Early clinical outcomes of hybrid brachytherapy for locally advanced cervical cancer: making adverse situations in a favorable scenario
Leonel Varela Cagetti, Christophe Zemmour, Eric Lambaudie, Magalie Provansal, Renaud Sabatier, Laura Sabiani, Guillaume Blache, Camille Jauffret, Marjorie Ferré, Agnès Tallet, et al.

To cite this version:
Leonel Varela Cagetti, Christophe Zemmour, Eric Lambaudie, Magalie Provansal, Renaud Sabatier, et al.. Early clinical outcomes of hybrid brachytherapy for locally advanced cervical cancer: making adverse situations in a favorable scenario. Journal of Contemporary Brachytherapy, 2022, 14 (4), pp.321 - 331. 10.5114/jcb.2022.118831 . inserm-04053267

HAL Id: inserm-04053267
https://inserm.hal.science/inserm-04053267
Submitted on 31 Mar 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.
Early clinical outcomes of hybrid brachytherapy for locally advanced cervical cancer: making adverse situations in a favorable scenario

Leonel Varela Cagetti, MD1, Christophe Zemmour2, Eric Lambaudie, MD, PhD3, Magalie Provansal, MD4, Renaud Sabatier, MD1,5, Laura Sabiani, MD6, Guillaume Blache, MD6, Camille Jauffret, MD6, Marjorie Ferré7, Agnès Tallet, MD1, Laurence Gonzague, MD1

1Department of Radiation Oncology, Institut Paoli-Calmettes, Marseille, France, 2Department of Clinical Research and Investigation, Biostatistics and Methodology Unit, Institut Paoli-Calmettes, Aix Marseille Univ, INSERM, IRD, SESSTIM, Marseille, France, 3Department of Surgical Oncology, Institut Paoli-Calmettes, Aix-Marseille Univ, CNRS, INSERM, CRM, Marseille, France, 4Department of Medical Oncology, Institut Paoli-Calmettes, Marseille, France, 5Département d’Oncologie Moléculaire, “Équipe labellisée Ligue Contre le Cancer”, Centre de Recherche en Cancérologie de Marseille (CRCM), Institut Paoli-Calmettes, INSERM UMR1068, CNRS UMR7255, Marseille, France, 6Institut Paoli-Calmettes, Oncology Surgery 2, Institut Paoli-Calmettes, Marseille, France, 7Department of Medical Physics, Institut Paoli-Calmettes, Marseille, France

Abstract

Purpose: To investigate the feasibility and early clinical outcomes of combined intra-cavitary (IC) and interstitial (IS) image-guided adaptive brachytherapy (IGABT) as curative and definitive treatment of patients treated with chemoradiotherapy (CCRT) for locally advanced cervical cancer (LACC).

Material and methods: Data from medical records of all consecutive patients with histologically proven cervical cancer (FIGO 2018 stage IB-IV), treated by brachytherapy after CCRT at our institution between 2017 and 2020 were reviewed.

Results: One hundred and forty-two patients with LACC FIGO 2018 stages (IB: 20.4%, II: 31.7%, III: 45.8%, IV: 2.1%) underwent brachytherapy at our institution, out of which 53.5% underwent combined brachytherapy technique (IC/IS). Median number of implanted catheters was 3 (range, 1-6 catheters). None of the 142 patients required invasive hemorrhage management. With a median follow-up of 21.6 (95% CI [confidence interval]: 19.1-23.5%) months, local relapse was observed in nine patients (6.3%), with four showing persistent and progressive disease. The estimated 2-year local and pelvic relapse-free survival were 92% (95% CI: 84-96%) and 90% (95% CI: 83-94%), respectively. The estimated 2-year disease-free survival for the entire population was 80% (95% CI: 71-87%). The 2-year overall survival (OS) rate for the entire population was 92% (95% CI: 84-96%). Acute toxicity G3 was reported in two (1.4%) patients. High-grade late toxicity (grade 3) was reported in 9 (6.3%) patients.

Conclusions: Combined IC/IS brachytherapy for LACC allows for recommended doses to achieve local control even in large tumors after CCRT improving target volume coverage, with low rates of acute morbidity. Hybrid brachytherapy technique (IC/IS) is essential to have a favorable scenario at the time of brachytherapy to correctly treat locally advanced cervical cancer patients.

J Contemp Brachytherapy 2022; 14, 4: 321–331
DOI: https://doi.org/10.5114/jcb.2022.118831

Key words: locally advanced cervical cancer, image-guided adaptive brachytherapy, interstitial brachytherapy, local control, vaginal morbidity.

Purpose

Cervical cancer is the fourth most common cancer in women, a disease mainly related to the infection with high-risk human papillomaviruses (HPV). Although most infections with HPV resolve spontaneously, an estimated 570,000 patients were diagnosed with cervical cancer in 2018, and more than a half died from the disease [1]. For early stage cervical cancer, no standard treatment is established, depending on the presence of risk factors. Hysterectomy, definitive external beam radiation therapy followed by brachytherapy, or pre-operative brachytherapy followed by surgery are the main options with excellent clinical results in terms of local and pelvic control rates [2-4]. For locally advanced disease,
Concomitant chemoradiotherapy (CCRT) followed by brachytherapy (BT) is considered as the standard treatment [5-7]. For many years, hysterectomy (HT) as completion treatment was adopted and performed [8]. Due to radiation-induced inflammation, vascular fibrosis, and adhesions, hysterectomy has an increased risk of significant post-operative entero-vesical and vesico-vaginal fistula, increasing morbidity, and thus compromises the quality of life of patients without clinical benefits [9-14]. Progress has been made in brachytherapy in the last decades. 2D approach based on conventional radiography was replaced by 3D images, and nowadays, magnetic resonance imaging (MRI) to perform image-guided adaptive brachytherapy (IGABT) is mandatory [2,15]. In our center, completion hysterectomy has been abandoned many years ago and simultaneously, brachytherapy implant techniques, i.e., intra-cavitary/interstitial (IC/IS), have been developed mainly in large and poor-responding tumors.

The aim of this retrospective study was to report and evaluate the feasibility and early outcomes of MR-IGABT in patients with locally advanced cervical cancer in the era of hybrid brachytherapy and dose escalation.

