Original article

Interstitial brachytherapy guided intensity modulated radiation therapy (IBGIMRT) in cervical cancer: a dosimetric study

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Abstract

Purpose: Interstitial brachytherapy (IBT) is used as an alternative to intracavitary radiotherapy in the management of cervical carcinoma. We have devised a new technique called interstitial brachytherapy guided intensity modulated radiotherapy (IBGIMRT) which can potentially reduce doses to organs at risk (OaRs). It utilizes IMRT planning on the target volume (TV) defined by implantation of IBT needles. This study compares the dosimetry of IBT and IBGIMRT.

Material and methods: CT scan images of 18 patients with cervical cancer, who have been already treated by HDR-BT, were used to generate two rival plans, IBT and IBGIMRT, for a prescription dose of 10 Gy. Following dosimetric factors were used for comparison: volume receiving 95% of prescription dose (V_{95}), conformity index (COIN) and external volume index (EI) for target and for OaR, dose received by volume of 1 cm^3 (D_{1cc}), 2 cm^3 (D_{2cc}), 5 cm^3 (D_{5cc}) and also volume receiving 50% and 75% of prescription dose (V_{50} and V_{75}).

Results: The two plans resulted in COIN difference of 49.8% ($p < 0.0001$) and EI difference of 36.4% ($p < 0.0028$) in favor of IBGIMRT. Mean D_{1cc}, D_{2cc} and D_{5cc} values for bladder were 8.3 Gy, 7.6 Gy and 6.4 Gy; and 7.8 Gy, 7.3 Gy and 5.8 Gy with IBT and IBGIMRT, respectively ($p > 0.05$). Similar figures for rectum with IBT vs. IBGIMRT were 11.2 Gy vs. 7.02 Gy, 10.5 Gy vs. 6.4 Gy and 9.1 Gy vs. 4.8 Gy respectively ($p < 0.01$).

Conclusions: Our novel technique, IBGIMRT, has shown its dosimetric superiority and therefore needs to be studied in clinical set up.

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Key words: cervical cancer, interstitial brachytherapy, HDR, dosimetry.

Purpose

Cervical cancer is mainly treated by radiotherapy which consists of external beam radiation therapy (EBRT) and intracavitary radiation therapy (ICRT). Due to technological advances, EBRT is becoming highly conformal. Intensity modulated radiation therapy (IMRT), a form of conformal radiation therapy, is increasingly being used nowadays in cervical cancer since several studies have reported dosimetric and clinical benefit over conventional whole pelvis EBRT [1-7]. Though ICRT is an integral part of treatment, IMRT is posing a challenge to it. It is being debated whether IMRT could replace ICRT. Interstitial brachytherapy (IBT) is used as an alternative to ICRT in patients with extensive disease in the cervix, obliteration of the cervical os, narrow vagina, extension of disease into the lower vagina and parametrical disease beyond the high dose range of the intracavitary applicators. Even though IBT is a better option in such patients, the associated morbidity due to physical injury and radiation dose to organs at risk (OAR) still remains a concern [8, 9]. IMRT, which has been suggested to replace ICRT, can potentially further reduce the OAR doses [10]. Concomitant use of IBT and IMRT will synergize the potential benefits, physical and biological, of both. For this, we have devised a new technique called interstitial brachytherapy guided intensity modulated radiotherapy (IBGIMRT) which can be highly conformal. This technique utilizes the IMRT planning on the tumor volume defined by implantation of IBT needles. Before its clinical application, we conducted a dosimetric study for comparing the treatment plans of IBT and IBGIMRT.

Material and methods

CT scan images of 18 patients with primary cervical carcinoma stage IIIB, who have been already treated by high dose rate (HDR) IBT following whole pelvis EBRT,

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were used for this study. The EBRT dose schedule consisted of 40 Gy in 22 fractions over 5.5 weeks to whole pelvis with four field box technique followed by 10 Gy in 5 fractions over 5 days with midline shield (split field). Following EBRT, they were assessed for standard ICRT application (HDR 7 Gy × 3, weekly) and were found unsuitable due to various geometrical and dosimetric reasons. We decided to treat them by IBT (2 sessions of HDR 10 Gy each, one week apart) instead of standard ICRT.

