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RESEARCH ARTICLE

THE ROLE OF HYBRID BRACHYTHERAPY IN MANAGEMENT OF LOCALLY ADVANCED CERVICAL CANCER: DOSIMETRIC STUDY AND INITIAL RESULTS

M. Hommadi¹, H. Bakkali², O. Houessou¹, M. Benlemlih¹, T. Elmorjani², N. Bendahou², I. Lahdiri², S. Boutayeb³, S. El mejjaoui⁴, H. Kacemi⁴, T. Kebdani⁴ and N. Benjaafar⁵

1. Resident in Radiation Oncology, Department Of Radiotherapy, The National Institute Of Oncology, Rabat, Department of Radiotherapy, The National Institute of Oncology, Mohammed V University in Rabat, Morocco.
2. Radiation Oncologist; Department of Radiotherapy, The National Institute of Oncology, Rabat, Department of Radiotherapy, The National Institute of Oncology, Mohammed V University in Rabat, Morocco.
3. Medical Physicist, Department of Radiotherapy, The National Institute of Oncology, Rabat, Department of Radiotherapy, The National Institute of Oncology, Mohammed V University in Rabat, Morocco.
4. Professor of Radiation Oncology; Department of Radiotherapy, The National Institute Of Oncology, Rabat, Department of Radiotherapy, The National Institute of Oncology, Mohammed V University in Rabat, Morocco.
5. Professor of Radiation Oncology; Head of Department of Radiotherapy, the national Institute of Oncology, Department of Radiotherapy, The national institute of Oncology, Mohammed V University in Rabat, Morocco.

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Abstract

Purpose: The aims of this study were to investigate the clinical feasibility and to report our preliminary treatment outcomes of combined intracavitary/interstitial brachytherapy (IC/IS BT), using a hybrid applicator and magnetic resonance imaging (MRI) based treatment planning in patients with locally advanced cervical cancer.

Methods and Materials: Between January 2017 and December 2018, eight patients with locally advanced uterine cervical cancer were treated with primary radiation therapy including hybrid BT. Patients with distant metastasis other than para-aortic lymph node spread were excluded from this study. A hybrid applicator for guidance of parametrial needles was used to perform high-dose-rate-brachytherapy (HDR BT) with MRI based treatment pre-planning. Parametrial extent of the disease or large residual disease in these patients was judged to exceed the coverage limit of intracavitary brachytherapy alone. The number of needles, chosen guiding holes through the ovoids, and insertion depths were based on the extent of residual disease. We investigated the dosimetric gain by comparing the clinical interstitial optimized plan (IC/IS clinical) with an additionally generated optimized plan without needle use (ICstudy).

Results: The clinical use of the hybrid applicator system proved to be feasible in all 32 treatment fractions. The applicator Fletcher interstitial 6mm or Utrecht interstitial consists of the IC tandem and two ovoids that serves as a template for needle insertion. MRI preplanning was performed the week before the implant in 5 cases and the day of application with applicator in place in 3 cases. Four to eight needles were placed per fraction, and overall a total of 152 needles were used.

Corresponding Author:- M. Hommadi

Address:- Resident in Radiation Oncology, Department Of Radiotherapy, The National Institute Of Oncology, Rabat, Department of Radiotherapy, The National Institute of Oncology, Mohammed V University in Rabat, Morocco.

Significant differences in IC/IS plan and IC study plan were derived for dose application to the target volume; D90 high-risk clinical target volume (D90 CTV HR) was 90.1 Gy (IC/IS clinical) vs 85.36 Gy (IC study) with an average gain of 4.74 Gy. Likewise, sparing of organs at risk differed significantly for bladder D2cc: 82.5 Gy (IC/IS clinical) vs 95.7 Gy (IC study) and rectum D2cc: 65.5 Gy (IC/IS clinical) vs 67.8 Gy (IC study). With an average follow-up of 27.25 months (range 18–34): no patient experienced local relapse, three patients experienced distant metastasis two of them died, no acute complications such as bleeding or organ penetration occurred due to needle placement, one patient developed recto-vaginal fistula.

Conclusions: Our preliminary clinical experience indicates that combined intracavitary and interstitial MRI-based brachytherapy in patients with significant residual disease extending up to the distal third of parametria after external-beam therapy is feasible and allows excellent local control and a low rate of morbidity.