Material and methods

Patients with locally advanced cervical cancer treated with a curative intent by definitive radiochemotherapy and IGABT from November 2017 to December 2020 were included (Fig. 1). Some patients were referred to our hospital after radiotherapy-chemotherapy (RT-CT) to perform brachytherapy in our institution. Patients with early stage, insufficient follow-up, or planned post-irradiation hysterectomy were excluded. Patients were staged according to

Fig. 1. Locally advanced cervical cancer, MRI at diagnosis. A) Sagittal and B) axial T2-weighted (T2w), and C) diffusion-weighted magnetic resonance imaging (DW-MRI) showing initial tumor extension (grey zones, T2w) and high signal intensity on DWI.
the International Federation of Gynecology and Obstetrics (FIGO) 2018 criteria. After confirmed biopsy, to evaluate local extension and tumor spread at diagnosis, gynecological examination, biomarkers, and pelvic MRI diffusion-weighted (DWI), and dynamic contrast-enhanced (DCE) were performed. In order to estimate regional and distant disease, all patients were assessed by F18-FDG positron emission tomography-computed tomography (PET-CT). Pelvic lymphadenectomy staging was not routinely performed. According to the extent of disease, laparoscopic para-aortic lymph node staging (PAL) was done, except for patients with severe morbidity or age ≥ 70 years [16]. PAL was completed from the common iliac vessels to the left renal vein. Local institutional ethic committee approved the study design and analysis.

**Treatment**

**External beam radiation therapy and concomitant chemotherapy**

All patients underwent normo-fractionated EBRT (1.8-2 Gy per fraction, 5 times a week) for a median total dose of 45 Gy (range, 45.0-50.4 Gy) [20]. Treatment was delivered to the pelvis (cervix, uterus, parametria, upper third of the vagina, or more depending on its involvement, bilateral external and internal iliac lymph node areas, ilio-obturator, pre-sacral, and common iliac areas, groins were included in case of distal vaginal invasion). Para-aortic lymph nodes (PAN) were irradiated taking into account findings of PET-CT, MRI, and laparoscopic para-aortic lymph node staging, and patients at high-risk for para-aortic nodal recurrence. Considering internal target motion of the uterus (mainly in anterior-posterior direction), two treatment planning CT scans were systematically performed (empty and filled bladder), and all images set were fused. Internal target volume (ITV) of the initial low-risk clinical target volume of the primary tumor (CTV-T LR) was created with adapted margins (usually: 10 mm anterior-posterior, 10 mm superior-inferior, and 5 mm lateral) for optimal target coverage. Patients were treated with three-dimensional conformal radiotherapy (3D-CRT), intensity-modulated radiation therapy, or volumetric modulated arc therapy (VMAT). Pathological lymph nodes were boosted sequentially or with simultaneous integrated boost (SIB) in a range of 55-65 Gy equivalent total dose in 2 Gy fraction dose (EQD2) [17, 18]. A systematic margin of at least 5 mm in all directions was added to generate planning target volume (PTV). Weekly cisplatin (CDP) was administrated in a dose of 40 mg/m² of body-surface area IV, applied during EBRT delivery.

**Image-guided adaptive brachytherapy**

High-dose-rate (HDR) brachytherapy with MR-compatible hybrid applicators (Utrecht or Venezia, Elekta, Veenendaal, The Netherlands) was carried out in all patients. Implant was performed under general anesthesia, with the patient in low-dorsal lithotomy position. Depending on the operator, to improve the accuracy of the implant and to avoid uterus perforation, real-time trans-abdominal ultrasound-guided tandem placement was employed [19]. Number, position, and tissue depth of needles were planned based on clinical examination and MRI performed at the end of radiochemotherapy (Fig. 2). After general anesthesia recovery, CT-scan and MRI in T2-weighted sequence (axial and sagittal without DWI and DCE analysis) were acquired. Dummy sources were inserted in catheters to facilitate the applicator reconstruction. The images were then transferred to On-centra® (Nucletron, an Elekta company, Stockholm, Sweden). Delineation of target volumes, including residual gross tumor volume (rGTV), high-risk and intermediate-risk clinical target volume (HR-CTV and IR-CTV) as well as organs at risk (OARs), including bladder, rectum, sigmoid, and bowel, were performed according to the GEC-ESTRO recommendation [20, 21]. Dose and target coverage were adapted to D90 HR-CTV (D90: minimal dose to 90% of clinical target volume) and to D90 IR-CTV. Whenever possible and feasible, dose was escalated systematically. At the time of brachytherapy, combined IC/IS technique were performed, especially in large residual tumors, with the objective of dose escalation and to decrease the dose in OARs. Planning aims were ≥ 80 Gy to D90 HR-CTV and ≥ 60 Gy to D90 IR-CTV (dose in 2 Gy equivalents – EQD2, summing EBRT and BT, and applying linear quadratic model with an α/β ratio of 10 Gy and a half-time repair of 1.5 h). Dose constraints were < 70 Gy to maximally 2 cm³ exposed areas of the rectum and sigmoid colon (D2 cm³), and 80 Gy to D2 cm³ of the bladder (EQD2, similar model with an α/β of 3 Gy). Optimization was performed manually later, in order to adapt dwell times to the topography of the implant. The dose was prescribed to D90 HR-CTV volume. Depending on the tumor response at the end of CCRT, two BT schedules were applied. For good responders or low-risk tumors, BT was performed with one implant and delivered in 2 fractions per day (6 h apart) during three consecutive days, with prescribed dose of 27.5 Gy in 5 fractions of 5.5 Gy at D90 HR-CTV [22]. For high-risk or poorly responders’ tumors requiring combined intra-cavitary and interstitial (or treatment adaptation due to insufficient target volume coverage during first implant), four fractions in two implants (two fractions each one) of HDR brachytherapy were delivered about 1 week apart (fraction 1, 2 and 3, 4). Prescribed dose was 2 × 7 Gy each week (total 4 × 7 Gy) at D90 HR-CTV, corresponding to a prescribed dose of ≥ 80 Gy EQD2 [23]. Two fractions were delivered at the first and at second hospitalization. The first fraction was delivered as soon as possible after the completion of treatment planning. Twenty-four hours later, before the second fraction, a CT scan was done to evaluate the necessity of gas evacuation to avoid rectal anterior wall displacements towards the cervix and high doses [24, 25]. If the rectum was filled with gas, the gas was evacuated and a new CT scan was completed. A new dose-volume histogram (DVH) value was calculated, and the same dosimetry performed for the first fraction was applied.

