Concomitant cervical and transperineal parametrial high-dose-rate brachytherapy boost for locally advanced cervical cancer

Caroline Bailleux, MD1, Alexander Tuan Falk, MD1, Marie-Eve Chand-Fouche, MD1, Mathieu Gautier, MSc1, Emmanuel Barranger, MD, PhD2, Jean-Michel Hannoun-Levi, MD, PhD1

1Department of Radiation Oncology, 2Department of Surgery, Antoine Lacassagne Cancer Center, University of Nice-Sophia, Nice, France

Abstract

Purpose: There is no consensus for parametrial boost technic while both transvaginal and transperineal approaches are discussed. A prototype was developed consisting of a perineal template, allowing transperineal needle insertion. This study analyzed acute toxicity of concomitant cervical and transperineal parametrial high-dose-rate brachytherapy (HDRB) boost for locally advanced cervical cancer.

Material and methods: From 01.2011 to 12.2014, 33 patients (pts) presenting a locally advanced cervical cancer with parametrial invasion were treated. After the first course of external beam radiation therapy with cisplatinum, HDRB was performed combining endocavitary and interstitial technique for cervical and parametrial disease. Post-operative delineation (CTV, bladder, rectum, sigmoid) and planification were based on CT-scan/MRI. HDRB was delivered in 3-5 fractions over 2-3 consecutive days. Acute toxicities occurring within 6 months after HDRB were retrospectively reviewed.

Results: Median age was 56.4 years (27-79). Clinical stages were: T2b = 23 pts (69.7%), T3a = 1 pt (3%), T3b = 6 pts (18.2%), and T4a = 3 pts (9.1%). Median HDRB prescribed dose was 21 Gy (21-27). Median CTV_C (16 pts) and HR-CTV_MRI (17 pts) were 52.6 cc (28.5-74.3), 31.9 cc (17.1-58), respectively. Median EQD2_αβ for D90_CTV and D90_HR-CTV were 82.9 Gy (78.2-96.5), 84.8 Gy (80.6-91.4), respectively. Median EQD2_αβ (CT/MRI) for D2cc bladder, rectum and sigmoid were 75.5 Gy (66.6-90.9), 64.4 Gy (51.9-77.4), and 60.4 Gy (50.9-81.1), respectively. Median follow-up was 14 months (ranged 6-51). Among the 24 pts with MFU = 24 months, 2-year LRFS rate, RRFS, and OS were 86.8%, 88.8%, and 94.1%, respectively. The rates of acute genitourinary and gastrointestinal toxicities were 36% (G1 dysuria = 8 pts, G2 infection = 2 pts, G3 infection = 2 pts), and 27% (G1 diarrhea = 9 pts), respectively. One patient presented vaginal bleeding at the time of applicator withdrawal (G3-blood transfusion); no bleeding was observed due to the parametrial implant.

Conclusions: Concomitant cervical and transperineal parametrial HDRB boost for locally advanced cervical cancer appears feasible and safe with no specific acute toxicity compare to cervical HDRB alone. Longer follow-up and larger patient cohort will be needed.

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modulated radiation therapy or stereotactic body radiation therapy, resulted in significantly lower OS (HR 1.86, 95% CI: 1.35-2.55, p < 0.01), confirming that BT boost was a critical component of locally advanced cervix carcinoma treatment [4].

Different applicators, such as ovoid or ring tandem, molds, and vaginal cylinders with intra-uterine tubes are commonly used. In most cases, a typical pear-shaped isodose results from the intra-vaginal and intra-uterine sources but in case of larger tumors and especially with parametrial involvement, dose distribution is often non-optimal. In order to improve parametrial coverage, some applicators combining intracavitary (IC) and interstitial (IS) approach were proposed without increasing the dose to the organs at risk (OAR): Vienna applicator: ring applicator plus 6 to 9 interstitial needles around intrauterine tandem (Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden) [5,6], Utrecht applicator: tandem ovoids + 10 needles (Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden) [7], and Nice Gynecologic Applicator: NGA – uterine tandem + vaginal cylinder + 8 needles within the cervix (Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden) [8].

Currently, there is no consensus for parametrial boost technic while both transvaginal and transperineal approaches are discussed. Recently, for locally advanced tumors with parametrial involvement, interstitial BT parametrial boost using trans-vaginal approach was shown to be dosimetrically superior to EBRT parametrial boost in terms of target volume coverage and OAR sparing [9]. In order to improve the parametrium coverage, we developed a prototype consisting of a dedicated perineal template fixed to the NGA allowing a transperineal needle insertion.

