and brachytherapy morbidities.

RESULTS

A total of 138 patients were included. Histological analysis showed a complete response in 68 patients (49,3 %) and a residual tumor < 1 cm in 36 patients (26 %).

With a median follow up of 132 months (60 - 204 months), DFS was 93,5% and 9 recurrences occurred -6 distant, 2 pelvic lymph node recurrences and 1 in the left pyramidalis muscle-.

In univariate analysis, a delay between the end of brachytherapy and surgery superior to 52 days is associated with a significant poorer DFS ($p = 0,004$, OR = 8,5, IC95 {1,5 ; 48,7}), and a pathological complete response is associated with a better DFS ($p = 0,03$ OR = 6,1 IC95 {1,8 ; 55,3}).

We have reported an overall late complication rate for brachytherapy of 17,3% ($n = 24$) (Chassagne glossary) and an overall rate of surgical urinary injuries of 6,5% ($n = 9$), with only 2 patients (1,5%) with grade 3 complications (Clavien and Dindo classification).

CONCLUSION

With a median follow up of 132 months, a radiosurgical management of early stage cervical cancers (less than IB3) including brachytherapy and type A laparoscopic hysterectomy seems to offer a reasonable rate of recurrences compared to LACC trial's results. This strategy may be an alternative to upfront radical hysterectomy in selected patients to maintain a minimal invasive approach.

KEY WORDS: cervical cancer, early stage, preoperative brachytherapy, hysterectomy type A, minimally invasive surgery.

Abbreviations

ARH: Abdominal Radical Hysterectomy

DFS: Disease Free Survival

ESCC: Early Stage Cervical Cancer

FIGO : Fédération international de gynécologie et d'obstétrique

HT: Hysterectomy

LACC: Laparoscopic Approach to Cervical Cancer

LRH: Laparoscopic Radical Hysterectomy

LVSI: LymphoVascular Space Involvement

MIS: Minimally Invasive Surgery

MISRH: Minimally Invasive Surgical Radical Hysterectomy

OH: Open Hysterectomy

POBT: Preoperative Brachytherapy

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1. INTRODUCTION

Early stage cervical cancer, defined as a tumor size less than 4 cm (< stage IB3 FIGO 2018) confined to the pelvis, with clinically and radiologically negative pelvic nodes, have no standard management and differs, according to the country.

Upfront surgery is the standard suggested by international guidelines (National Comprehensive Cancer Network NCCN (1)), ESGO (European Society of gynecological oncology (2)) and ESMO (European Society for medical Oncology (3)). The surgical procedure is represented by a radical hysterectomy Type B1 for low risk, B2 for intermediate risk or C1 for high risk according to The Querleu - Morlow classification (4), associated with pelvic lymph nodes staging.

According to ESGO and French guidelines (2, 5), an option might be a preoperative intracavitary uterovaginal brachytherapy (POBT) followed by type A hysterectomy, even if this option is used in a limited number of centers, mostly in France.

The superiority of one of the two methods has never been established, but the feasibility and safety of the POBT has been already reported in several studies (6-14).

Furthermore, the minimally invasive approach (conventional laparoscopy or robotic assisted laparoscopy) have been recently developed and is considered as the standard approach for early stage cervical cancer treatment, since the demonstration, for several years, of its feasibility, surgical and oncological safety compared to open surgery (17,18,19).

However, since 2018 and the LACC (Laparoscopic Approach to Cervical Cancer) trial's publication (20), a new question has emerged: is laparoscopic approach as safe as previously published concerning oncological outcomes in this indication? In the subgroups of patients with

stage < IB3 FIGO 2018, after upfront surgery, the author reported a higher rate of recurrence with the minimal invasive approach compared to open surgery with a significant impairment of the survival (8.8% vs 2,9% after a follow up of 3 years, and 14% vs 3.5 % for open surgery, after a follow up of 4.5 years).

Questions remain concerning the methodology of this "real life" trial, but we must take into account its results to inform our patients. Results of upfront surgery in FIGO IB1-IB2 cancers may be compared to other options including minimal invasive surgical approach, particularly in the subgroup of patients with tumor size between 2 and 4 cm.

The objective of this study is to report our surgical and oncological results from an historical cohort of patients managed with pre operative brachytherapy followed by laparoscopic hysterectomy for early stage cervical cancer, and to compare it to the literature's results.