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Introduction:-

The standard of care for advanced cervical cancer is considered to be external-beam radiotherapy (EBRT) with concomitant *cis*-platinum based chemotherapy and brachytherapy (BT) (1–5). Intracavitary techniques are widely used, with encouraging local control rates of 75% to 95% for small tumors (6). In cases of locally advanced disease, currently available intracavitary applicators often lead to inadequate target coverage and dose inhomogeneity for the lateral tumor parts. Local control rates in these patients remain low, ranging between 45% and 80% (6). Large tumors with distal parametrial involvement at diagnosis, insufficient response, and/or unfavorable topography after radio chemotherapy represent a therapeutic challenge for the radiation oncologist.

MRI-based planning was implemented for BT of cervical cancer because it has been proven to be highly appropriate to assess the tumor size and configuration (7), thus ensuring ideal tumor delineation and identification of high or intermediate-risk areas for local recurrence, based on the recommendations of the GEC- ESTRO BT committee, a standardized terminology has been implemented (8).

The concept of image-guided adaptive brachytherapy (IGABT) requires MRI of the tumor on the day of BT with an MRI-compatible BT applicator in place for assessment of tumor extension and localization of organs at risk (OAR). However, the treatment of larger and/or irregular-shaped tumors proves challenging. The dose distribution is limited by the doses applied to the OAR, such as the bladder, the sigmoid colon, the small intestines, and the rectum.

A technical solution to the problem of irregular vertical extension of the tumor (e.g., in cases of parametrial infiltration) is the implementation of interstitial (IS) BT complementing the intracavitary (IC) BT using a hybrid applicator system (IC/IS). Several devices have successfully been adopted to conquer these shortcomings such as the Vienna applicator (tandem-ring), and the Utrecht applicator (tandem-ovoid) are examples of MRI-compatible applicators that can be used for combined (IC/IS) BT. Through holes in the ring or ovoids, which serve as a template, additional needles can be inserted. In a further development, recently the Venezia applicator (Elekta, Sweden) was introduced, allowing for even more degrees of freedom for even more advanced tailoring of dose distribution.

In this study we present data from the first 8 patients treated with the hybrid applicator in our department. We investigated the benefit of the combined IC/IS approach over the intracavitary approach alone and analyzed the clinical use of the needles.

Methods And Materials :-

Patients :

Between January 2017 and December 2018, a total of 8 patients with biopsy proven advanced cervical cancer not eligible for surgical therapy underwent curative intended chemoradiotherapy followed by BT using a hybrid

applicator at the national institute of oncology of Rabat. the IC BT using the intrauterine tandem and two ovoids was complimented by interstitial needles. Staging was performed using CT scanner and pelvic MRI, as well as cystoscopy or rectoscopy, in cases of suspect organ infiltration.

Chemoradiotherapy:

A planning CT scan was obtained with a slice thickness of 5 mm, with the application of intravenous contrast. Target volume delineation, treatment planning, and dose concepts were made according to the GEC-ESTRO recommendations (9). The clinical target volume included the primary tumor, the uterus the vagina the parameters, the internal iliac, external iliac, common iliac, obturator, and presacral lymph node regions. In cases of positive para-aortal lymph nodes, the para-aortic lymph node region was included in the CTV. The prescribed dose was 46 Gy in 23 fractions to the primary tumor and the lymphatic pathways; in case of lymph nodal involvement, a boost of 10 to 20 Gy was applied. External beam radiotherapy (EBRT) was delivered by conformal radiotherapy on an Elekta Synergy Linac with weekly image guidance . Cisplatin was given intravenously once a week with a dose of 40 mg/m² of body surface area.

Applicator :

The Utrecht Interstitial CT/MR Applicator (image 1) has been specifically developed for combined intracavitary / interstitial treatment for cervical cancer, with a combination of intracavitary and interstitial brachytherapy. Its design is based on the Fletcher CT/MRI Applicator, and uses the ovoids as a template for interstitial needle placement. A needle guiding system, consisting of guiding tubes anchored in drilled holes through the ovoids, is used for needle placement (image 2). Each ovoid (having different sizes with 20, 25, or 30 mm of distance between the source channels) contains five needle holes in a 15 angle so that the needles are more or less parallel to the tandem. As many as 10 needles can be inserted, and insertion depth is variable. Through the combination of intracavitary and interstitial functionality, optimally conformal cervical and parametrial dose coverage can be achieved.