This study aimed to assess feasibility, reproducibility, and acute toxicity of concomitant cervical and transperineal parametrial high dose rate brachytherapy (HDRB) boost for locally advanced cervix carcinomas.

Material and methods

Patient features

From January 2011 to December 2014, 33 patients (pts) presenting a histology proven locally advanced cervix carcinoma with parametrial invasion were retrospectively analyzed regarding dosimetric data, acute toxicities, and early clinical outcomes. All patients underwent parametrial HDRB boost. A local ethics committee initially approved this therapeutic approach.

All patients had a clinical exam and follow-up performed by trained physicians. Patients underwent cervical, vaginal, and rectal examination. Computed tomography scan (CT), pelvic magnetic resonance imaging (MRI), and positron emission tomography/computed tomography (PET) were performed. Para-aortic lymph node dissection was performed at the discretion of the physician in order to improve cancer staging and EBRT target volume definition. Tumors were staged using UICC-TNM classification [10].

Treatment features

After the first course of EBRT with concomitant plat-in-based chemotherapy, a single implantation of HDRB was performed combining endocavitary and interstitial technique for cervical disease, and transperineal interstitial approach for parametrial extension.

Concomitant radio-chemotherapy

The first part of the treatment consisted of EBRT with concurrent chemotherapy. EBRT delivered a total dose of 45 to 46 Gy (ICRU point) in 25 or 23 fractions, based on a 3-dimensional conformal technique with or without modulated intensity using > 10 MV X-photons. Gross tumor volume (GTV) was determined clinically and radiologically for the primary tumor and any pathological nodes. The clinical target volume (CTV) included the GTV and surrounding subclinical disease. CTV involved the uterus, parametrial tissue, upper vagina (or whole vagina for T3a disease), and broad and utero-sacral ligaments. All pelvic-lymph nodal stations were included in the CTV with a recommended 7 mm margin around the blood vessels. Planning target volume (PTV) included the CTV plus margin to account for internal organ movements, setup, and delivery uncertainties. Concomitant chemotherapy mainly consisted in weekly platin-based chemotherapy using the following protocols: weekly cisplatin 40 mg/m², weekly carboplatin 100 mg/m², weekly cisplatin 40 mg/m² + gemcitabin 125 mg/m², monthly cisplatin 50-75 mg/m² for 1 day + 5-fluorouracile 1000 mg/m² from day 2 to day 5, weeks 1 and 5.

Brachytherapy

Brachytherapy was planned after the completion of radio-chemotherapy (RCT) with a time interval between the last RCT session and brachytherapy of less than 21 days. The single brachytherapy implantation was performed under general anesthesia starting by a gynecologic examination in order to evaluate the clinical response obtained after RCT.

Endocavitary and interstitial procedure for central disease

The endocavitary and interstitial procedure for central disease was already described [8]. Briefly, uterine tandem was introduced in the uterus cavity; it is then preceded to the placement of a vaginal cylinder including eight equidistant channels allowing the placement of eight plastic needles (240 mm Sharp Needles™; Elekta company, Elekta AB, Stockholm, Sweden) using flexible chucks, within the cervical tissue (40 mm depth). Vaginal cylinder was sutured to the skin through a skin suture chucks, within the cervical tissue (40 mm depth). Vaginal cylinder was sutured to the skin through a skin suture

Interstitial procedure for parametrial disease

The perineal template punched by a total of 6 holes was fixed to the vaginal cylinder before its introduction into the vaginal cavity. Due to the ischium, this perineal
Parametrial brachytherapy boost

The perineal template has to be placed under the bone structure but has also to be obliquely oriented allowing the upper-inner parametrial needle to cross the uterus tandem at the distal part of the vaginal cylinder (Figures 1B, 1C, 1D). Once the perineal template was fixed on the skin perineum, parametrial transperineal 240 mm needles (Sharp Needles™, Elekta Company, Elekta AB, Stockholm, Sweden) were placed into the parametrium through the perineal template, using rigid chucks. Number of needles (2 to 6) was defined according to the pre-treatment target volume and clinical examination performed during HDRB (Figure 1E).

After recovery, post-implant planning CT scan (until 12.2013), then MRI (after 01.2014) was performed for treatment planning purposes. CTV (CT scan planning), high-risk CTV (HR-CTV), and intermediate-risk (IR-CTV) (MRI planning) as well as OARs (bladder, rectum, and sigmoid) were delineated according to the Gyn GEC-ESTRO recommendations [11] (Figure 1F).