2. MATERIAL AND METHODS

It is a retrospective single center study concerning patients managed between 2001 to 2012 at Paoli Calmettes Institute, comprehensive cancer center (Marseille, France) for early stage cervical cancer (< stage IB3 FIGO 2018).

2.1. Characteristics of Patients

Inclusion criteria were: histologically confirmed carcinoma of the uterine cervix, operable tumor (size less than 4 cm of diameter, stages IA1 with lympho vascular space involvement (LVSI), IA2, IB1, IB2 according to the new classification International Federation of Gynecology and Obstetrics FIGO 2018) (21), with disease confined to the cervix. Systematic pre therapeutic pelvic lymphadenectomy has been performed in all patients.

Exclusion criteria were lymph nodes metastasis and/or adjuvant treatment: radiotherapy or chemotherapy.

For each patient, we collected data from their medical files: age, comorbidities, body mass index (BMI), history of the oncologic disease, surgical procedure's characteristics (surgical approach), number of lymph nodes removed, post-operative outcomes (complications, readmissions), definitive pathology, and tumor characteristics (tumor size, histology, Lymphovascular space invasion LVSI).

Tumor size was assessed clinically and then adjusted based on MRI findings or by results of histology of the initial conization.

2.2. Treatments

2.2.1 Preoperative Brachytherapy (POBT)

For all patients, pN0 status was proven by a systematic laparoscopic pelvic lymph node dissection, before preoperative low dose rate (LDR) uterovaginal brachytherapy.

The brachytherapy procedure aimed at delivering 60 Gy (0,5-0,8 Gy/h) to the cervix, the proximal part of the parametria and the upper third of vagina, according to the guidelines in Report No.38 of the International Commission on Radiation Units and Measurements (ICRU) (22).

Dosimetry was done from radiographs (2D) or from 3D acquisition with CT scanner, using Cesium sources (¹³⁷Cesium), during an average time of 120 hours.

Brachytherapy complications were graduated according to the Chassagne glossary (16).

The complications examined are those that have persisted 2 months after the end of Brachytherapy.

2.2.2 Surgery

Six to eight weeks after brachytherapy, patients underwent type A laparoscopic or open hysterectomy according to Querleu-Morrow classification (4), with bilateral salpingectomy-oophorectomy. Per and post-operative complications were collected according to the Clavien-Dindo classification (15), from grade 1 for lower toxicity (no treatment needed) to grade 5 (death).

After surgery, no adjuvant treatment was performed.

2.3 Follow-up

The follow up was carried out as follows: a clinical monitoring including speculum and pelvic examination was performed 3 – 4 weeks after Brachytherapy, then 4 weeks after surgery, then every 4 months the following three years, then every 6 months the following two years then every years.

MRI or CT scan has only been realized in the case of biological or clinical abnormalities.

Disease free survival (DFS) time was calculated from the date of diagnosis of cancer to the date of diagnosis of recurrence.

2.4 Statistical analysis

All statistical analyses were performed at the significance level $\alpha=0.05$ and using Xlstat software (version 16.34). Patients' characteristics were summarized using counts (frequencies) for categorical variables and means (standard deviations) or median (min-max) for quantitative variables. Data were managed and analyzed with an Excel database.

The Kaplan Meier method was used to estimate the survival distribution.

The Cox proportional hazards model was used to account for the influence of multiple variables.

Intra-group differences in categorical variables were analyzed by independent Fisher's exact test and in continuous variables by the Student's t-test.

This study was approved by our ethical committee (Paoli-Calmettes Institute's review board), with the number CURIHYST IPC-2019- 058.

3. RESULTS

3.1 Characteristics of patients and pathology

From 2001 to 2012, 138 patients were included retrospectively, with early stage cervical cancer strictly inferior to FIGO IB3 and negative pelvic nodes. All were treated by low dose intracavitary uterovaginal brachytherapy followed by type A hysterectomy.

The baseline characteristics of patients are reported in Table 1.

Median age was 49 years (28 - 81). Concerning tumor stage, 64 patients (46,3 %) had IB1 stage and 64 patients (46,3 %) had IB2 stage according to FIGO 2018 classification.