**Treatment response and follow-up**

Patients were evaluated at 8 weeks with an abdominal-pelvic MRI, clinical examination, and biomarkers as
squamous cell carcinoma antigen (SCC-Ag) or carcino-embryonic antigen (CEA). In case of doubt of complete response, MRI, PET-CT, and biomarkers were repeated 2 months later, and in case of relapse suspicion, a biopsy was performed. In case of complete remission, patients were followed every 3 months the first year, then every 6 months for 2 years, and thereafter annually, with clinical examination and tumor markers. MRI was repeated systematically at least once a year. Acute and late toxicities were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events v. 5.0 scale [26].

Data and statistical analyses
All statistical analyses were performed at a significance level of $\alpha = 0.05$ using SAS® 9.4 software. Patients characteristics were summarized with counts and frequencies (calculated on the number of available data) for categorical variables, and with means ± standard deviations or medians and ranges for quantitative endpoints. Univariate and multivariate logistic regressions evaluated the impact on the occurrence of local relapse (respectively pelvic relapse) of brachytherapy parameters ($D_{90}$ HR-CTV, $D_{90}$ IR-CTV, and HR-CTV volume), FIGO 2018 stage (III-IV vs. I-II), and overall treatment time ($\geq 50$ vs. $< 50$ days). Only significant factors in univariate analyses were included in the multivariate model. Associated odds ratios (OR) were estimated with their Wald’s bilateral CIs and tests for significance. Similar analyses were performed to evaluate the impact of specific brachytherapy parameters on the occurrence of a grade $\geq 2$ global (respectively vaginal) toxicity. Local (respectively pelvic) relapse-free survival was defined as the time from date of diagnosis to date of local (respectively pelvic) relapse. Disease-free

Fig. 2. MRI at the time of brachytherapy. Partial response post-CCRT, axial, and A) sagittal, B) T2-weighted (T2w) and C) diffusion-weighted magnetic resonance imaging (DW-MRI)
survival was defined as the time from date of diagnosis to
date of local or pelvic or distant relapse or death. Overall
survival was defined as the time from date of diagnosis
to date of death. Patients without an event were censored
at the date of last follow-up. Pointwise estimations with
their bilateral confidence intervals were performed using
the classic Kaplan-Meier’s method. Follow-up was esti-
mated with the reverse Kaplan-Meier’s method.

Results

A total of 142 patients were included. Patients’ and
tumors’ characteristics are summarized in Table 1. Most
patients presented locally advanced disease FIGO stage ≥ II (79.6%). At diagnosis, 39.4% showed pathological
PET-CT lymph node uptake. At the end of radiochemo-
therapy, clinical examination and MRI were performed to
plan the brachytherapy strategy, and the mean residual
tumor was 26 ±12.9 mm.

IGABT was based on MRI for all the patients and for
each implant. Interstitial BT was performed in seventy-six (53.5%) patients. In 43 (30.2%) patients, brachytherapy
was performed with one implant and in 99 (69.7%) patients with two implants. In 30 (21.1%) patients treated
with two implants, interstitial BT was not necessary. However, when BT implant was planned only with in-
tra-cavitary technique and the volume target coverage
was insufficient, a second implant with interstitial tech-
nique (and intra-cavitary) was performed in 31 (21.8%) patients, with the aim to rectify the first implant and to
reach brachytherapy planning aims. On the contrary, the
number of patients treated with planned combined IC/IS
technique for both implants was 38 (26.8%) (Fig. 3).

The D90 HR-CTV median volume for exclusive IC
technique was 17.2 cc (range, 6.3-45.6 cc), and for patients
requiring at least one implant with the addition of inter-
stitial technique, the median volume was 24.4 cc (range,
5.1-59.7 cc). Comparing the time of general anesthesia for
patients requiring IS BT at the second implant, the ad-
dition of IS technique increased significantly the mean
general anesthesia time (64 ±14.2 min for IC implants vs.
72 ±15.8 min for combined technique; p < 0.001). In gen-
eral, for IS BT, the median number of catheters required
was 3 (range, 1-6 catheters). Brachytherapy characteris-
tics are described in Table 2.

Local and pelvic control

The primary endpoint was local control, and complete
response was achieved in 133 patients (93.7%). Local con-
trol was not achieved in nine patients (6.3%), four of them
showed locally persistent and progressive disease, with
three concomitant pelvic relapses and one patient with
concomitant distant relapse; one patient had concomitant
progressive disease and distant relapse and four were
exclusives local failures. Local relapse occurred after
a median time of 12.3 months (range, 4.8-20.2 months)
(Table 3). Twenty-three patients presented a bulky resid-
ual disease at the time of brachytherapy (HR-CTV vol-
ume ≥ 30 cc), and local control was achieved in 95.7% of
the patients.

| Table 1. Patients and tumor characteristics |
| Characteristics | All patients |
|-----------------|-------------|
| Median age (years), (mean ± standard deviation) | 57.0±14.9 |
| Histological sub-type, n (%) | |
| SCC | 120 (84.5) |
| AC | 18 (12.7) |
| Other | 4 (2.8) |
| Grade, n (%) | |
| Well-differentiated | 33 (30.3) |
| Moderately differentiated | 49 (45.0) |
| Poorly differentiated | 27 (24.8) |
| FIGO stage (2018), n (%) | |
| IB | |
| IB2 | 2 (1.4) |
| IB3 | 27 (19) |
| II | |
| IIA1 | 1 (0.7) |
| IIA2 | 9 (6.3) |
| IIB | 35 (24.6) |
| III | |
| IIIC | 43 (30.3) |
| IIIIC | 13 (9.2) |
| IV | 3 (2.1) |
| PET-CT, lymph node uptake, n (%) | |
| Pelvic | 52 (36.6) |
| Pelvic + PAN | 11 (7.7) |
| PAN | 0 (0.0) |
| Negative | 79 (55.6) |
| PET-CT tumor uptake (mean ± standard deviation) | 17.5±8.0 |
| EBRT field, n (%) | |
| Pelvic | 112 (78.9) |
| Pelvic + groins | 1 (0.7) |
| Pelvic and para-aortic | 29 (20.4) |
| Para-aortic lymph node staging (PAL), n (%) | |
| Positive | 4 (4.7) |
| Negative | 82 (95.3) |
| Concomitant chemotherapy, n (%) | 139 (97.9) |
| Nodal boost, n (%) | 58 (40.8) |
| Overall treatment time (days) (mean ± standard deviation) | 49.8±5.6 |
| MRI initial tumor size (mm) (mean ± standard deviation) | 49.6±14.0 |