HDRB dose was delivered in respect to the current Gyn. GEC-ESTRO dose constraint rules recommending EQD2$_{\alpha\beta_{10}}$ for D90$_{HR-CTV} > 80$ Gy and EQD2$_{\alpha\beta_{3}}$ for D2cc$_{bladder} < 90$ Gy, and for D2cc$_{rectum/sigmoid} < 75$ Gy. Brachytherapy dose was delivered in 3 to 5 fractions over

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**Fig. 1.** Overview of the applicator allowing concomitant endocavitary and interstitial implant for cervical and parametrial disease. A) Different pieces of the applicator before assembling. B) Assembled applicator showing the oblique orientation ($\alpha$ angle) of the perineal template allowing the upper-inner parametrial needle to cross the uterus tandem at the distal part of the vaginal cylinder. C) Overview of the assembled applicator. D) Frontal proximal view of the assembled applicator. E) Post-operative view of the applicator showing vaginal and parametrial needles. F) Post-operative 3D reconstruction.
2 to 3 consecutive days. Total dose and dose per fraction changed also according to the year of treatment. Between 2011 and 2012, the total delivered dose was 25 Gy in 5 fractions over 3 days, while 1 fraction of 7 Gy was delivered the day of implantation and 2 fractions of 4.5 Gy twice daily (at least 6 hours apart) for two days (EQD2\(\alpha\beta=10\) = 32 Gy/EQD2\(\alpha\beta=3\) = 41 Gy). Since May 2013, in order to make brachytherapy less uncomfortable, the number of fractions was reduced from 5 to 3 with a total dose of 21 Gy in 3 fractions over 2 days with 1 fraction of 7 Gy delivered the day of implantation, and 2 fractions of 7 Gy (at least 6 hours apart) the day after (EQD2\(\alpha\beta=10\) = 30 Gy/EQD2\(\alpha\beta=3\) = 42 Gy). Total dose and dose per fraction could also vary according to the clinical response observed at the time of HDRB.

Dose volume adaptation was manually achieved using graphical optimization (Oncentra Brachy, Elekta Company, Elekta AB, Stockholm, Sweden) by dwell location and time variation (Figure 2). Patient stayed in supine position during all the hospitalization in a non-shielded room receiving specific care such as massages and anti-thrombotic therapy. The patient was transferred to her bed to the brachytherapy bunker for each fraction. After the last brachytherapy session and analgesic pre-medication, applicator and needles were removed, paying attention to the risk of vaginal and perineal bleeding. The patient left the hospital the day after in the absence of early complications.

**Follow-up and evaluation**

Patients were followed-up at first and 6 months after HDRB completion; then every 6 months alternatively by the radiation oncologist and the gynecologic surgeon. Surveillance consisted of clinical examination while CT, MRI, and PET were used in case of suspicion of local, regional, or distant progression. RCT and HDRB were proposed as definitive treatment, while post-RCT hysterectomy was proposed only in case of persistent residual disease or local recurrence.

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**Fig. 2.** Post-operative MRI-planning dose distribution analysis: A) transversal view, B) frontal view, C) mid-sagittal view, D) para-sagittal view
Acute toxicities occurring within the 6 months after HDRB were graded using the NCI-Common Toxicity Criteria version 4.0 (CTCV4.0) [12] based on the following items: urinary disorders (hematuria, increase in frequency, urgency, dysuria, nocturia, incontinence), gastrointestinal disorders (diarrhea, proctitis), infections (urinary tract, kidney, uterine, and pelvic infections), hemorrhages (intra and post-operative, vaginal, retroperitoneal).

**Statistical analysis**

Quantitative data were represented as median, extremes, and standard deviation. Qualitative data were represented as percentage and extremes. For a subgroup of patients who had a median follow-up of 24 months, local-relapse free survival (LRFS), regional-relapse free survival (RRFS), and overall survival (OS) were calculated (Kaplan-Meier method – 24 and 36 months) with standard errors. The follow-up was calculated between the date of the first fraction of RCT, and the date of local recurrence and the date of last follow-up. Patients were censored at the moment of their death or their last follow-up.