Brachytherapy procedure

The implant was performed under spinal/epidural anesthesia using Martinez Universal Perineal Interstitial Template (MUPIT) with the assistance of trans-rectal ultrasonography (TRUS). Foley's tri-lumen urinary catheter was inserted and the bulb was inflated with 7 cm^3 of contrast material (2 cm^3 Hypaque and 5 cm^3 of normal saline). Thorough clinical examination and TRUS imaging of the pelvis was done before inserting the stainless steel needles with blind ends. Number of needles to be inserted was determined by the target volume decided by pretreatment clinical and radiological (CT/MRI) findings as well as operative clinical & TRUS findings. Needle injury to various pelvic organs like urinary bladder, rectum and small bowel was avoided as they were well visualized on TRUS. Thus the target area was adequately covered by the needles, maintaining adequate distance from the normal structures. Generally, average of 18 needles (range 14-26) were implanted. After the completion of the needle implantation, template was fixed to the perineal skin with the help of stitches. The patient was treated using Microselectron® HDR remote afterloading unit after IBT plan approving. A dose of 10 Gy was delivered and the template was removed immediately after completing the treatment. After a gap of 1 week another implant was repeated for delivering 10 Gy.

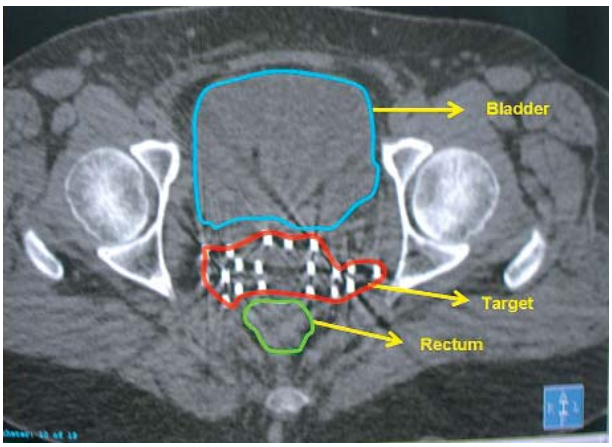

Fig. 1. CT scan image showing the interstitial brachytherapy needles, contouring of target volume, bladder and rectum

Treatment planning

A planning CT scan of the whole pelvis was done with slice thickness of 2.5 mm. Brachytherapy planning was performed in PLATO planning system, version 14.1 (Nucletron®, Netherlands) where target and OaR were delineated. The contour drawn by the line joining the outermost needles on the each CT slice constituted the boundary of the target (Fig. 1). However the cranio-caudal extent of the target was decided by selecting the length of needles keeping in mind the clinical findings. Due to overlapping of the target and OaR volumes, minimal modifications were done while finalizing the target volume. Once the target volume and OaR volumes were finalized, the same were transferred to external beam IMRT Eclipse planning system (version 7.35, Varian Medical System®, USA) through DICOM-RT. For IBT planning, implant needles were also marked on each slice in order to reconstruct the needle length. Simultaneously two comparative plans were generated, one each on Plato (IBT) and Eclipse (IBGIMRT) for a prescription dose 10 Gy to the target. For IBT plan, step size of 2.5 mm was selected. Only dwell positions within the target volume were activated. If needed, optimization was done to achieve the best plan. For IMRT plan, 7-9 co-planar 6 MV photon beams (MLC width 10 mm, dynamic IMRT) were chosen. Dose constraints were set to minimize the volume of normal tissue receiving the prescription dose without compromising target coverage.

Dosimetric comparison

Dose conformality and normal tissue avoidance were used to compare the two rival plans. Following dosimetric indices were used for comparison: volume receiving 95% of prescription dose (V_{95}), conformal index (COIN) and external volume index (EI) for target. COIN is a unique index that accounts for the entire dose inside the treated volume, not just inside the target volume, but also outside of any contoured structures. We calculated the COIN by using the following formula [11]:

$$\frac{(TV_{ref}/TV)}{(TV_{ref}/V_{ref})}$$

TV_{ref} was defined as the volume within target volume (TV) that was also within the referenced isodose, and V_{ref} was defined as the volume (inside and outside of TV) within the reference isodose.

EI was defined as the ratio of the volume of normal tissue that received a dose equal to or greater than the reference dose to the target volume [12].