A total of 74 patients (53,6%) have tumor size less than 2 cm, and 64 patients (46,3%) have a tumor size between 2 to 4 cm.

Median tumor size was 19 mm (3 - 39 mm).

The histopathology distribution showed a majority of squamous cell carcinoma (61.6%; n = 85).

The diagnostic has been confirmed with a conization in 92 patients (66,7%) or with a simple biopsy for 43 patients (31,2%).

3.2 Surgical outcomes

Pelvic lymphadenectomy was performed in all patients, and all patients had negative pelvic lymph nodes.

The median time between POBT and surgery was 53 days (32-145). Surgical approach was laparoscopic in 117 patients (84,8%) and open surgery in 21 patients (15,2%). Conversion to open surgery was observed in 2 patients (1,5%).

At definitive pathology, LVSI was found in 2,2% of cases (0 for IA1 to IB1 stage and 3 for IB2 stage).

Positive margins were found in 1 patient (0,7%) with initial IB2 FIGO stage.

3.3 Disease free survival and recurrences

All patients received a radiation dose of 60 Gy. After low dose brachytherapy and surgery, a pathological complete response (pCR) was observed in 68 patients (49,3%). A residual tumor less than 1 cm was observed in 36 patients (26%) and a residual tumor superior to 1 cm was observed in 6 patients (4,3%).

Median follow up was 132 (range 60-204) months. DFS was 93,5% and 9 recurrences occurred in our cohort (6,5%): 6 metastatic diseases, 2 pelvic nodes recurrences and 1 local recurrence (left pyramidalis muscle). We did not report any vaginal recurrence.

Figure 1 described the survival curve of the study population.

All the characteristics of recurrences are described in table 2.

The rate of recurrences was also examined according to surgical approach: in the subgroup of patients with laparoscopic approach, recurrences occurred in 6 of 117 patients (5,1%).

In the subgroup of patients with IB2 stage according to FIGO 2018 classification, we reported 4 recurrences on 64 patients (6,2%).

In univariate analysis, a pathological complete response is associated with a better DFS ($p = 0,03$ OR = 6,1 IC95 {1,8 ; 55,3}).

The strongest prognostic factor of recurrence (local or metastatic) in our study is the time between the end of brachytherapy and surgery. If this time is superior to 52 days, it is associated with a poorer DFS ($p = 0,004$ OR = 8,5 IC95 {1,5 ; 48,7}).

Surgical approach (open surgery or mini invasive surgery) does not impaired the DFS ($p=0,11$ OR=0,33 IC 95 % { 1,62, 2,774 }).

Concerning initial tumor or patient characteristics, none of the others factors studied (tumor size > 2 cm, histological type or BMI) were statistically significant for DFS.

3.4 Toxicities of brachytherapy and surgery

Complications following therapeutic sequence (brachytherapy followed by surgery) were encountered in 43 patients (31,1%) distributed as follows:

After brachytherapy, we reported 24 late complications (17,3%), most of them were grade 1 and 2 complications (15,9 %, n = 22) as urinary dysfunctions, dyspareunia and rectitis or proctitis.

We observed 2 grade III complications: 1 vaginal stenosis and 1 uretero vaginal fistula.

Concerning post operative morbidity, we reported 19 complications (13,7 %),

12 grade I - II complications (8,7%) : 3 hematoma, 1 lymphoedema , 7 dysuria, 1 dyspareunia.

7 grade III complications (5%) : 3 abscess to pelvic wall, 2 vaginal scare disunion, 1 ureteral stenosis and 1 uretero vaginal fistula.

4. DISCUSSION

Surgical management of early stage cervical cancer using minimal invasive surgery is nowadays strongly debated in relation with the recent publications of LACC trial (20).

We report in this study our oncological and surgical outcomes after a combined treatment for early stage cervical cancer (IA1 to IB2 according to FIGO 2018 classification, (21)) using POBT and a systematic simple hysterectomy, with a majority of laparoscopy (84,8%), and we compare our results to the recent literature.

With one of the greatest follow up reported in the literature (132 months), we described a DFS of 93,5% (n = 9 recurrences in 138 patients). We observed 6 recurrences in 117 patients with laparoscopic approach (DFS = 94,8%), in our cohort of patients with a tumor size less than 4 cm, with a great tumor local control (TLC) (only 1 pelvic recurrence and 2 pelvic lymph nodes recurrences).