**Results**

**Patients and treatments**

Patient and treatment characteristics are reported in Tables 1 and 2, respectively. Median age was 56.4 years (27-79). Histological type was squamous cell carcinoma, adenocarcinoma, and adenoid basal carcinoma for 29 pts (87.9%), 3 pts (9.1%), and 1 pt (3%), respectively. According to the UICC-TNM classification [10], patients were

| Data | N/Median | %/[Min-max] |
|------|----------|-------------|
| Age (years) | 56.4 | [27-79] |
| Tumor stage | | |
| T2b | 23 | 69.7 |
| T3a | 1 | 3.0 |
| T3b | 6 | 18.2 |
| T4a | 3 | 9.1 |
| Parametrial involvement | | |
| Right | 10 | 30.3 |
| Left | 18 | 54.5 |
| Bilateral | 5 | 15.2 |
| Tumor size (mm) | 45 | [13-83] |
| Lymph node status | | |
| N– | 18 | 54.5 |
| N+ | 15 | 45.5 |
| Metastatic status | | |
| M– | 32 | 97.0 |
| M+ | 1 | 3.0 |
| Histological type | | |
| Epidermoid carcinoma | 29 | 87.9 |
| Well differentiated | 7 | 12.3 |
| Moderately differentiated | 9 | 15.8 |
| Poorly differentiated | 11 | 19.3 |
| Undifferentiated | 1 | 1.8 |
| Unknown | 1 | 1.8 |
| Adenocarcinoma | 3 | 5.3 |
| Other | 1 | 1.8 |

SFU – 5-fluorouracile, EBRT – external beam radiation therapy, CT – chemotherapy, HDRB – high-dose-rate brachytherapy
staged as: T2b (23 pts – 69.7%), T3a (1 pt – 3%), T3b (6 pts – 18.2%), and T4a (3 pts – 9.1%). Fifteen pts (45.5%) presented pelvic-lymph node involvement diagnosed after MRI (6 pts) and/or PET-scan (9 pts). Median initial tumor size defined on MRI was 45 mm (13-83). Five patients had bilateral parametrial extension. Thirty-two patients (97%) received concomitant chemotherapy: weekly cisplatin (27 pts), weekly carboplatin (3 pts), weekly cisplatin-gemcitabine (1 pt), and 5 fluorouracil-cisplatin (W1-W5, 1 pt). Median EBRT dose was 46 Gy (45.5-50.6). Median HDRB dose was 21 Gy (21-27) in 3 to 5 fractions with a median treatment time of 2 days. Median number of parametral implanted needles was 4. Median overall treatment time was 54 days (44-72) and median delay between EBRT

| Data | CT (n = 16) | MRI (n = 17) |
|------|-------------|--------------|
| CTV  | Median 52.6 | –            |
|      | Min-max 28.5-74.3 | –  |
| D90CTV | (%) 118.0 | – |
|      | Min-max 108.0-127.6 | –  |
|      | SD 13.1 | – |
| D90HR-CTV | (%) – | – |
|      | Min-max – | 122.4 |
|      | SD – | 107.9-135.9 |
| D90IR-CTV | (%) – | – |
|      | Min-max – | 25.7 |
|      | SD – | 22.7-27.85 |
| QD2EQD2αβ | (Gy) 82.9 | – |
|      | Min-max 78.2-96.5 | –  |
|      | SD 5.7 | – |
| HR-CTV | Median 31.9 | – |
|      | Min-max 17.1-58.0 | 11.7 |
| D90HR-CTV | (%) – | – |
|      | Min-max – | 84.8 |
|      | SD – | 80.6-91.4 |
| D90HR-CTV | (%) – | – |
|      | Min-max – | 27.5 |
|      | SD – | 22.7-28.5 |
| V100 | Median 99.0 | – |
|      | Min-max 95.3-100 | 1.2 |
|      | SD 98.6 | – |
| V150 | Median 52.2 | – |
|      | Min-max 28.3-69.4 | 11.2 |
|      | SD 57.2 | – |
| V200 | Median 16.1 | – |
|      | Min-max 11.6-39.6 | 7.5 |
|      | SD 23.9 | – |

Bladder

| Data | CT (n = 16) | MRI (n = 17) |
|------|-------------|--------------|
| D0.1ccb | (%) 100.8 | – |
|      | Min-max 84.8-125.1 | –  |
|      | SD 10.2 | – |
| D1ccb | (%) 88.6 | – |
|      | Min-max 72.0-106.5 | 8.8 |
|      | SD 85.0 | – |
| D2cccb | (%) 83.8 | – |
|      | Min-max 65.0-100.4 | 9.5 |
|      | SD 79.6 | – |
| EQD2αβ EQD2αβ | (Gy) 76.8 | – |
|      | Min-max 66.6-90.9 | 6 |
|      | SD 74.5 | – |