Imaging, contouring, treatment planning, and dose reporting:

Combined (IC/IS BT) was conducted after completion of EBRT with a planning aim to the high-risk clinical target volume (HR-CTV) with a biologically equivalent dose of 90-95 Gy (D90) in four BT sessions. MRI was obtained before initial treatment and during the last week of EBRT to assess treatment response (image 3). Preplanning for BT was based on tumor anatomy assessed by clinical examination and MRI. The extension of the cervical tumor and the flexion of the cervix were measured to determine the choice of the IC applicator and the ovoids. An estimate of the vertical extension, including infiltration of the parametria, was conducted to determine the number, position and the depth of interstitial needles.

BT was applied as HDR- BT in four fractions within two implants, once a week. The intra uterine utrecht applicator was positioned on epidural anesthesia, using ultrasound guidance. To verify correct positioning of interstitial needles, a planning CT was obtained and adjustments of needle position were made in the following applicationif required. With the hybrid applicator in place, an MRI was obtained for BT treatment planning on a 3 Tesla MRI (image 4). All patients followed a bowel preparation and bladder filling protocol to minimize internal organ motion. A planning CT with OAR delineation for dose optimization was performed for every single treatment fraction.

The treatment target volumes: gross tumoral volume (GTV), HR-CTV, and intermediate-risk CTV (IR-CTV) were delineated according to GEC-ESTRO recommendations using an Oncentra Brachy treatment planning software (Elekta, Sweden). OARs such as rectum, bladder, sigmoid colon, and small intestines were defined. The EQD2 of all BT fractions and EBRT fractions were calculated, an α/β of 10 Gy was assumed for target volume and α/β of 3 Gy was used for OARs.

Plan comparison:

To investigate the dose and dose distribution advantages of the applied optimized IC/IS treatment plan, we generated an additional treatment plan (IC_{study}). The IC_{study} plan was optimized by changing the source dwell position and dwell times of the tandem and ovoid only, leaving the interstitial part aside. This optimized IC_{study} plan was not used clinically (image 5). We compared dose volume histogram (DVH) parameters, dose distributions, and source loading patterns of the IC_{study} and the IC/IS_{clinical} treatment plans. Each applied needle was evaluated: we registered the number of needles, the positions through the ovoids, and insertion depths. These needle choices were compared with the location of the HR-CTV. We registered the source dwell times for all active source and dwell

positions of the IC/ISclinical plan. The total and individual needle treatment times per application were calculated and compared with the treatment times of tandem and ovoids.

Follow-up:

Follow-up investigations were carried out 6 and 12 weeks after the last treatment and at 3 months intervals thereafter. Response to treatment was evaluated by clinical examination and by appropriate imaging studies (MRI, CT) 3 months after completion of radiotherapy. Acute side effects of treatment were assessed at least weekly during treatment and late side effects were assessed at time of each follow-up evaluation.

Statistical analyses:

Statistical analyses were conducted using IBM SPSS Statistics 23.0. Patient and treatment characteristics were analyzed using descriptive statistics. The dosimetric differences between the optimized ICstudy plans and the optimized IC/ISclinical plans were calculated for HR-CTV and OARs.

Results:-**Patients, tumor and treatment characteristics:**

The clinical use of the hybrid application system was clinically feasible in the eight patients. The average age was 47.7 years (25-68 years), three patients had stage IIB according to the FIGO 2010 classification, three patients had stage IIIB and two patients had stage IVA. All patients received concomitant radio chemotherapy with a total external radiotherapy dose of 46 Gy on the pelvis, 2 Gy per fraction using a 3D conformal technique, combined with weekly cis-platinum chemotherapy, no patients received external parametrial boost irradiation.