For OaR, dose received by volume of 1 cm^3 (D_{1cc}), 2 cm^3 (D_{2cc}), 5 cm^3 (D_{5cc}) and also volume received by 50% (V_{50}) and 75% (V_{75}) of prescription dose were evaluated for both bladder and rectum.

Statistical analysis

The statistical analysis was done using paired t-test and a p-value of < 0.05 was considered significant.

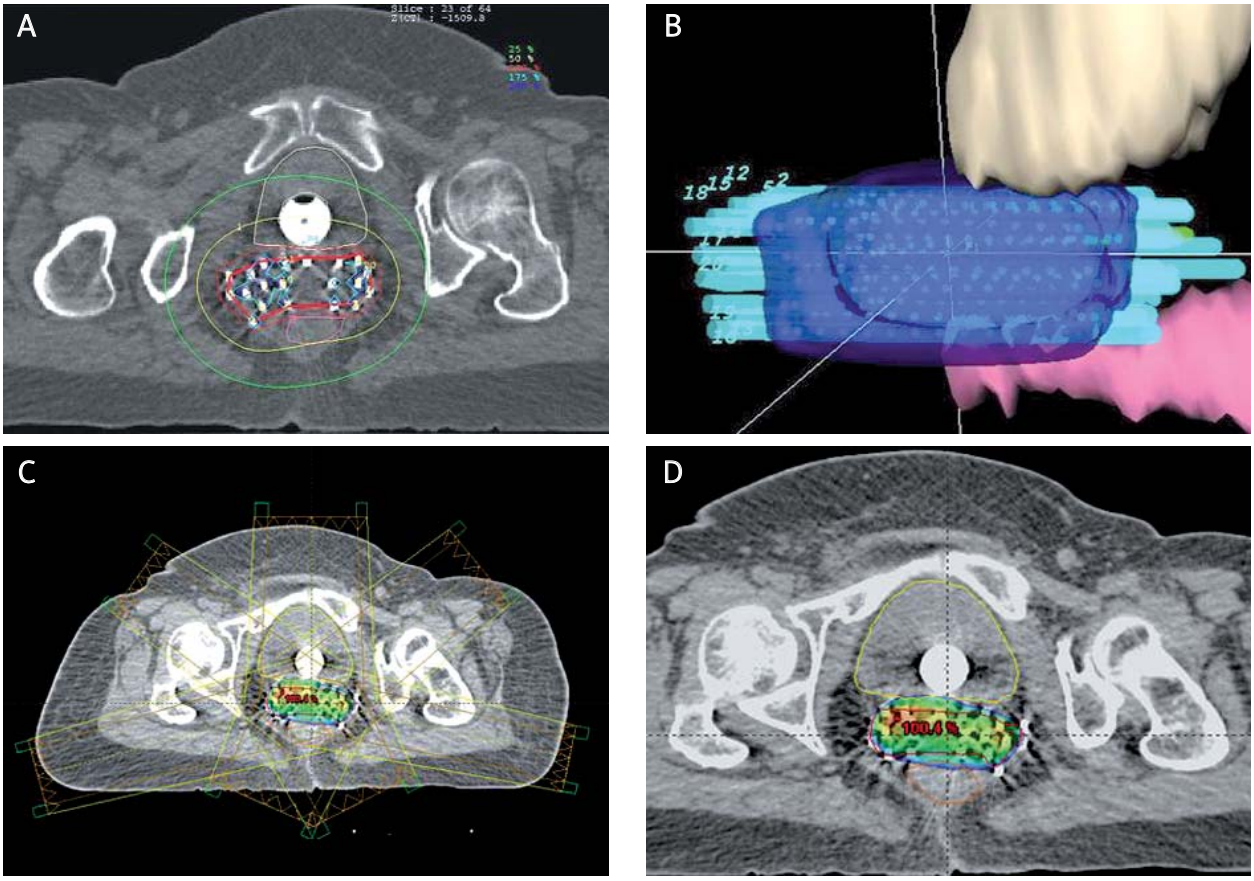

Fig. 2. Example of a patient showing the comparison of two plans. (A) shows the distribution by HDR IBT plan on Plato system. Target volume is shown by thick red color line while prescription isodose line is shown by thin red line outer to target. (B) shows the three dimensional view of the same plan. (C) IMRT plan of the same patient with 7 beam arrangement. (D) IMRT dose distribution of the same patient