Rectum

| Data | CT (n = 16) | MRI (n = 17) |
|------|-------------|--------------|
| D0.1ccr | (%) 86.5 | – |
|      | Min-max 29.6-104.0 | 21.1 |
|      | SD 82.2 | – |
| D1ccr | (%) 72.6 | – |
|      | Min-max 213.8-85.3 | 18.4 |
|      | SD 68.4 | – |
| D2cccr | (%) 65.1 | – |
|      | Min-max 19.0-77.8 | 15.1 |
|      | SD 60.7 | – |
| EQD2αβ EQD2αβ | (Gy) 66.4 | – |
|      | Min-max 51.9-77.4 | 7.6 |
|      | SD 64.3 | – |

Sigmoid

| Data | CT (n = 16) | MRI (n = 17) |
|------|-------------|--------------|
| D0.1ccs | (%) 78.8 | – |
|      | Min-max 61.1-129.6 | 23.9 |
|      | SD 75.2 | – |
| D1ccs | (%) 70.0 | – |
|      | Min-max 50.2-106.0 | 17.6 |
|      | SD 56.5 | – |
| D2cccs | (%) 60.9 | – |
|      | Min-max 46.0-97.8 | 17.2 |
|      | SD 52.4 | – |
| EQD2αβ EQD2αβ | (Gy) 59.8 | – |
|      | Min-max 53.4-81.1 | 8.5 |
|      | SD 60.7 | – |

\( CT – \) planification based on CT-scan = 16 patients (pts); MRI – planification based on MRI = 17 pts; CTV – clinical target volume; HR-CTV – high-risk CTV; IR-CTV – intermediate-risk CTV, D90CTV – dose delivered to 90% of the CTV, D90HR-CTV – dose delivered to 90% of the HR-CTV, D90IR-CTV – dose delivered to 90% of the IR-CTV, EQD2αβ – equivalent dose at 2 Gy per fraction for \( \alpha \beta = 10 \) (tumor), EQD2αβ – equivalent dose at 2 Gy per fraction for \( \alpha \beta = 3 \) (normal tissues), V100 – volume receiving 100% of the prescribed dose; V150 – volume receiving 150% of the prescribed dose; V200 – volume receiving 200% of the prescribed dose; D0.1ccs – dose delivered to 0.1% of the bladder volume; D0.1ccr – dose delivered to 0.1% of the rectum volume; D0.1ccs – dose delivered to 0.1% of the sigmoid volume; D0.1ccr – dose delivered to 1% of the bladder volume; D0.1ccs – dose delivered to 1% of the rectum volume; D0.1ccr – dose delivered to 1% of the sigmoid volume; D0.1ccs – dose delivered to 2% of the bladder volume; D0.1ccr – dose delivered to 2% of the rectum volume; D0.1ccs – dose delivered to 2% of the sigmoid volume; SD – standard deviation.
and HDRB was 17 days (5-47). Three patients underwent adjuvant hysterectomy after a median time interval [HDRB-surgery] of 59 days (49-70): 2 pts presented a complete pathological response and macroscopic residual disease was observed in 1 pt. Median follow-up for the whole cohort was 14 months (6-51) while 24 pts (72.7%) had a median follow-up of 24 months (8-51).

**Dosimetric data**

Dosimetric data are reported in Table 3. Planification was performed on CT for 16 pts (48.5%) and on MRI for 17 pts (51.5%). Median CTV, HR-CTV, and IR-CTV were 52.6 cc (28.5-74.3), 31.9 cc (27.1-58.0), and 83.1 cc (53.0-129.0), respectively. EQD2 of D90, D90, HR-CTV and D90, IR-CTV were 82.9 Gy (78.2-96.5), 84.8 Gy (80.6-91.4) and 70.5 Gy (59.9-78.3), respectively. Median V100 of the whole cohort was 99.0% (95.3-100.0) while 24 pts (72.7%) had a median follow-up of 24 months (6-51).