Evaluation:

The evaluation of the response after the end of the concomitant radio chemotherapy was double clinical and radiological by MRI. The clinical size of the tumor residue varied between 3 and 6.2 cm in the major axis with an average of 4.4 cm. Four patients received an MRI the day before the first BT session and three patients received an MRI on the day of the first application applicator in place (table 1).

brachytherapy technique:

The high dose rate brachytherapy (HDR) protocol used was 4x7 Gy in two applications spaced one week apart. The applicator used is Utrecht interstitial or fletcher interstitial 6mm. Four to eight needles were placed per fraction and a total of 152 needles were used for all applications. The choice of number and position of needles was based on the topography of the tumor residue on the MRI and the extent of parametrial infiltration. A suprapubic and endorectal ultrasound exam was performed during the insertion in four patients. Contouring of target volumes is done on MRI in 3 patients and on CT for the other 5 patients, dosimetry is done on CT. (image 6)

Plan comparison :

The average CTV HR volume is 25.15 cc (15-36cc). A single ICstudy treatment plan generated for each application is used to make a dosimetric comparison with the constraints of the hybrid application (IC / IS) (image 7). Significant differences between the IC / IS and IC alone plans were noted: the mean CTV HR D90 was 90.1 Gy (IS/ICstudy) vs 85.36Gy (ICstudy) in EQ2D with α / β of 10. From even, the savings of the organs at risk differed significantly, for the bladder the D2cc is 82.5Gy (IC / IS) vs 95.7Gy (IC) and for the rectum D2cc is 65.5Gy (IC / IS) vs 67.8Gy (IC) in EQ2D with α / β of 3.(table 2)

The follow-up and Clinical results:

The follow-up of the patients did not show a local recurrence with an average follow-up of 26,5 months (15-35 months), three patients experienced distant metastasis two of them died, treatment was well tolerated no bleeding or perforation of organ was noted, only one patient developed rectovaginal fistula.

Discussion:-

MRI-based BT is well established in the treatment of cervical cancer and should be considered clinical standard. Improved imaging allows for a better delineation of target volumes and OARs. More sophisticated delineation frequently results in complex-shaped target volumes that require elaborate means of dose tailoring. However, even with dose optimisation, the CTVHR dose coverage may be compromised when using IC BT in case of large tumours or unfavorable topography between the CTVHR and organs at risk [10]

Historically, various interstitial needle placement techniques have been performed, ranging from free hand to template guided. These were introduced to improve treatment and to reduce local failures in patients with extensive parametrial disease. To date, transperineal template techniques remain the most frequently used methods for interstitial treatment in such cases. However, the main impediments to general acceptance of these methods are: difficulty in achieving accurate positioning of the implant and a good parallelism of the needles, and considerable risk of serious complications (11,12,13).

The use of a hybrid applicator combining IC and IS BT is the best “all-in-one” technical solution available to date and facilitates the implementation of the combined BT in centers without special expertise in free-hand or perineal template-based IS BT

When using IC/IS applicators, the ovoide serves as a “template” and provides a fixed geometry between the tandem and the needles. The “template” (ovoide), as compared with the perineal techniques, lies in proximity to the parametria and thus to the target, resulting in a shorter interstitial path of the needles.

In our study the use of the IC/IS applicators proved to be feasible, we note a prolongation of time needed for implantation and treatment planning, compared with ICBT alone. Moreover, no severe injuries were caused by the implantation procedure. No considerable prolongation of hospitalization time, as compared with ICBT alone. This technique translated into good regional local control in our study.

The actual indication of ICBT, hybrid BT (HBT), and multi-catheter ISBT is a challenging topic which needs clinical experience in order to select the most appropriate brachytherapy modality depending on tumor size and shape [13]. Whatsoever, in our study lateral tumor extent with parametrial involvement or large residual disease was well controlled with HBT.

The number of needles, maximum insertion depth, weight of the needle dwell times compared with other applicator parts, loading pattern in needles, and placement of the needle tip in relation with HR-CTV are still subjects of investigation. Our institutional choices are based on international and institutional experiences and discussions.

Only mono- institutional studies have so far reported clinical outcome of patient cohorts where the IC/IS technique has been systematically applied [14,15]

Our study is in line with the Vienna applicator data (16), Utrecht applicator dose data (17), and the Venezia applicator data (18). The dosimetric gain in our situation for D90 HR-CTV was 4.74 Gy, for the Vienna applicator, a total benefit in dose of 9 Gy has been published, for the Utrecht publication a 4,4 Gy dosimetric gain was noted and for venizia applicator data the dosimetry gain was 9,9 Gy.

A recent analysis from the retroEMBRACE cohort enhanced the importance of meticulous dose tailoring. The study included 610 patients from eight institutions and was able to show that with the systematic use of a combined IC/IS BT, the D90 of HR-CTV significantly increased (83 Gy vs 92 Gy; p=0.01) with no difference in doses to OARs. Fokdal et al. could demonstrate that this was even correlated with an increase of 3-year local control rate in patients with a large HR-CTV volume (30 cm³) [19].