Results

Figure 2 demonstrates the example of a patient planned by both IBT and our new technique IBGIMRT. The mean value with standard deviation for all target conformality indices (COIN, EI and V_{95}) are shown in Table 1. The percentage difference was calculated with respect to IBT plan. Both plans provided good target coverage, but overall conformality was better with IBGIMRT. Though the V_{95} was better with IBT, COIN and EI were better with IBGIMRT. The maximum difference in V_{95} between IBT and IBGIMRT plans was 20.1% which was statistically

Table 1. Comparison between IBT and IBGIMRT planning

IBT			IBGIMRT	
Target				
V_{95} (in cc)	95.1 ±17.6		90.4 ±16.5	
COIN	0.61 ±0.02		0.72 ±0.05	
EI	0.59 ±0.05		0.09 ±0.01	
OAR	**Bladder**	**Rectum**	**Bladder**	**Rectum**
D_{1cc} (in Gy)	8.3 ±1.8	11.2 ±0.56	7.8 ±0.02	7.02 ±0.23
D_{2cc} (in Gy)	7.56 ±2.1	10.53 ±0.51	7.3 ±0.52	6.4 ±0.29
D_{5cc} (in Gy)	6.4 ±2.4	9.06 ±0.54	5.8 ±1.4	4.8 ±0.41
V_{50} (in cc)	12.5 ±1.7	4.3 ±0.45	10 ±1.04	2.8 ±0.9
V_{75} (in cc)	1.38 ±0.48	1.0 ±0.23	1.08 ±0.5	0.5 ±0.2

IBT – interstitial brachytherapy, IBGIMRT – interstitial brachytherapy guided intensity modulated radiotherapy

significant ($p < 0.0047$). The similar difference in COIN was 49.8% ($p < 0.0001$). The maximum difference in EI between IBT and IBGIMRT plan was 36.4% ($p < 0.0028$).

Comparison of the dose volume histograms for OaR (bladder and rectum) by two rival plans resulted in overall better avoidance of OaR with IBGIMRT. As shown in Table 1, Mean D_{1cc}, D_{2cc} and D_{5cc} values for bladder were 8.3 Gy, 7.6 Gy and 6.4 Gy; and 7.8 Gy, 7.3 Gy and 5.8 Gy with IBT and IBGIMRT, respectively; however the difference was not statistically significant ($p > 0.05$). Similar observations for rectum with IBT vs. IBGIMRT were 11.2 Gy vs. 7 Gy, 10.5 Gy vs. 6.4 Gy and 9.1 Gy vs. 4.8 Gy respectively and the difference was statistically significant for all the values ($p < 0.01$). The V_{50} and V_{75} values for bladder were slightly better with IBGIMRT as compared to IBT but statistically no significant. Similar values for rectum were significantly low with IBGIMRT ($p < 0.005$).

Discussion

There is an emerging feeling among the radiation oncologists worldwide that IMRT has a potential of replacing the most brachytherapy (BT) treatments whether it is ICRT for cervix or IBT for prostate cancer. Though studies relating cervical cancer have already shown the benefit of IMRT over conventional EBRT in terms of dosimetry and toxicity, there are very few studies comparing ICRT and IMRT [13-15], and none comparing the IBT and IMRT.

A study by Roeske *et al*. [13] evaluated the use of IMRT as a replacement for BT in cervical cancer by generating boost plans in 10 patients. Though the study did not compare directly the ICRT and IMRT dosimetry, authors found that a total dose of 79 Gy was possible (45 Gy pelvic RT plus a 34 Gy IMRT boost). Subsequently, a study by Low *et al*. [14] compared the dosimetry of ICRT with IMRT. They observed that IMRT dose distributions covered point A isodose surfaces while reducing the dose to the bladder and rectum. In a patient with unfavorable anatomy, significantly better dose coverage of the target tissues was achieved with IMRT compared with ICRT. Kavanagh *et al.* [15] used IMRT instead of ICRT, adopting simultaneous integrated boost IMRT (SIBIMRT) technique and reported that bladder and rectum doses were significantly better with the use of IMRT. Based on these 3 reports, the issue of IMRT replacing BT in cervical cancer is being debated with arguments in favor and against [16, 17]. Mundt [17] has speculated that IMRT may entirely replace the BT in cervix.