**Acute toxicities**

Acute toxicities occurring within the 6 months after HDRB using the CTCAE 4.0.; results expressed as a number of events and a percentage of patients. Total number of toxicities expressed as a number of patients in whom at least one toxicity scored G0, G1, G2, G3, or G4 occurred

| Toxicities | G0 pts | % | G1 pts | % | G2 pts | % | G3 pts | % | G4 pts | % |
|------------|--------|---|--------|---|--------|---|--------|---|--------|---|
| GU         | 25     | 75.8 | 8       | 24.2 | 0      | 0 | 0      | 0 | 0      | 0 |
| GI         | 24     | 72.7 | 9       | 27.3 | 0      | 0 | 0      | 0 | 0      | 0 |
| Bleeding   | 32     | 97.0 | 0       | 0    | 0      | 0 | 1      | 3 | 0      | 0 |
| Infectious | 29     | 87.9 | 0       | 0    | 2      | 6.1| 6      | 6.1| 0      | 0 |
| Total      | 16     | 48.5 | 14      | 42.4 | 2      | 6.1| 3      | 9.1| 0      | 0 |

GU – genito-urinary toxicities, GI – gastro-intestinal toxicities

Current, standard brachytherapy technique is based on pulsed dose rate (PDR) or HDR [13]. In case of parametrial involvement, the combination between endocavitary and interstitial brachytherapy is generating a lot of interest [14]. Indeed, increasing the “field” number makes dose distribution optimization easier and more accurate. However, the parametral boost technique remains under discussion. Historically, parametral boost was performed through EBRT, before or after brachytherapy increasing not only treatment protraction but also the risk of overlap of irradiated volumes between EBRT-boost and cervical brachytherapy. Besides those clinical considerations, Mohamed et al. compared parametral boost dose distribution delivered either by EBRT or interstitial brachytherapy (ISBT) [9]. The authors confirmed that ISBT was superior to EBRT in terms of organ sparing (less normal tissue exposure to intermediate doses – V0.95 and target coverage (more conformal).

Currently, interstitial parametral brachytherapy boost can be performed through a transvaginal or a transperineal technique. In this study, the results of a transperineal approach were reported. Regarding dose distribution analysis, D2cc EQD2 of the bladder matched the GEC-ESTRO dose constraint recommendations (< 90 Gy), constraints were also respected for D2cc EQD2 of the rectum and sigmoid (< 75 Gy) [15]. However, considering more rigorous OAR dose constraints as discussed during the 5th EMBRACE Annual Meeting in Vienna (17th-18th January, 2014), bladder D2cc EQD2 was superior to 80 Gy for 3 patients (9%), rectum D2cc EQD2 was superior to 70 Gy for 6 pts (18%), and sigmoid D2cc EQD2 was superior to 75 Gy for 1 pt (3%).

Besides the transperineal approach described in this study, mainly Vienna and Aarhus teams presented a transvaginal technique. Berger et al. reported dosimetric and clinical outcome of 6 patients who underwent oblique needle implantation from the vagina using a modified Vienna applicator [16]. HR-CTVs of mean 50 cc were treated with mean D90 of 86 Gy. Based on 2 to 3 implants of
PDR brachytherapy Lindegaard et al. described an oblique needle implantation from the vagina [14]. The authors obtained a mean D90 HR-CTV of 87 Gy in tumors with a mean HR-CTV of 53 cc. More recently, Mohamed et al. reported the dosimetric results of a cohort of 23 patients who underwent 2 PDR implants (1 week apart) based on endocavitary and oblique needle implantation from the vagina [9]. The authors calculated D90 HR-CTV > 84 Gy for all patients. Transperineal interstitial approach has been criticized for bleeding risk due to vascular injury at the time of needle insertion. In the present study, one patient presented vaginal bleeding at the time of applicator withdrawal but no bleeding was observed due to parametrial implant. Indeed, at least six experimented brachytherapy teams analyzed the feasibility of transperineal brachytherapy technique for gynecological malignancies [17,18,19]. Among a total of 481 patients, no severe bleeding complications were reported. Bleeding risk remains a rare but potential event, which is strongly correlated to inter-individual heterogeneity in blood vessel architecture.