AC – adenocarcinoma, MRI – magnetic resonance imaging, PAN – para-aortic
lymph nodes, PET-CT – positron emission tomography-computed tomography,
SCC – squamous cell carcinoma
In univariate analysis for local control FIGO stage (OR = 0.10, 95% CI: 0.01-0.84%, \( p = 0.034 \)), overall treatment time (OR = 0.11, 95% CI: 0.01-0.92%, \( p = 0.042 \)), HR-CTV volume (OR = 0.94, 95% CI: 0.89-1.0%, \( p = 0.47 \)), and \( D_{90} \) IR-CTV (OR = 0.83, 95% CI: 0.70-1.0%, \( p = 0.47 \)) appeared to be the main risks factors for local control, without independent significant factor in multivariate analysis (Table 4).

Nodal metastasis was present in 56 (39.4%) of patients at the time of diagnosis, out of which, 48 patients were treated with simultaneous integrated (SIB) or sequential boost, seven patients underwent surgical staging without boost, and one patient was not boosted (referred to BT, EBRT in another center). Laparoscopic para-aortic lymph node staging (PAL) was performed in 86 (60.6%) patients, and positive para-aortic lymph nodes were found in 4 (2.8%) patients.

Pelvic relapse occurred in twelve (8.5%) patients, eight of them in non-boosted lymph nodes. The mean time to pelvic relapse was 7 ± 5.6 months. Six pelvic relapses occurred simultaneously with distant relapse, two were concomitant with local failure, and three had isolated pelvic relapse; one patient showed a multi-site recurrence. Univariate analyses for pelvic relapse showed FIGO stage (OR = 0.16, 95% CI: 0.03-0.76%, \( p = 0.022 \)) and overall treatment time (OR = 0.91, 95% CI: 0.83-1.0%, \( p = 0.042 \)) were considered the main risks factors for pelvic relapse; however, the multivariate analysis did not reveal independent significant factors.

**Recurrence-free and overall survival**

The median follow-up was 21.6 months (range, 19.1-23.5 months). The estimated 2-year local and pelvic relapse-free survival were 92% (95% CI: 84-96%) and 90% (95% CI: 83-94%), respectively. The estimated 2-year disease-free survival for the entire population was 80% (95% CI: 71-87%). The 2-year OS rate for the entire population was 92% (95% CI: 84-96%). Clinical outcomes are described in Table 5.

**Morbidity**

**Interstitial brachytherapy-related complications**

Needles implantation for IS BT was technically feasible for all patients requiring this approach. At the end of each implant/treatment and to prevent bleeding complications, applicator removal was performed at the operation room; if bleeding was observed at discharge, continuous compression for at least 5 min was sufficient and the patients were observed overnight. None of the patients (53.5%) required invasive intervention, such as operative hemostasis or arterial occlusion.

**Toxicity**

High-grade (grade ≥ 3) toxicity was observed in 10 (7%) patients, and acute toxicity G3, including blood toxicity (anemia) related to CCRT was reported in two (1.4%) patients before brachytherapy. High-grade late toxicity (grade ≥ 3) was reported in 8 (5.6%) patients, including three vaginal toxicity G3 (stricture), four bone G3 fracture (increased fracture incidence due to osteoporosis), and one symptomatic lymphocele G3. No late grade 4/5 toxicity was observed.

**Brachytherapy dosimetric analyses for toxicity**

Dosimetric parameters in patients presenting at least one toxicity G ≥ 2 were reviewed. Univariate analyses
were performed taking into account: IS BT (present vs. absent), $D_{90}$ HR-CTV (≥ 85 vs. < 85 Gy), HR-CTV at the time of brachytherapy (≥ 30 vs. < 30 cc), $D_{90}$ IR-CTV (≥ 60 vs. < 60 Gy). No factor increasing the risk of toxicity was observed. Regarding vaginal toxicity, a more specific univariate analysis was performed with dedicate parameters, such as International Commission on Radiation Units & Measurements (ICRU) recto-vaginal point, ICRU bladder point, posterior-inferior border of symphysis (PIBS) and PIBS + 2 point, bilateral vaginal point dose at 5 mm, and dwell times (%) (tandem, ring/ovoids, and needles). None of these dosimetric factors were significantly associated with vaginal toxicity.

**Discussion**

During the last decades, the development of IGABT provided clinical evidence of improved clinical outcomes of modern brachytherapy in cervical cancer [2, 15, 27-32]. The use of MRI plays an important role in the accurate delineation of tumor and critical organs, allowing dose escalation to clinical target volumes (CTVs) [20-23]. In small tumors and those with a favorable response to chemoradiotherapy, intra-cavitary brachytherapy is an adequate and effective modality of brachytherapy [2]. On the contrary, unfavorable situations are usually present with large residual advanced disease, leading to insufficient target volume coverage at the time of brachytherapy. In the past, this group of patients has been treated with EBRT (parametrial boost), exposing organs at risk (rectum, sigmoid, and bladder) to high doses without optimal doses to target volumes [33, 34]. Nowadays, for ‘unfavorable situations’, hybrid technique (IC/IS) is mandatory [35]. The addition of interstitial brachytherapy for cervical cancers represents an opportunity to improve local control, transforming adverse situations into a favorable scenario [15]. In the RetroEMBRACE protocol (1998-2012) [15], IC/IS BT was performed in 23% of patients, and in EMBRACE-I protocol (2008-2015) [35], 43% of patients underwent combined intra-cavitary and interstitial brachytherapy. Approximatively, 70% of patients in both protocols were staged as FIGO IIB-IIIB (73% and 67%, respectively). In our study, 53.5% of the patients required IC/IS BT technique to achieve correct target volume coverage. This high requirement of IS BT was due to the characteristics of our patient population and the BT modality (four fractions in two implants), allowing for correction and improvement of first unsatisfactory IC implant.