However, recent studies open the debate concerning the oncological safety of the minimally invasive approach for the management of early stage cervical cancer.

The LACC study (20) showed that Minimally invasive Surgery (MIS) is associated with a poorer prognostic: after 4,5 years follow up, MIS arm had more recurrences (14%) than open surgery (3,5%) and more deaths (6,2% versus 1%). Then, several studies have reported their own retrospective cohort results in the literature that corroborate with LACC's Trial. Melamed and al. (23), with a retrospective cohort of 2461 patients diagnosed with IA2 to IB1 stage of cervical cancer, demonstrated a worse Overall Survival (OS) after 4 years, for patients treated with MIS

approach compared to open surgery (90,9% vs 94,7%; $p = 0.002$) with an HR of 1,65 (95% CI, 1,22-2,22).

Cusimano and al (24), examined data from a retrospective cohort of 958 patients between 2006 to 2017, to compare outcomes of patients with stage IA1, IB1 and IIa who underwent upfront surgery performed by open abdominal versus MIS approaches. Patients with stage IB1 who underwent MIS had decreased 7 years survival and DFS compared with those undergoing open surgery (HR of 2,20 (95% CI, 1,15 - 4,19); HR of 1,97 (95% CI, 1,10 - 3,50)).

This level A of Evidence Based Medicine should not be ignored, and several centers have disrupted their daily practices in the management of early stage cervical cancer.

NCCN's new 2019 recommendations (25) report that taking into account these recent studies who showed poorer oncologic outcomes and survival with the MIS approach, “women should be carefully counseled about the oncologic risks and potential short-term benefits of the different surgical approaches”.

At the same time, preoperative brachytherapy is only suggested as an option in the European (ESMO) and French (SFCO) recommendations (3,5).

However, our rate of DFS corroborate with those observed in the literature:

First, with the publications evaluating preoperative brachytherapy followed by surgery:

UZAN and al (8) in 2012, with a retrospective cohort of 162 patients who underwent POBT followed by MISRH surgery, reported a DFS of 94,3% after a follow up of 39 months, and Escande et al. (6), reported a DFS of 93,6% after a median follow up of 54 months for a cohort of 182

patients who underwent POBT followed by a majority of laparoscopic radical hysterectomy (Piver type II or III).

Vizkeley and al. (13), in a randomized controlled trial, compared POBT followed by laparoscopic surgery and upfront laparoscopic surgery, reported no difference, with a DFS of 95,7 % for TLC and 93,2% for distance relapse for the POBT arm, and a DFS of 97,5 % for the upfront surgery arm, after a median follow up of 29 months.

Second, several studies have evaluated upfront surgery, and DFS rates are lower than in our study: For Kim et al. (26) with a median follow up of 113 months, a cohort of 207 Patients and stage IB1 and IB2, after upfront surgery, DFS was statistically different between MISRH approach (78,5%) and ARH approach (89 %).

Ramirez et al. (20), with a follow up of 54 months presented a DFS of 86% for upfront MISRH and 96,5% for upfront ARH with a strong RCT of 631 patients (LACC trial).

Even with all the safety procedures, (no uterine manipulator to limit spillage of tumor cells, creation of a vaginal cuff to exclude the tumor and a minimal handling of the uterine cervix), Doo and al. (27), described in a retrospective study concerning with a cohort of 105 patients who underwent upfront surgery, a DFS of 76% for MISRH and 86% for ARH after 25 months. Kanao et al. (28) published the results of a retrospective study with a cohort of 163 patients treated by upfront MIS surgery or open surgery. After a median follow up of 30 months, no statistical difference was noted: DFS of 90,9% for upfront ARH, and 94,4 % for upfront MISRH ($p = 0,591$).

A complete literature review of series of different treatments including more than 100 patients is reported in table 4.

Looking at literature results, and to maintain the place of MIS in the management of early stage cervical cancer, POBT before surgery may be an alternative to upfront surgery:

First, to optimize the rate of local tumor control before surgery compared to surgery alone.

The rate of pathological complete response (pCR) in our study is 49,3% (68 patients) and local recurrences are very rare, one pelvic recurrence in our study.