In this study, we reported the results of a single implant allowing delivering 3 to 5 fractions based on HDRB. According to our knowledge, this is the first analysis of such approach while combination between endocavitary and interstitial brachytherapy was mainly reported using HDR brachytherapy and always with at least 2 implants 1 week apart. Utrecht and Aarhus teams described their results. Jürgenliemk-Schulz et al. reported the results of 24 patients with a mean D90 HR-CTV of 84 Gy [20]. Norden et al. analyzed the dosimetric results of 20 patients treated with two pulsed dose rate applications combining endocavitary and interstitial, and noticed a mean D90 HR-CTV of 83.9 Gy [7]. More recently, Aarhus University published the results of 71 patients treated with 2 PDR implants with a mean D90 HR-CTV of 94.5 Gy while mean EQD2 D2cc of bladder, rectum, and sigmoid were 68.5, 61.0, and 64.9 Gy, respectively [21]. Fokdal et al. reported only minor morbidity, which was resolved at a 3 month follow-up after 3 implants of endocavitary and interstitial PDR BT in 58 patients [22]. The American Brachytherapy Society recommends a cumulative delivered dose of approximately 80-90 Gy as a component of the definitive treatment of locally advanced cervix carcinoma while precise applicator placement remains necessary to maximize the probability of achieving local control without major side effects [23]. For HDRB, the recommended D90 EQD2_{αβ} is 80 to 90 Gy, depending on tumor size at the time of brachytherapy [24,25]. Dimopoulos et al. demonstrated that a local control superior to 90% can be achieved if the D90 EQD2_{αβ} was at least 86 Gy [26]. Pötter et al. study’s generated satisfying results in terms of local control after EBRT with or without chemotherapy followed by HDRB (4 × 7 Gy) with the objective of D90 HR-CTV EQD2_{αβ} > 85 Gy. In this study, brachytherapy was guided by clinical examination and MRI and the authors reported a 3-year local-control rate of 96% and 86% for stage IIB and IIIB, respectively [27]. In our study, median D90 HR-CTV EQD2_{αβ} (CT-scan data) and median D90 HR-CTV EQD2_{αβ} (MRI data) ranged between 80 to 90 Gy (82.5 Gy and 84.8 Gy, respectively) in respect to the GEC-ESTRO dose constraint recommendations [15]. No patient received less than 80 Gy and we calculated a D90 HR-CTV EQD2_{αβ} > 84 Gy for 12 patients (71%) in the MRI-planning group. However, Tanderup et al. recently suggested that D90 HR-CTV EQD2_{αβ} > 90 Gy and > 85 Gy for small and large residual tumors, respectively, could improve local control rate by 3-4% [28]. In order to reach the dose levels suggested by Tanderup et al., it would be necessary to increase our prescribed dose up to 24 Gy in 3 fractions over 2 days. Computer simulation modeling revealed that this increase would allow reaching a D90 HR-CTV EQD2_{αβ} of 94.5 Gy (86.2-102.7) with an acceptable increase of D2cc EQD2_{αβ} for OARs (data not shown).

However, those dose constraints derived from different prescription dose protocols, which do not take into account treatment protraction, which could significantly impact on the final biological effect. Here, we propose a single implant of HDRB for cervical and parametral disease with 3 fractions over 2 consecutive days. Biological impact on target volume and OARs of 21 Gy delivered over 2 days (3 × 7 Gy) could be different than the same physical dose delivered during a longer treatment scheme (2 to 3 weeks) and 3 different implants.

Conclusions

Short follow-up, small cohort of patient, and retrospective approach are the principal limiting factors of this study. However, concomitant cervical and transperineal parametral HDRB boost for locally advanced cervical cancer appears feasible and safe with no specific acute toxicity compare to cervix HDRB alone. More specifically, transperineal parametral HDRB boost does not increase the risk of bleeding. This technique allows respecting dose constraints for HR-CTV and OARs. Longer follow-up and larger patient cohort will be necessary to confirm this approach.

Disclosure

Prof. Jean-Michel Hannoun-Levi declares association with ELEKTA, related to the patent No 8834339: Assembly for performing brachytherapy treatment of a tumour tissue in an animal body (http://www.google.com.au/patents/US8834339 [1]). The other authors report no conflict of interest.