Table 1:- Patient and treatment characteristics.

Age	47.7 years (25-68 years)
Histology	SQUAMOUS CELL CARCINOMA (100%)
Initial stage (FIGO2010)	IIB:3 cases IIIB: 3 cases IVA: 2 cases
Concomitant radio-chemotherapy (CRC)	EBRT: 46 Gy, 2 Gy /Fr, 23 fractions CHEMOTHERAPY: CDDP 40mg/m ² /week
Clinical evaluation after CRC	Vaginal exam = tumor residue 4,4cm (3 - 6,2 cm) Rectal exam = Distal parametrial involvement in all patients
Radiological evaluation after CRC	MRI after CRC

	5 cases:the week before the implant 3 cases:the day of application with applicator in place
Brachytherapy protocol	4x7 Gy in two applications spaced a week apart
Applicator	50 %Fletcher interstitial 6 mm 50 % Utrecht interstitial
Needels	5 by application (4-8)
Depth (median)	4 cm (3 – 5 cm)
Ultrasound control	50% of cases
Acute complications	1 case of intra-mural uterine hematoma
Late complications	1 case of recto-vaginal fistula
Target volume delineation	MRI :3 cases CT : 5 cases
CTV HR volume	25,15 cc (15 - 36 cc)
Dosimetry	CT
Dwell times IC (average)	24,58 sec (9,35 - 41,33)
Dwell times IS (average)	2,3 sec (1,23 - 4)
Follow up (average)	27,25 months (range 18–34). No local relapse 3 distant metastases (2 Deaths)

Table 2:- Plan evaluation for DVH parameters of CTV HR and OARs.

	IC/IS		IC study	
	AVERAGE	INTERVAL	AVERAGE	INTERVAL
EQD2 (Gy) D90 CTV HR (α/β 10)	<u>90,1</u>	80,4-92,8	<u>85,36</u>	72,3-91,4
EQD2 (Gy) D90 CTV IR (α/β 10)	67,4	65,1-69,5	57,6	54,4-61,4
EQD2(Gy) D2cc BLADDER (α/β 3)	<u>82,5</u>	67,8-90,7	<u>95,7</u>	83,7-113,1
EQD2(Gy) D2cc RECTUM(α/β 3)	<u>65,5</u>	61,3-72,6	<u>67,8</u>	58,3-75,2
EQD2(Gy) D2cc SIGMOIDE (α/β 3)	62,2	53,2-76,5	60,8	52,1-67,2
EQD2(Gy) D2cc BOWELL(α/β 3)	60,4	51,5-73,2	60,5	55-70,5



Figure 1:-Utrecht interstitial CT/MR applicator (Nucletron, Veenen- daal, The Netherlands).

Figure 2:- The holes through ovoids are used as a template for interstitial needle placement.