In the literature, pCR rates in cohorts of patients treated with the radio surgical combination are between 55% (Bruand-Charra (29)), 70% (Escande and al. (6)) and 71,6% (Resbeut and al.(11)).

It probably decreases the risk of tumor spillage during the surgery and reduces local recurrences.

Moreover, in our study, a residual tumor after POBT is a prognostic factor of recurrence.

Second, European and French Guidelines allow for a less radical hysterectomy, type A according to Querleu and Morlow for the patients with early stage cervical cancer with intermediate or high risk tumor (size less than 2 cm with LVSI or tumor size between 2 and 4 cm) treated by POBT (2,3).

By reducing the radicality of the surgery, we minimize the rate of perioperative urinary injuries with parametrial dissection.

After POBT followed by type A hysterectomy, we report in our study a rate of surgical urinary injuries of 6,5% (n=9), 7 grade I - II complications (5%) and only 2 (1,5%) grade III complications.

With upfront surgery (Piver II or III hysterectomy), literature show a rate of grade III - IV complications (stenosis or fistulas) more than 5% (Pellegrino and al. 10% (30), Lee and al. 5% (31), Yan and al. 7% (18)).

Moreover, Landoni and al. (32) has demonstrated that a reduction of the radicality for hysterectomy offered similar oncological outcomes without differences concerning recurrences, but also a decrease of urinary toxicities (28% for Piver III vs 13 % for Piver II).

Third, POBT minimize the need of adjuvant EBRT (External Beam Radiotherapy), by reducing the histological factors of poor prognosis, such as LVSI, parametrial invasion (estimated at less than 1% in several studies), marginal resection or tumor size.

Atlan and al. (14) compared POBT followed by surgery with upfront surgery followed par pelvic radiotherapy. The author showed a significative higher rate of grade 3 - 4 late toxicities complications in the group with adjuvant radiotherapy (22% versus 7% $p = 0,0002$).

In others retrospective studies evaluating radical upfront hysterectomy for the management of early stage cervical cancer, the rate of adjuvant treatment for IB1 and IB2 patients are between 24% (Pellegrino and al.30) to 39% (Yan and al. (18)).

Thus, in most patients treated by upfront surgery for cervical cancer with poor prognostic factors (tumor size > 2 cm or LVSI), the need for postoperative radiotherapy could be avoided by using preoperative brachytherapy.

POBT brachytherapy reduces poor prognostic factors: in our cohort, only 3 patients (2,2%) have post operative LVSI after surgery, whereas in the literature, the rate of LVSI in patients with early-stage cervical cancer (tumor size < 4 cm) is approximately 26% (Dabi and al.) or 35% (Wright et al.).

POBT brachytherapy reduces the rate of positive margins after surgery. In our cohort, only one patient had positive margins (0,7%).

These results corroborate those of the prospective randomized study of Vizkelety and al. (13) comparing in a RCT, upfront surgery to POBT in which positive margins was observed for 1,5% for patients with POBT followed by surgery, versus 11,5% of patients with upfront surgery.

So, we therefore report a benefit of preoperative brachytherapy in the management of early stage cervical cancer (tumor size less than 4 cm).

Nevertheless, the current trend is to decrease the radicality of surgery, even in the case of exclusive surgery, in selected patients (SHAPE trial, phase III, in progress, aiming to evaluate the oncological safety of a simple hysterectomy compared to a radical hysterectomy in patients with early stage cervical cancer < 2 cm, without risk factor of recurrence).

In addition, in the LACC trial, analysis of the subgroup of patients with tumors less than 2 cm in size showed no statistically significant difference between the open and minimally invasive approach, suggesting the possibility of maintaining the minimally invasive approach for this subgroup of patients.

One may assume, for optimal management of these patients:

an exclusive first surgery by minimally invasive approach to patients with low-risk cervical cancer (< 2 cm without LVSI or lymph node invasion) and offer preoperative brachytherapy to patients with cervical tumors < 2 cm with risk factors of recurrence and tumors between 2 and 4 cm, followed by a minimally invasive type A hysterectomy, as an alternative to a more radical abdominal hysterectomy.

Then, a quality preoperative evaluation of tumor size and invasion of the parameters is necessary.

The new FIGO classification system (2018) (21) makes it possible to regain this precision, with the need for an evaluation of tumor size by MRI, which offers greater precision than clinical examination alone.