References

1. Ferlay J, Soerjomataram I, Dikshit R et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136: E359-386.
2. Lanciano RM, Martz K, Coia LR et al. Tumor and treatment factors improving outcome in stage III-B cervix cancer. Int J Radiat Oncol Biol Phys 1991; 20: 95-100.
3. Han K, Milosevic M, Fyles A et al. Trends in the utilization of brachytherapy in cervical cancer in the United States. Int J Radiat Oncol Biol Phys 2013; 87: 111-119.
4. Gill BS, Lin JF, Krivak TC et al. National Cancer Data Base analysis of radiation therapy consolidation modality for cervical cancer: The impact of new technological advancements. Int J Radiat Oncol Biol Phys 2014; 90: 1083-1090.
5. Dimopoulos JC, Kirisits C, Petric P et al. The Vienna applicator for combined intracavitary and interstitial brachytherapy.
of cervical cancer: clinical feasibility and preliminary results. *Int J Radiat Oncol Biol Phys* 2006; 66: 83-90.
6. Kiritsis C, Lang S, Dimopoulos J et al. The Vienna applicator for combined intracavitary and interstitial brachytherapy of cervical cancer: design, application, treatment planning, and dosimetric results. *Int J Radiat Oncol Biol Phys* 2006; 65: 624-630.
7. Nomden CN, de Leeuw AA, Moerland MA et al. Clinical use of the Utrecht applicator for combined intracavitary/interstitial brachytherapy treatment in locally advanced cervical cancer. *Int J Radiat Oncol Biol Phys* 2012; 82: 1424-1430.
8. Hannoun-Levi J-M, Chand-Fouche M-E, Gautier M et al. Interstitial preoperative high-dose-rate brachytherapy for early stage cervical cancer: dose-volume histogram parameters, pathologic response and early clinical outcome. *Brachytherapy* 2013; 12: 48-155.
9. Mohamed S, Kallehaug J, Fokdal L et al. Parametrial boosting in locally advanced cervical cancer: Combined intracavitary/interstitial brachytherapy vs. intracavitary brachytherapy plus external beam radiotherapy. *Brachytherapy* 2015; 14: 23-28.
10. Sobin L, Gospodarowicz M, Wittekind CE. TNM Classification of Malignant Tumors. 7th ed. Wiley-Blackwell, Oxford 2009.
11. Haie-Meder C, Pötter R, Van Limbergen E et al. Recommendations from Gynaecological (GYN) GEC-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.
12. CTCAE.4. National Cancer Institute Common Terminology Criteria for Adverse Events v4.0. NCI, NIH, DHHS. May 29, 2009. NIH publication # 09-7473.
13. Migliorini P, Malhaire J-P, Gosduff G et al. Cervix cancer brachytherapy: high dose rate. *Cancer Radiother* 2014; 18: 452-457.
14. Lindegaard JC, Tanderup K. Counterpoint: Time to retire the parametrical boost. *Brachytherapy* 2012; 11: 80-83.
15. Pötter R, Haie-Meder C, Van Limbergen E et al. Recommendations from gynaecological (GYN) GEC-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.
16. Berger D, Pötter R, Dimopoulos JCA et al. New Vienna applicator design for distal parametrical disease in cervical cancer. *Brachytherapy* 2010; 9: S23-S102.
17. Martinez A, Cox RS, Edmundson GK. A multiple-site perineal applicator (MUPIT) for treatment of prostatic, anorectal, and gynecologic malignancies. *Int J Radiat Oncol Biol Phys* 1984; 10: 297-305.
18. Weitmann HD, Knocke TH, Waldhäusl C et al. Ultrasound-guided interstitial brachytherapy in the treatment of advanced vaginal recurrences from cervical and endometrial carcinoma. *Strahlenther Onkol* 2006; 182: 86-95.
19. Mahantshetty U, Shrivastava S, Kalyani N et al. Template-based high-dose-rate interstitial brachytherapy in gynecologic cancers: a single institutional experience. *Brachytherapy* 2014; 13: 337-342.
20. Jürgenliemk-Schulz IM, Tersteeg RJ, Roessink JM et al. MRI-guided treatment-planning optimization in intracavitary or combined intracavitary/interstitial PDR brachytherapy using tandem ovoid applicators in locally advanced cervical cancer. *Radiother Oncol* 2009; 90: 322-330.
21. Mohamed S, Nielsen SK, Fokdal LU et al. Feasibility of applying a single treatment plan for both fractions in PDR image guided brachytherapy in cervix cancer. *Radiother Oncol* 2013; 107: 32-38.
22. Fokdal L, Tanderup K, Hokland SB 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.
23. Viswanathan AN, Thomadsen B. American Brachytherapy Society Cervical Cancer Recommendations Committee, American Brachytherapy Society. American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part II: general principles. *Brachytherapy* 2012; 11: 33-46.
24. Viswanathan AN, Beriwal S, De Los Santos JF et al. American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part III: low-dose-rate and pulsed-dose-rate brachytherapy. *Brachytherapy* 2012; 11: 53-57.
25. Lee LJ, Das IJ, Higgins SA et al. American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part IV: magnetic resonance image-guided brachytherapy. *Radiother Oncol* 2009; 93: 311-315.
26. Pötter R, Georg P, Dimopoulos JC 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.
27. Tanderup K, Fokdal L, Sturdza A. Dose and Volume Response for Local Control in Locally Advanced Cervical Cancer Treated With EBRT Combined With MRI-Guided Adaptive Brachytherapy. *Int J Radiat Oncol Biol Phys* 2014 Suppl. Abstract S92.