Fokdal et al. [36] investigated 58 patients, and reported the feasibility of combined IC/IS BT performing a virtual pre-planning of the interstitial component. They found that the combined treatment was reproducible, and clinical goals were acquired without significant acute morbidity at 3 months. We presented results of IC/IS BT at 21.6 months, and 2 cases of anemia grade 3 (post-radiochemotherapy) were observed with no late grade 4/5 toxicity. Furthermore, the mean time in general anesthesia was on average 8 min longer in IC/IS implants, without compromising the operating room efficiency.

Residual tumor disease after CCRT is a challenge. In this sense, even in adverse situations as large HR-CTV volume at the time of BT, IS BT technique allows appropriate target volume coverage. Mahantshetty et al. [37] showed that distal parametrial/pelvic wall disease can be treated by IC/IS BT. However, intra-operative and

### Table 2. Brachytherapy parameters

| Dosimetric parameters | Statistics |
|-----------------------|------------|
| **Brachytherapy type, n (%)** |
| Intra-cavitary (IC) |
| First implant | 36 (25.4) |
| Second implant | 30 (21.1) |
| Intra-cavitary + interstitial (IC + IS) |
| First implant | 7 (4.9) |
| Second implant | 69 (48.6) |
| **Median number of IS catheters** | 3 (range, 1-6) |
| **General anesthesia time (min)** | | 64 |
| **Hybrid technique (IC/IS)** | 72 |
| **Volume (cm³) (mean ± standard deviation)** |
| HR-CTV | 21.0 ±9.7 |
| IR-CTV | 68.5 ±21.3 |
| **$D_{90}$ GTV (Gy) (mean ± standard deviation)** |
| $D_{90}$ | 81.9 ±4.9 |
| $D_{90}$ | 73.9 ±4.8 |
| $D_{90}$ | 122.7 ±7.3 |
| **IR-CTV ($G_{Y_{W/B}}$) (mean ± standard deviation)** |
| $D_{90}$ | 64.4 ±3.7 |
| $D_{90}$ | 59.2 ±4.9 |
| **OARs (mean ± standard deviation)** |
| Bladder $D_{2cm³}$ ($G_{Y_{W/B}}$) | 71.0 ±7.6 |
| Rectum $D_{2cm³}$ ($G_{Y_{W/B}}$) | 59.8 ±4.7 |
| Sigmoid $D_{2cm³}$ ($G_{Y_{W/B}}$) | 56.3 ±6.7 |
| **Points of interest: cumulative EBRT + BT ($G_{Y_{W/B}}$) (mean ± standard deviation)** |
| Point A mean (Gy) | 73.5 ±35.0 |
| ICRU recto-vaginal point | 63.8 ±5.6 |
| ICRU bladder point | 64.2 ±12.0 |
| PIBS point | 48.9 ±6.7 |
| PIBS + 2 point | 71.8 ±44.0 |
| Vaginal point dose at 5 mm R | 65.2 ±8.2 |
| Vaginal point dose at 5 mm L | 65.7 ±8.5 |
| **Dwell times % (mean ± standard deviation)** |
| Tandem | 60.2 ±8.1 |
| Ring/ovoids | 33.9 ±6.5 |
| Needles (IS) | 15.6 ±6.9 |
| **TRAK mean (cGY/m²) (mean ± standard deviation)** | 2.7 ±0.7 |

| CTV – clinical target volume, $D_{90}$ point – minimal dose to the most exposed 2 cm³, $D_{90}$ HR-CTV – dose delivered to $D_{90}$ of high-risk clinical target volume, $D_{90}$ IR-CTV – dose delivered to $D_{90}$ of intermediate-risk clinical target volume, Gy – Gray, TRAK – total reference air kerma, PIBS – posterior-inferior border of symphysis

**TRAK mean (cGY/m²) (mean ± standard deviation)**

2.7 ±0.7
during applicator removal complications were frequent (active bleeding, uterus perforation, vaginal lacerations). Generally, this type of complications can be managed without invasive treatments, and in our center, applicator removal is systematically performed at the operating room to avoid urgencies related to acute bleeding.

With the evidence supported by the RetroEMBRACE and EMBRACE-I studies, IGABT is thoroughly validated in clinical practice. The prospective observational study RetroEMBRACE demonstrated excellent local and pelvic control results. The mean HR-CTV volume was $37 \pm 24 \text{ cm}^3$ and the mean $D_{90}$ HR-CTV was $87 \pm 18 \text{ Gy}$. The total 3/5-years actuarial local and pelvic control rates were $91\% / 89\%$ and $87\% / 84\%$, respectively [15]. EMBRACE-I [35], a prospective, observational and multicenter cohort study was recently published, with a median HR-CTV volume of $28 \text{ cc}$ (95% CI: 20-40 cc) and median dose to $D_{90}$ HR-CTV of 90 Gy (95% CI: 84-94 Gy). Moreover, actuarial overall 5-year local control and pelvic control were 92% (95% CI: 90-93%) and 87% (95% CI: 85-89%), respectively. Although 25% of patients received less than 85 Gy to the target volume ($D_{90}$ HR-CTV), the acquired control local was excellent and superior to the results of RetroEMBRACE. In our study population, 26.7% of the patients received a dose lower than 85 Gy. Despite early results, the present study, showed promis-

### Table 3. Patterns of local relapse

| Isolated local relapse | Time to relapse (months) | FIGO stage | MRI tumor residual disease (mm) | OTT (months) | HR-CTV, IR-CTV volume at BT | $D_{90}$ HR-CTV, $D_{98}$ IR-CTV dose | Type of BT | Salvage treatment |
|------------------------|-------------------------|------------|--------------------------------|--------------|---------------------------|-------------------------------------|-----------|------------------|
| 1                      | 16                      | IIIC1      | 20.0                           | 55           | 20, 72 cc                 | 78, 64 Gy                           | IC        | CT               |
| 2                      | 14                      | IIB        | 0.45                           | 50           | 26, 85 cc                 | 86, 59 Gy                           | IC/IS     | Surgery          |
| 3                      | 10                      | IIIB       | 30.0                           | 50           | 18, 85 cc                 | 80, 55 Gy                           | IC/IS     | Surgery          |
| 4                      | 13                      | IIIC1      | 70.0                           | 48           | 29, 88 cc                 | 86, 58 Gy                           | IC/IS     | CT               |
| 5                      | 15                      | IIIB       | N.A.                           | 65           | 46, 106 cc                | 84, 62 Gy                           | IC/IS     | CT-IMM           |