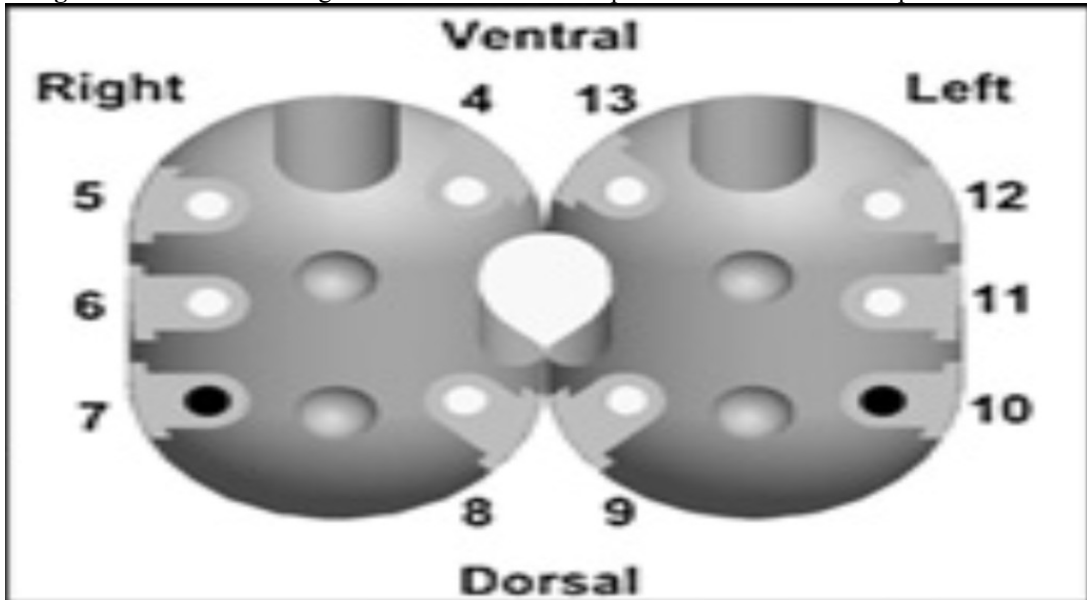


Figure 3:- T2-weighted sagittalMRI to assess treatment response

A: before initial treatment
B: during the last week of EBRT

A

B

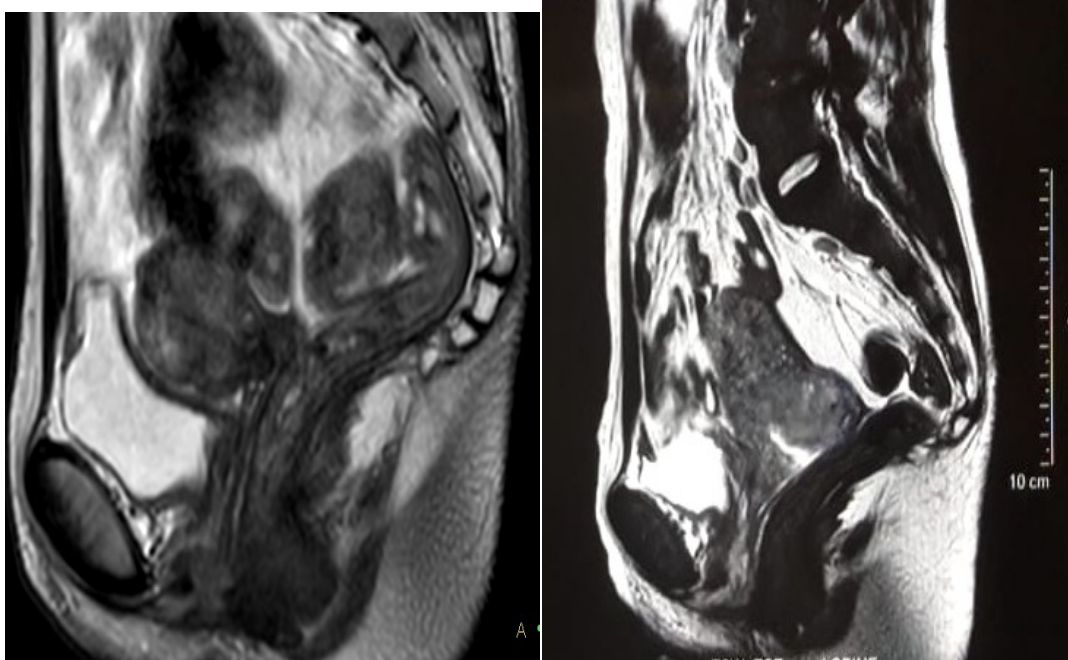


Figure 4:- T2-weighted transverse MRI showing applicator in place with ovoids and inserted needles.