So far, there is no study in the literature comparing IBT and IMRT in cervix. IBT plays an important role in patients not eligible for ICRT. It delivers a concentrated dose of radiation to the target area; and minimal dose to OAR as compared to ICRT. Though, in use for last 30 years or so, it had not gained wide popularity neither among patients or radiation oncologists due to various reasons: invasive & cumbersome procedure, lack of expertise, associated morbidity and lack of convincing data. Various series [8, 9] on IBT in gynecological malignancies, primary as well as recurrent, have reported 4-18% risk of severe late toxicity like recto-vaginal fistulas. On the contrary, IMRT has many attractive features making it convenient to both patients and physicians. Considering the increasing popularity of IMRT and emerging data on BT-IMRT comparison in various sites like breast [18, 19] and prostate [20], IBT in cervix is likely to face, sooner or later, a stiff challenge. Both techniques have good potentials and we believe in their complementary use rather than substitute of each other. With this aim, we have proposed a new technique, IBGIMRT. Before its clinical use, we have conducted the present study for testing its dosimetric superiority by comparing with IBT.

Ours is a unique study since no study in the literature, so far, has compared, directly or indirectly, IBT with IMRT (IBGIMRT) in cervical cancer. For a strict and head to head comparison, we have tried to keep many factors constant. We have kept the target volume same for both plans even though, a certain margin outside the CTV, for creating PTV, is mandatory in IMRT planning for countering the day to day setup errors. In brachytherapy planning, CTV and PTV are mostly same. We have chosen 10 Gy as the prescription dose since our treatment protocol uses IBT of HDR 10 Gy each in 2 sessions, one week apart.

The results of our dosimetric study in 18 patients have shown that IBGIMRT in comparison to IBT provided significantly better overall conformality and reduced doses to OaR, proving its dosimetric superiority. Rectum experienced better dose reduction as compared to bladder. Since rectum is more susceptible to radiation injury, this dose reduction can be of good help in clinical practice. Some of the indices are better with IBT (V_{95}) and hence our hypothesis of combining the two techniques seems justifiable.

The first advantage of this new technique is better definition of the target area. The visualization of the tumor, especially the parametrial disease, on the CT/MRI scan is not very good. With our technique, while the IBT needles are being inserted under anesthesia, there is a better clinical appreciation of the pelvic disease. Simultaneously the real time use of TRUS provides additional information of the tumor and pelvic structures. Correlation of this clinical disease assessment during anesthesia with imaging findings helps in better definition of the target volume.

Secondly, the IBT treatment is usually fractionated spread over 2-3 days. During the course of IBT, the patient is treated by external beam IMRT on the IBGIMRT plan. The 50% of the treatment is carried out with IBT and rest with IBGIMRT with similar dose per fraction and number of fractions. The proportion of the two may be changed according to the respective dosimetric evaluations. For example in a given patient, if IBT dosimetry is equally good or better, then higher dose may be given by IBT and rest by IMRT. Thus, various biological and physical advantages of both are exploited in order to improve the clinical outcome.

Thirdly, various pelvic structures especially uterus, cervix and hence the tumor are mobile structures since they are suspended by the ligaments. Movements of these structures can be detrimental in the treatment like IMRT. The IBT needles in situ fix the target region and hence minimize the risk of target movement which is key to any radiation treatment especially EBRT and more so,

treatment like IMRT. For the same reason, we have kept the target volume same for both IBT and IBGIMRT planning in this present study.

As it happens with every new technique, we expect readers to question some of the points in our new technique, IBGIMRT. For example, all forms of conformal EBRT treatments (like IMRT); require application of strict immobilization devices which might be problematic in a patient having implant needles in situ. During the IMRT treatment, IBT needles might interfere with the dose delivery. But these shortcomings can be slowly overcome in the subsequent study involving its clinical use.

To conclude, the novel technique IBGIMRT devised by us has shown it's dosimetric superiority over IBT in cervical cancer. It is worth conducting a clinical study for testing its clinical utility.

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