This new staging system also proposes a subdivision of the former stage IB, grouping patients with a tumor size < 4 cm into IB1 (tumor size < 2 cm), IB2 (tumor size between 2 and 4 cm) and IB3 (>3 cm) and removes from this category patients with lymph node involvement, for an accurate evaluation of a treatment plan adapted to each patient.

Brachytherapy

One of the most important point is the delay between POBT and surgery. Our study found that an interval time more than 52 days between brachytherapy and surgery was a risk factor of recurrence. This factor had been already suggested by Escande and al. in a study published in 2016 (p=0,03).

Concerning POBT morbidity, it has previously been investigated and appears to be very low, particularly since the era of radio-guided BT (6-14).

In our study, long term morbidity of brachytherapy concerned 24 patients (17,3%), with a majority of grade I and II complications (22 patients 15,9%), a majority of dyspareunia (11 patients (8%)).

Moreover, cervical cancer is a great indication for brachytherapy, since the source is easily implanted by the vagina and the surrounding organs at risk (bladder, rectum, sigmoid) are radioresistant. Finally, SCC (more than 90% of all cervical tumors) is commonly considered as radiosensitive (35).

Lately, the main evolution in gynecological brachytherapy has been the development of tridimensional (3D) dosimetry with optimization, realized on MRI or CT imaging and then the development of high dose rate and pulsed dose rate (Huertas and al. (35)).

The dosimetric scanner or MRI allows the delineation of target volumes and organs at risk (OAR) according to the recommendations of the European group in Gynecological brachytherapy (GYN-GEC-ESTRO) (36,37).

A French prospective multicenter study, conducted by Charra-Brunaud in 2012 (29), showed that brachytherapy based on CT and MRI improved the rate of local control of the disease and reduced morbidity.

Two-dimensional brachytherapy using the International Commission on Radiation Units and Measurements (ICRU) (22) points for the bladder and rectum underestimates (or sometimes overestimates) the dose delivered to organs at risk (Pelloski and al. (38)).

In our comprehensive center in Marseille, low dose rate intrauterine brachytherapy with 2D treatment plan using guidelines of ICRU for the plan treatment, is no longer used since 2012, and currently the main technique is high dose rate brachytherapy with tridimensional CT scanner according to the GEC ESTRO guidelines (36,37).

This may account for the low rate of pathological complete response (pCR) in our study, compares to the literature (49,3% for Marseille versus 75,3% for Uzan and al.).

5. LIMITATIONS

The retrospective nature of the study constitutes its most important limitation which impaired data collection concerning complications, follow up and quality of life.

6. CONCLUSION

With a median follow up of 132 months, a radio surgical management of early stage cervical cancers (less than IB3) including brachytherapy and type A laparoscopic hysterectomy seems to offer a reasonable rate of recurrences compared to LACC trial's results. This strategy may be an alternative to upfront radical hysterectomy in selected patients to maintain a minimal invasive approach. Further studies are necessary to confirm these results.

THÈSE SOUTENUE PAR : Clémence BEYER

TITRE :

Is there a place for pre operative brachytherapy followed by Laparoscopic Hysterectomy in less than IB3 cervical cancer after LACC trial?
Oncological Outcomes of a retrospective study

CONCLUSION :

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VU ET PERMIS D'IMPRIMER

Grenoble, le : 19/02/20

LE DOYEN



Pr. Patrice MORAND

LE PRÉSIDENT DE LA THÈSE

Pr. Didier RIETHMULLER

Pour le Président
et par délégation
—
Le Doyen de Médecine
Pr. Patrice MORAND



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ANNEXES

	N = 138
<i>Median Age</i> (years, min , max)	49 (28 - 81)
BMI (kg/m2) < ou = 25 > 25 Data missing	47,1 % (n = 65) 23,9 % (n = 34) n = 39
<i>Tumor size</i> < 2cm 2-3cm 3-4cm Data missing	53, 6% (n= 74) 21,7 % (n= 30) 20,3% (n=28) n = 6
<i>Stage of cervical cancer according to FIGO 2018</i> IA1 IA2 IB1 IB2	0,7 % (n=1) 4,3 % (n = 6) 46,3 % (n = 64) 46,3 % (n = 64)
<i>Histology</i> Adenocarcinoma Squamous cell carcinoma Mixed carcinoma (Adeno squamous)	28,3 % (n = 39) 61,6 % (n = 85) 3,6 % (n = 5)
<i>Lymph nodes invasion</i> N0 N1	100% 0
<i>Lymphovascular spaces involvement (after surgery)</i>	2,17 % (n=3)