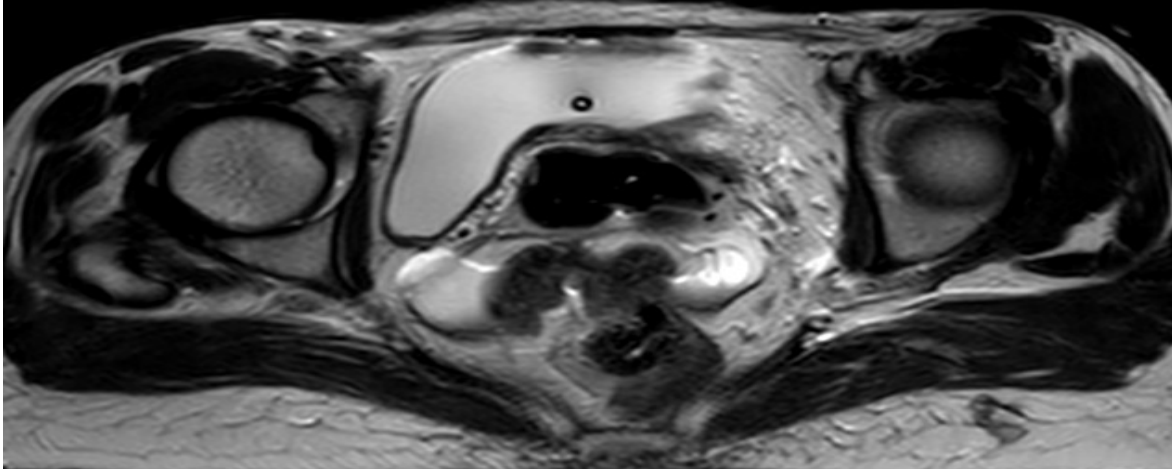


Figure 5:- Combined intracavitary and interstitial brachytherapy technique

1. Spinal anesthesia
2. material preparation with asepsis
3. Placement of a urinary catheter and hysteroscopy,
4. assembly of the interstitial applicator: metal guide, needle holder and needle in the ovoids positions
5. Vaginal applicator is then fixed with the uterine tandem, and introduced into the vagina
6. Using a special gun, we introduce the needles according to the chosen depth
7. Ultrasound check: position of the tandem, needles and search for complications (bladder perforation)
8. numbering of needles position.

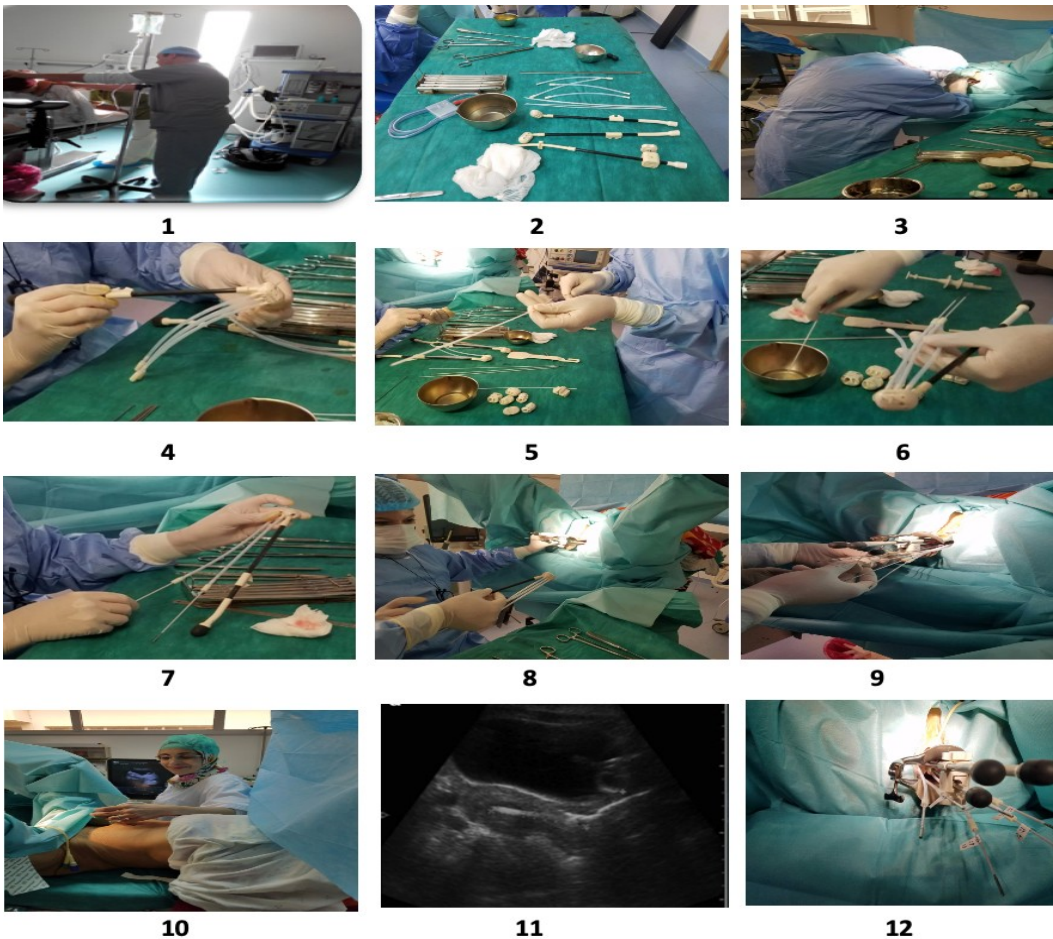
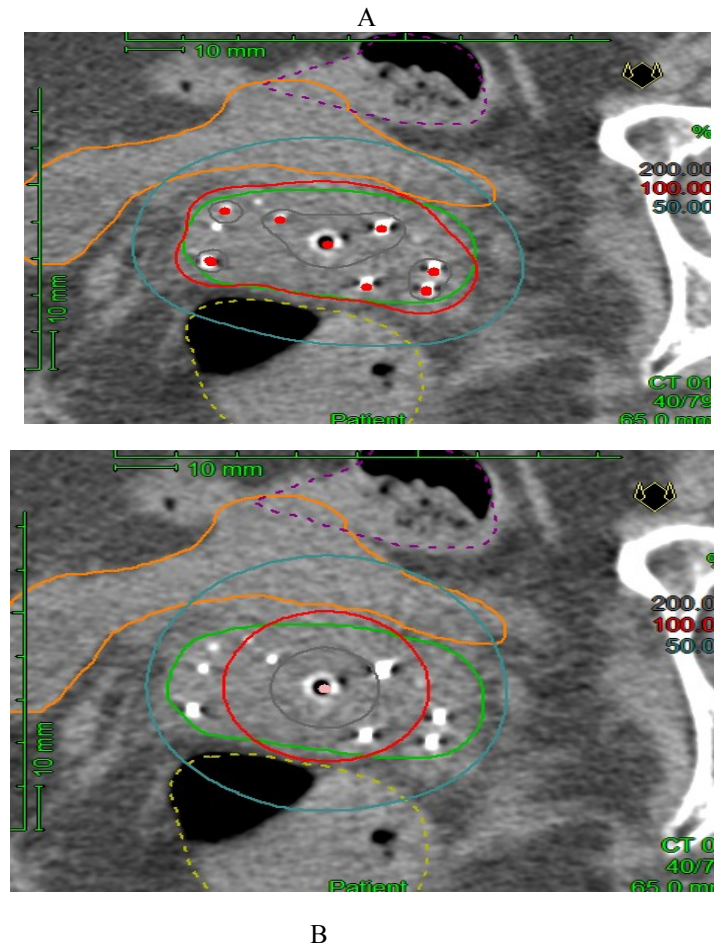