OTT – overall treatment time, CT – chemotherapy, IC – intra-cavitary, IS – interstitial, IMM – immunotherapy

### Table 4. Univariate and multivariate analyses for local control

| Effect                  | Univariate analysis | Multivariate analysis |
|-------------------------|---------------------|-----------------------|
|                         | Odds ratio (95% CI) | p-value               | Odds ratio (95% CI) | p-value               |
| $D_{90}$ HR-CTV          | 0.94 (0.80-1.09%)   | 0.412                 |                      |                       |
| $D_{98}$ IR-CTV          | 0.83 (0.70-1.0%)    | 0.047                 | 0.84 (0.67-1.04%)    | 0.109                 |
| FIGO stage 2018 III-IV vs. I-II | 0.10 (0.01-0.84%) | 0.034                 | 0.13 (0.01-1.23%)    | 0.075                 |
| Overall treatment time ≥ 50 vs. < 50 | 0.11 (0.01-0.92%) | 0.042                 | 0.17 (0.02-1.44%)    | 0.104                 |
| HR-CTV volume            | 0.94 (0.89-1.0%)    | 0.047                 | 0.98 (0.91-1.06%)    | 0.613                 |

Significant value – $p < 0.005$

### Table 5. FIGO stage and clinical outcomes

| FIGO stage | No. of patients | HR-CTV volume | $D_{90}$ HR-CTV | $D_{98}$ IR-CTV | % of BT IC/IS | 2-yr local relapse-free survival (%) | 2-yr pelvic relapse-free survival (%) | 2-yr overall survival (%) |
|------------|----------------|---------------|-----------------|----------------|--------------|------------------------------------|--------------------------------------|--------------------------|
| IB2        | 2              | 18.6 ±9.8     | 82.2 ±6.9       | 58.7 ±5.9      | IC (100.0)   | 100.0                              | 100.0                               | 100.0                    |
| IB3        | 27             | 14.3 ±9.8     | 84.0 ±5.6       | 59.5 ±3.2      | IC/IS (33.0) | 100.0                              | 92.0                                | 100.0                    |
| IIA1       | 1              | 6.3           | 79.8            | 54.9           | IC (100.0)   | 100.0                              | 100.0                               | 100.0                    |
| IIA2       | 9              | 14.1 ±5.1     | 79.8 ±4.4       | 58.6 ±4.9      | IC/IS (55.0) | 100.0                              | 100.0                               | 100.0                    |
| IIIB       | 35             | 17.3 ±8.4     | 84.0 ±8.4       | 58.5 ±2.9      | IC/IS (49.0) | 96.0                               | 100.0                               | 100.0                    |
| IIIA       | 3              | 31.7 ±11.5    | 82.0 ±13.4      | 57.5 ±3.3      | IC/IS (100.0)| 100.0                              | 100.0                               | 100.0                    |
| IIIB       | 6              | 25.2 ±5.6     | 72.7 ±5.3       | 55.5 ±3.1      | IC/IS (80.0) | 63.0                               | 100.0                               | 100.0                    |
| IIIC1      | 43             | 22.2 ±9.9     | 83.5 ±4.6       | 59.9 ±3.1      | IC/IS (61.0) | 8.01                               | 75.0                                | 83.0                     |
| IIIC2      | 13             | 20.3 ±7.7     | 84.1 ±3.6       | 60.3 ±4.1      | IC/IS (46.0) | 100.0                              | 84.0                                | 62.0                     |
| IVA        | 3              | 24.5 ±5.2     | 84.1 ±1.1       | 58.1 ±0.4      | IC/IS (100.0)| 100.0                              | 100.0                               | 100.0                    |

BT – brachytherapy, IC/IS – intra-cavitary/interstitial, LRFS – local relapse-free survival, PRFS – pelvis relapse-free survival, OS – overall survival
Early clinical outcomes of hybrid brachytherapy for locally advanced cervical cancer: making adverse situations in a favorable scenario

Morbidity is a challenge in brachytherapy. Dose-volume (D2cm3, D90,1cm3) and dose point (D ICRU ) parameters are crucial to estimate and predict the risk of toxicity. Mazeron et al. [39] showed that a D2cm3 ≤ 65 Gy was associated with minor rectal morbidity, whereas a D2cm3 ≥ 75 Gy was associated with major rectal morbidity. Regarding vaginal morbidity, Kirchheiner et al. [40] assessed this parameter from the EMBRACE study. A plan-sparing technique allowed to increase the dose of D90 to ICBT without compromising target dose [41]. Our study showed a mean ICRU recto-vaginal and bladder point of 63.8 ±5.6 and 64.2 ±12.0, respectively, and a mean vaginal loading (ovoid/ring) of 33.9 ±6.5%. These dosimetric recommendations had a favorable impact regarding chronic toxicity in our population; three (2.1%) vaginal toxicities G3 (stricture) were reported without late grade 4/5 toxicity.

In locally advanced cervical cancer (LACC), pelvic and para-aortic positive lymph nodes treatment and control are crucial, and nodal relapse seems to be a relatively early event after treatments. In 2010, Beadle et al. reported a median time to regional recurrence of 16 months (range, 2-85 months), with a mean follow-up of 42 months [42]. In a more recent study, Vargo et al. reported the clinical results of PET/CT positive pelvic nodal disease treated by pelvic and para-aortic irradiation. Patients were assessed by PET/CT at 12 to 16 weeks. The median time to recurrence was 16 months (range, 10-36 months), with a 3-year regional control rate of 94%. Authors found that the nodal remission at the first PET/CT after treatment was a strong predictor for favorable long-term outcomes [43]. In our study, nodal metastasis was present in 36 (39.5%) patients at the time of diagnosis, and most of them received a lymph node boost. In our cohort, 4 patients (2.8%) relapsed in boosted lymph nodes, with the mean time to pelvic relapse of 7 ±6.0 months.