<i>Positives margins (histological analyse after surgery)</i> <i>IB1 and less</i> <i>IB2</i>	0% 0,7 % (n= 1)
Surgical approach Laparoscopy Open surgery conversion to open	84,8 % (n = 117) 15,2% (n = 21) 1,5 % (n = 2)
<i>Complete response rate</i> pathological complete response residual tumor < 1 cm residual tumor > 1 cm Data missing	49,3% (n= 68) 26% (n=36) 4,3 % (n=6) 20,3% (n=28)

Table 1: Patients and tumors characteristics

Treatment	Tumor size (mm)	Time between diagnosis and recurrence (months)	Recurrence site	time between BT and surgery < 52 days or > 52 days	FIGO stage (2018)	residual tumor after brachytherapy	Histological type
BT + HT type A	35	96	Left iliac vessels	< 52	IB2	No	SCC
BT + HT type A	29	6	peritoneal carcinosis/ bones	> 52	IB2	> 1 cm	Adc
BT + HT type A	33	36	lung	> 52	IB2	No	SCC
BT + HT type A	32	48	peritoneal carcinosis	> 52	IB2	< 1 cm	Adc
BT + HT type A	< 20	96	pelvic, left iliac vessels, liver	> 52	IB1	< 1 cm	Adc
BT + HT type A	< 20	12	iliac vessels	> 52	IB1	< 1 cm	Adc
BT + HT type A	< 20	60	peritoneal carcinosis, lung	> 52	IB1	< 1 cm	Adc
BT + HT type A	< 20	24	peritoneal carcinosis	< 52	IB1	< 1cm	SCC
BT + HT type A	< 20	37	left pyramidalis muscle	> 52	IB1	No	SCC
p-value (Fisher test)	p = 0,61	/	/	p = 0,004	/	p = 0,03	p = 0,9

Table 2: Characteristics of recurrences. SCC : Squamous Cell carcinoma Adc : Adénocarcinoma

Surgery complications	
Grade (according to Clavien et Dindo)	13,7 % (n = 19)
<u>Urinary injuries</u>	
Grade I Bladder retention	2,9 % (n= 4)
Grade II stress urinary incontinence	2,17 % (n = 3)
Grade III ureteral stenosis	0,7% (n=1)
uretero vaginal fistula	0,7% (n =1)
<u>Others injuries</u>	
Grade I hematom	2,1% (n=3)
lymphoedema	0,5% (n=1)
dyspareunia	0,5% (n=1)
Grade II	0
Grade III Abscess of abdominal wall	2,17 % (n = 3)
Vaginal Scare disunion	1,5 % (n= 2)

Late Toxicity of brachytherapy (after 2 months) according to Chassagne glossary	17,3 % (n = 24)
Grade 1	5 % (n = 7)
dyspareunia	2,1 % (n = 3)
Urinary troubles	
Grade 2	
dyspareunia	2,9% (n = 4)
Proctitis	3,1% (n = 5)
lymphatics	2,1 % (n = 3)
Grade 3	
vaginal stenosis	0,7% % (n=1)
uretero vaginal fistula	0,7% (n=1)

