ORIGINAL ARTICLE

Computed Tomography-based Three-dimensional Image-guided Brachytherapy for Cancer of the Cervix Uteri

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ABSTRACT

Objective: To clarify the treatment results of three-dimensional (3D) image-guided brachytherapy (IGBT) for cancer of the cervix uteri in Hong Kong.

Methods: Between January 2014 and June 2016, 52 patients underwent computed tomography (CT)-based 3D IGBT, in which three patients had interstitial needles inserted. Contouring was done with dose volume parameters recorded, as recommended by the GEC-ESTRO guidelines. Recorded parameters included HRCTV D90 mean dose (dose delivered to 90% of the high-risk clinical target volume), HRCTV V100 (percentage of HRCTV receiving 100% of the prescribed dose), and D2cc (minimum dose in the most exposed 2 cm³ volume) of rectum, sigmoid colon, and bladder. One-way analysis of variance with Bonferroni’s multiple comparison post-hoc tests for normally distributed data or Dunn’s multiple comparisons test were used to assess any statistically significant differences.

Results: The HRCTV D90 mean doses in 2014, 2015, and 2016 were 75.1 Gy, 77.8 Gy and 82.1 Gy, respectively. The corresponding HRCTV V100 values were 88.7%, 91.6%, and 94.4%, respectively. The HRCTV D90 value in 2016 was found to be significantly higher than that in 2014. The D2cc value of sigmoid colon in 2016 was significantly lower than that in 2014 or 2015. The D2cc value of bladder in 2016 was significantly higher than that in 2015 but still within acceptable limits. None of the patients developed grade 3 to 4 acute radiation toxicities. There was one patient with persistent disease in the cervix after radiotherapy, three patients with distant failure, and one patient with both local and distant failure.

Conclusion: The CT-based 3D IGBT treatment for cancer of the cervix uteri with interstitial needle insertion is feasible in the local setting. There is potential to give higher dosages to the HRCTV by the 3D IGBT technique, while the doses to organs at risk can still be limited to acceptable levels.

Key Words: Brachytherapy; Radiation dosage; Radiotherapy, image-guided; Uterine cervical neoplasm

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Ethics Approval: This study was approved by the HKU/HA HKW IRB (Ref UW 19-542), and that consent requirement was waived.
INTRODUCTION

For premenopausal women with early-stage cancer of the cervix uteri (FIGO [International Federation of Gynecology and Obstetrics] stages IA and IB1, non-bulky \(\leq 4\) cm stage IIA), surgery is preferred because of its more favourable toxicity profile (eg, it can preserve ovarian function and avoid vaginal stenosis). However, primary radiotherapy (± concurrent chemotherapy in indicated cases) followed by brachytherapy may be a better option, particularly in postmenopausal patients or those with high-risk disease (FIGO stages IB2, bulky >4 cm IIA, IIB-IVA).\(^1,2\)

Three-dimensional image-guided brachytherapy (3D IGBT) has been established in an increasing number of centres both internationally and locally in Hong Kong, but the treatment results of 3D IGBT have not been studied locally. Moreover, various international guidelines on three-dimensional brachytherapy planning have already been published, and 3D IGBT can result in much better delineation between tumour and normal tissue.\(^3\) A conventional two-dimensional (2D) X-ray-based technique was previously used in the Department of Clinical Oncology, Queen Mary Hospital for all brachytherapy planning for cancer of the cervix uteri. In 2014, computed tomography (CT)–based 3D IGBT for cancer of the cervix uteri was implemented in our department. The CT scanner is located inside our brachytherapy room, so that applicator insertion and CT image acquisition can be done at the same location to minimise patient mobilisation, thus lowering risk of applicator displacement and maximising patients’ comfort. We have published our initial experience in a separate article.\(^4\) Starting from December 2015, we have expanded interstitial needle insertion to at least bulky stage IIB disease (tumour width \(\geq 6\) cm at 0-1 cm from cervical os and/or tumour width \(>4\) cm at \(\geq 1\) cm from cervical os). This will hopefully further improve our therapeutic ratio with the potential of dose escalation.

The aim of the present single-centre study was to clarify the efficacy of CT-based 3D IGBT for cancer of the cervix uteri in Hong Kong.

METHODS

Data were collected from our in-house patient database.
All patients with cancer of the cervix uteri treated with 3D IGBT at Queen Mary Hospital, Hong Kong, between January 2014 and June 2016 were included. The two patients who did not have all four brachytherapy treatments planned using 3D IGBT technique were excluded from statistical analyses for simplicity. This will be further specified below.