Overall treatment time (OTT) in LACC is one of the most significant prognostic factors. The Retro-EMBRACE study showed that increasing the overall treatment time by one week was equivalent to a loss of 5 Gy in D 90 HR-CTV [15]. In order to avoid schedule and logistic-related problems, patients who were referred at our center to undergo only brachytherapy (post-CCRT) received a first consultation before CCRT. The mean OTT in our study was 49.8 ±5.6 days.

Our study found that hybrid technique allows for excellent rates of local control without impact on toxicity, even in large residual tumors after CCRT. On the contrary, distant control remains to be improved. An Out-back trial randomized CCRT and BT vs. CCRT, BT, and adjuvant chemotherapy, with 4 cycles of carboplatin and paclitaxel in LACC. At 5 years, overall survival and progression-free survival were similar in both groups: 72% vs. 71%, p = 0.91 and 63% vs. 61%, p = 0.61, respectively. Patterns of disease recurrence were similar in these two treatment groups [44]. Immune check-point inhibitors, such as PD-1/PD-L1 inhibitors, can be a promising approach for cervical cancer treatment [45, 46]. In France, evidence is awaited form ongoing AtezoLACC study (EudraCT Number: 2017-005622-33), a randomized phase II trial evaluating the benefits of the addition of immunotherapy (given concurrently and as adjuvant treatment) compared to standard CCRT and BT.

Our study has some limitations, such as single-center study and the retrospective nature of the data susceptible to biases. Although longer follow-up remains necessary in our analysis, early clinical outcomes of this report confirm the safety and routine application of interstitial brachytherapy for LACC.

Conclusions

Modern brachytherapy allows for excellent local control rates while reducing morbidity. Targeted therapies for patients to be at high-risk of distance relapse are needed, and randomized trials are awaited.

Disclosure

The authors report no conflict of interest.

References

1. Global strategy to accelerate the elimination of cervical cancer as a public health problem. World Health Organization, Geneva 2020. Licence: CC BY-NC-SA 3.0 IGO.
2. Pötter R, Georg P, Dimopoulos J et al. Clinical outcome of protocol based image (MRI) guided adaptive brachytherapy combined with 3D conformal radiotherapy with or without chemotherapy in patients with locally advanced cervical cancer. Radiother Oncol 2011; 100: 116-123.
3. Barillot I, Horiot JC, Pignieux J et al. Carcinoma of the intact uterine cervix treated with radiotherapy alone: a French cooperative study: update and multivariate analysis of prognostics factors. Int J Radiat Oncol Biol Phys 1997; 38: 969-978.
4. Varela Cagetti L, Gonzague-Casabianca L, Zemmour C et al. The impact of modern preoperative high-dose-rate brachytherapy in early-stage cervical cancer. Gynecol Oncol 2021; 161: 166-172.
5. Morris M, Eifel PJ, Lu J et al. Pelvic radiation with concurrent paclitaxel in LACC. At 5 years, overall survival and progression-free survival in LACC. N Engl J Med 1999; 340: 1137-1143.
6. Whitney CW, Sause W, Bundy BN et al. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: A Gynecologic Oncology Group and Southwest Oncology Group study. J Clin Oncol 1999; 17: 1339-1348.
7. Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri. *Int J Gynaecol Obstet* 2018; 143 Suppl 2: 22-26.
8. Keys H, Bundy B, Stehman F et al. Radiation therapy with and without extracapsular hysterectomy for bulky stage IB cervical cancer: a randomized trial of the Gynecologic Oncology Group. *Gynecol Oncol* 2003; 89: 343-353.
9. Ferrandina G, Ercoli A, Fogatti A et al. Completion surgery after concomitant chemoradiation in locally advanced cervical cancer: a comprehensive analysis of pattern of postoperative complications. *Ann Surg Oncol* 2014; 21: 1692-1699.
10. Touboul C, Uzan C, Mauguen A et al. Prognostic factors and morbidities after completion surgery in patients undergoing initial chemoradiation therapy for locally advanced cervical cancer. *Oncofertil* 2010; 15: 405-415.
11. Houvenaeghel G, Lelievre L, Buttarelli M et al. Contribution of surgery in patients with bulky residual disease after chemoradiation for advanced cervical carcinoma. *Eur J Surg Oncol* 2007; 33: 498-503.
12. Colombo PE, Bertrand MM, Gutowski M et al. Total laparoscopic radical hysterectomy for locally advanced cervical cancer (stages IB, IIA and bulky stages IB) after concurrent chemoradiation therapy: surgical morbidity and oncological results. *Gynecol Oncol* 2009; 114: 404-409.
13. Varela Cagetti L, Zemmour C, Minsat M et al. Lessons from radiochemotherapy and modern image-guided adaptive brachytherapy followed by hysterectomy. *Gynecol Oncol* 2015; 136: 528-534.
14. Castelnuovo-Marchand P, Chargari C, Bouaïta R et al. What to expect from immediate salvage hysterectomy following concomitant chemoradiation and image-guided adaptive brachytherapy in locally advanced cervical cancer. *Cancer Radiother* 2015; 19: 710-717.
15. Sturdza A, Pöttner R, Fokdal L et al. Image guided brachytherapy in locally advanced cervical cancer: improved pelvic control and survival in RetroEMBRACE, a multicenter cohort study. *Radiother Oncol* 2016; 120: 428-433.
16. Yildirim Y, Sehirali S, Avci ME et al. Integrated PET/CT for the evaluation of paraaortic nodal metastasis in locally advanced cervical cancer patients with negative conventional CT findings. *Gynecol Oncol* 2008; 108: 154-159.
17. Lee SP, Leu MY, Smathers JB et al. Biologically effective dose distribution based on the linear quadratic model and its clinical relevance. *Int J Radiat Oncol Biol Phys* 1995; 33: 375-389.
18. Nag S, Gupta N. A simple method of obtaining equivalent doses for use in HDR brachytherapy. *Int J Radiat Oncol Biol Phys* 2000; 46: 507-513.
19. Pareek V, Barthwal M, Giridhar P et al. A phase III randomised trial of trans-abdominal ultrasound in improving application quality and dosimetry of intra-cavitary brachytherapy in locally advanced cervical cancer. *Gynecol Oncol* 2021; 160: 375-378.
20. Haie-Meder C, Pottier R, Van Limbergen E et al. Recommendations from gynaecological (GYN) CEC-ESTRO working group (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. *Radiother Oncol* 2005; 74: 235-245.
21. Pottier R, Haie-Meder C, Van Limbergen E et al. Recommendations from gynaecological (GYN) CEC-ESTRO working group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. *Radiother Oncol* 2006; 78: 67-77.
22. Ogorodnichtouh O, Aunier J, Boussarsar A et al. Five-fraction HDR brachytherapy in locally advanced cervical cancer: a monocentric experience. *Cancer Radiother* 2021; 25: 463-468.
23. Potter R, Dimopoulos J, Georg P et al. Clinical impact of MRI assisted dose volume adaptation and dose escalation in brachytherapy of locally advanced cervix cancer. *Radiother Oncol* 2007; 83: 148-155.
24. Ferré M, Varela Cagetti L, Zemmour C et al. Reducing dose to rectum by placement of a rectum-emptying tube in cervical cancer patients treated with brachytherapy. *Brachytherapy* 2020; 21: 748-754.
25. Mazeron R, Champoudry J, Gilmore J et al. Intraluminal organs movement in three-dimensional image-guided adaptive pulsed-dose-rate cervical cancer brachytherapy: assessment and dosimetric impact. *Brachytherapy* 2015; 14: 260e266.
26. NCI, CTCAE. Available from: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0/
27. Thomeer M, Vandecasteeve V, Braun L et al. Evaluation of T2-W MR imaging and diffusion-weighted imaging for the early post-treatment local response assessment of patients treated conservatively for cervical cancer: a multicentre study. *Eur Radiol* 2019; 29: 309.
28. Narayan K, van Dyk S, Bernshaw D et al. Ultrasound guided conformal brachytherapy of cervix cancer: survival, patterns of failure, and late complications. *J Gynecol Oncol* 2014; 25: 206-213.
29. Ribeiro I, Janssen H, De Brabandere M et al. Long term experience with 3D image guided brachytherapy and clinical outcome in cervical cancer patients. *Radiother Oncol* 2016; 120: 447-454.
30. Lindegaard J, Fokdal L, Nielsen S et al. MRI-guided adaptive radiotherapy in locally advanced cervical cancer from a Nordic perspective. *Acta Oncol* 2013; 52: 1510-1519.
31. Rijkmans E, Nout R, Rutten I et al. Improved survival of patients with cervical cancer treated with image-guided brachytherapy compared with conventional brachytherapy. *Gynecol Oncol* 2014; 135: 231-238.
32. Lakos F, De Cuyper P, Viet Nguyen P et al. Clinical efficacy and toxicity of radiochemotherapy and magnetic resonance imaging-guided brachytherapy for locally advanced cervical cancer patients: a mono-institutional experience. *Acta Oncol* 2015; 54: 1558-1566.
33. Wolfson A, Abdel-Wahab M, Arnold M et al. A quantitative assessment of standard vs. customized midline shield construction for invasive cervical carcinoma. *Int J Radiat Oncol Biol Phys* 1997; 37: 237-242.
34. Fenkell L, Assenholt M, Nielsen SK et al. Parametral boost using midline shielding results in an unpredictable dose to tumor and organs at risk in combined external beam radiotherapy and brachytherapy for locally advanced cervical cancer. *Int J Radiat Oncol Biol Phys* 2011; 79: 1572-1579.
35. Pöttner R, Tanderup K, Schmied M et al. MRI-guided adaptive brachytherapy in locally advanced cervical cancer (EBRACE-I): a multicentre prospective cohort study. *Lancet Oncol* 2021; 22: 538-547.
36. Fokdal L, Tanderup K, Bjørre Hokland S et al. Clinical feasibility of combined intracavitary/interstitial brachytherapy in locally advanced cervical cancer employing MRI with a tandem/ring applicator in situ and virtual preplanning of the interstitial component. *Radiother Oncol* 2013; 107: 63-68.
37. Mahanthshetty U, Sturdza A, Naga CP et al. Vienna-II ring applicator for distal parametral/pelvic wall disease in cervical cancer brachytherapy: An experience from two institutions: Clinical feasibility and outcome. *Radiother Oncol* 2019; 141: 122-129.
38. Berek J, Stubblefield P. Anatomic and clinical correlates of uterine perforation. *Am J Obstet Gynecol* 1979; 135: 181-184.
39. Mazeron R, Fokdal L, Kirchheiner K et al. Dose-volume effect relationships for late rectal morbidity in patients treated with chemoradiation and MRI-guided adaptive brachytherapy for
locally advanced cervical cancer: Results from the prospective multicenter EMBRACE study. *Radiother Oncol* 2016; 120: 412-419.