Table 3a: Surgery complications Table 3b: Brachytherapy toxicities

STUDY, country	Number of patients	Stages (FIGO 2018)	Preoperative treatment	Type of hysterectomy	Type of surgical approach (OH / MISRH)	Follow-up (months)	DFS
POBT followed by surgery : retrospective cohorts							
Marseille , 2019	138	IB1 , IB2	POBT	Type A	MISRH (n=117)	132	93,5 %
Uzan & al, France, 2012 (8)	162	B1, IB2	POBT	Type B or C	MISRH	39	94,3 %
Escande & al. France, 2017 (6)	182	B1, IB2	POBT	Type B	MIS + OH	54	93,6 %
POBT followed by surgery versus upfront surgery : Randomized controlled trial							
Vizkelety & al. Hungary, 2015 (13)	70	IA2, IB1, IB2	POBT	Type C	MISRH	29	97,5 %
	80		None	Type C	MISRH		95,7 %
Upfront surgery , MISRH versus OH : Randomized controlled trial							
LACC 2018 Ramirez & al (19)	312	IA2, IB1, IB2	None	Type II ou III	OH	54	96,5 %
	319		None		MISRH		86 %
Upfront surgery , MISRH versus OH : Retrospective cohorts							
Alfonso & al. Sweden, 2019 (29)	236	IA1, IA2, IB1	None	Type B or C	OH	60	84%
	628				MISRH		88%
Kim and al. Korea, 2019 (25)	101	IB1, IB2	None	Type B or C	OH	114	89,7 %
	207		None		MISRH		78,5 %
Doo and al. USA, 2018 (39)	56	IB1, IB2	None	Type B or C	OH	25	86 %
	49				MISRH		76 %
Cusimano, 2019	485	IA, IB	None	Type B or C	OH	84	89,1%
	473				MISRH		87,9%

Table 4 Literature review of series evaluating different therapeutic strategies reporting more than 100 cases

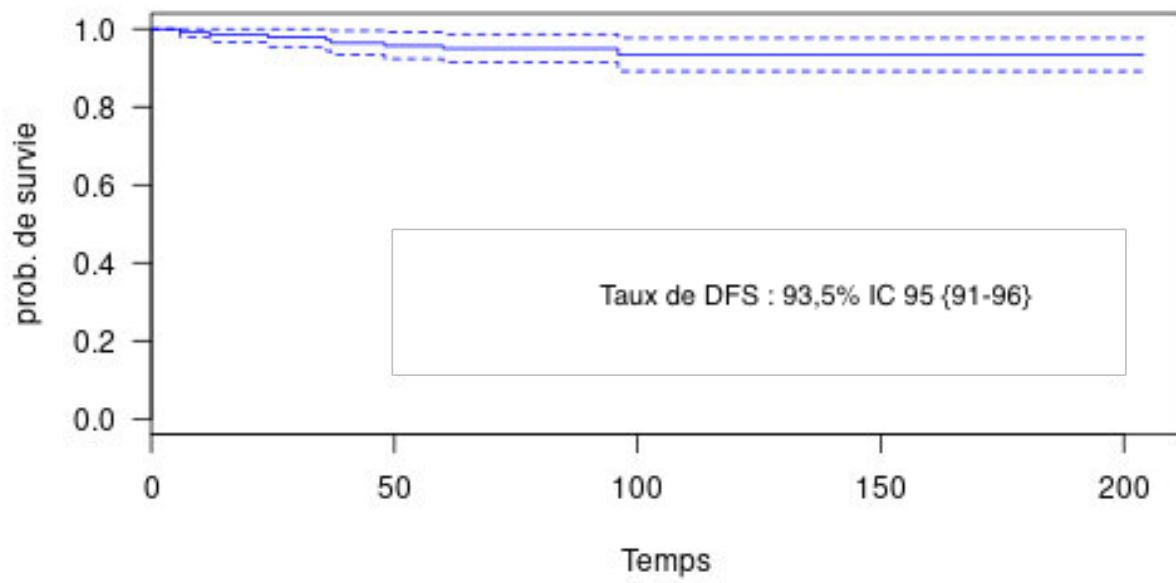
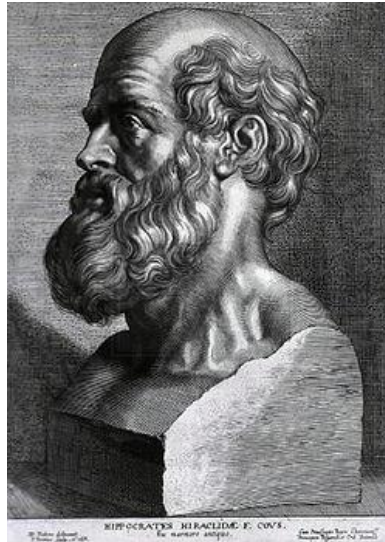


Figure 1 Disease free survival of the study population



SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,

Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.

Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.

Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.

Je garderai le respect absolu de la vie humaine.

Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.

Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.