Figure 6:- CT scanner showing CTV HRextension (green), 100% isodose (red), inserted needles, and OARs
 A: IC study plan without activation of needles
 B: IC/IS clinical plan with activation of needles



Conclusion:-

Combined IC/IS BT makes it possible to deliver significantly higher dose to the CTVHR without increasing the dose to bladder, rectum or sigmoid. These dosimetric findings result improved therapeutic index with significantly higher local control for large high-risk target volumes without adding further late bladder, or gastro- intestinal morbidity to treatment.

Abbreviations list:

IC/IS BT: intracavitary/interstitial brachytherapy
 MRI: magnetic resonance imaging
 CT: computed tomography
 HDR BT: high-dose-rate brachytherapy
 CTV HR: high-risk clinical target volume
 EBRT: external-beam radiotherapy
 IGABT: image-guided adaptive brachytherapy
 OAR: organs at risk
 DVH: dose volume histogram
 FIGO: international federation of gynecology and obstetrics
 HBT: hybrid BT

Ethics approval and consent to participate:

Informed consent (verbal) was obtained from all participants. This study was submitted to and approved by research and ethics committee of the national institute of oncology of Rabat.

Competing interests:

We (authors) declare that we have no conflict of interest.

Authors' Contribution:

M. HOMMADI, H. BAKKALI, performed research and share the first position in this manuscript; O. HOUESSO, M. BENLEMLIH collected the clinical data, H. BAKKALI, I. LAHDIRI, S. BOUTAYEB, S. EL MEJJAOUI, H. KACEMI, T. KEBDANI, N. BENJAAFAR designed and coordinated research and drafted the manuscript. All authors read and approved the final manuscript.

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