40. Kirchheiner K, Nout R, Lindegaard et al. Dose-effect relationship and risk factors for vaginal stenosis after definitive radio(chemo)therapy with image-guided brachytherapy for locally advanced cervical cancer in the EMBRACE study. *Radiother Oncol* 2016; 118: 160-166.

41. Mohamed S, Lindegaard J, De Leeuw A et al. Vaginal dose de-escalation in image guided adaptive brachytherapy for locally advanced cervical cancer. *Radiother Oncol* 2016; 120: 480-485.

42. Beadle B, Jhingran A, Yom S et al. Patterns of regional recurrence after definitive radiotherapy for cervical cancer. *Int J Radiat Oncol Biol Phys* 2010; 76: 1396-1403.

43. Vargo J, Kim H, Choi S et al. Extended field intensity modulated radiation therapy with concomitant boost for lymph node positive cervical cancer: analysis of regional control and recurrence patterns in the positron emission tomography/computed tomography era. *Int J Radiat Oncol Biol Phys* 2014; 90: 1091-1098.

44. Mileshkin L, Moore K, Barnes E et al. Adjuvant chemotherapy following chemoradiation as primary treatment for locally advanced cervical cancer compared to chemoradiation alone: The randomized phase III OUTBACK Trial (ANZGOG 0902, RTOG 1174, NRG 0274). *J Clin Oncol* 2021; 39 (suppl 15; abstr LB3).

45. Yuncong L, Li W, Ruizhan T et al. PD-1/PD-L1 inhibitors in cervical cancer. *Front Pharmacol* 2019; 10: 65.

46. Meng Y, Liang H, Hu J et al. PD-L1 expression correlates with tumor infiltrating lymphocytes and response to neoadjuvant chemotherapy in cervical cancer. *J Cancer* 2018; 9: 2938-2945.