All patients received four sessions of brachytherapy: one fraction per day, two fractions per week (on 2 non-consecutive days) over 2 weeks. Patients selected for interstitial needle insertion had pre-IGBT planning with reference to the pre-brachytherapy magnetic resonance imaging (MRI). Schematic diagrams of the tumour size and contour were drawn, specifying the position of each required interstitial needle and their planned insertion depth. Each brachytherapy treatment was done under general anaesthesia (from applicator insertion, CT image acquisition, contouring, dosimetry optimisation, and radiation delivery to applicator removal). Either a New Rotterdam or Utrecht applicator (ovoid, tandem interstitial needles) was used. A Nucletron microSelectron® HDR was used as an afterloader. A Foley’s urinary catheter was inserted before applicator insertion. Patients were instructed to take oral bisacodyl 10 mg and use a per rectal fleet enema the night before the procedure to ensure bowel emptying.

The high-risk clinical target volume (HRCTV) and organs at risk including rectum, sigmoid colon, and bladder were contoured according to Group Européen de Curiethérapie–European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) guidelines.\textsuperscript{5,6} The contours were then transferred to the brachytherapy planning software (Oncentra® system; Elekta AB, Sweden), in which physicists and doctors would manually modify the source positions and dwell times to optimise the dosimetry plan. These planning steps were repeated for each brachytherapy treatment, and a new plan was used each time.

As recommended by GEC-ESTRO guidelines for IGBT, we recorded HRCTV D90 (i.e. the dose delivered to 90% of HRCTV) mean dose, HRCTV V100 (percentage of the HRCTV receiving 100% of the prescribed dose [6.5 Gy]), and D2cc (the minimum dose in the most exposed 2 cm³ volume) of rectum, sigmoid colon, and bladder in each brachytherapy dosimetry plan.\textsuperscript{5,6} We aimed to achieve at least 6.5 Gy per fraction in the HRCTV D90 while limiting the D2cc of rectum and sigmoid colon to 4.8 Gy and that of bladder to 6.5 Gy if possible (some degrees of deviation were allowed to achieve a reasonable dose to the HRCTV D90). We chose this planned dose for the HRCTV based on the GEC-ESTRO protocol (which suggests that the dose to cure macroscopic disease corresponding to HRCTV range of 75-90 GyEQD2, and above).\textsuperscript{2} Tanderup et al. also reported that HRCTV D90 ≥85 Gy delivered in 7 weeks provides 3-year control rates of >94% in an HRCTV of limited size (20 cc), >93% in one of intermediate size (30 cc), and >86% in one of large size (70 cc). We chose the constraints regarding organs at risk according to the GEC-ESTRO protocol, which uses 90 GyEQD2 for bladder and 70 GyEQD2 for rectum and sigmoid colon.\textsuperscript{9}

Statistical analysis (Kolmogorov-Smirnov Test for Normality, one-way analysis of variance with Bonferroni’s multiple comparison post-hoc tests for data with normal distribution – D2cc of bladder; Dunn’s multiple comparisons tests otherwise – HRCTV D90 mean dose, D2cc of rectum / sigmoid, HRCTV V100) was used to determine whether there are any statistically significant differences in HRCTV D90 mean dose, HRCTV V100, or D2cc of rectum, sigmoid colon and bladder between the years 2014, 2015, and 2016.

RESULTS

Between January 2014 and June 2016, 52 patients with cervical cancer were treated with 3D IGBT (No. of 3D IGBT plans: 206). One out of these 52 patients omitted her fourth brachytherapy session, and another patient had her fourth brachytherapy done using a 2D planning technique due to changes in the patient’s condition and logistic reasons, respectively. Three patients had interstitial needles inserted (No. of plans: 11, No. of needles inserted: 3-4 per plan, 3.2 needles per plan on average). The median age of all 52 patients was 55 years (range, 28-83 years).

The patients’ clinicopathological features are shown in Table 1. Thirty-seven (71%) patients had squamous cell carcinoma, whereas 15 (29%) patients had adenocarcinoma, of whom three (6%) patients had adenosquamous carcinoma. Seven patients had FIGO stage IB1, three had stage IB2, four had stage IIA1, seven had stage IIA2, 13 had stage IIB, three had stage IIIA and 15 had stage IIIB disease. One out of the three patients who had interstitial needle insertion was at stage IIIA, and the other two were at stage IIIB. The tumour sizes of all 52 patients ranged from 2.3 cm to 8.5 cm, with 23 (44%) of the tumours being >5 cm in diameter, whereas the tumour sizes in the patients with interstitial...
Table 1. Clinicopathological features of patients who received three-dimensional image-guided brachytherapy.

<table>
<thead>
<tr>
<th>FIGO stage</th>
<th>No. of patients</th>
<th>Histology</th>
<th>Positive LNs</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Adenocarcinoma</td>
<td>Squamous cell carcinoma</td>
<td>Local</td>
</tr>
<tr>
<td>IB</td>
<td>10</td>
<td>4*</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>IIA/B</td>
<td>24</td>
<td>7</td>
<td>17</td>
<td>1 (Adenocarcinoma)</td>
</tr>
<tr>
<td>IIIA/B</td>
<td>18</td>
<td>4†</td>
<td>14</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: FIGO = International Federation of Gynecology and Obstetrics; LNs = lymph nodes.
* Include 2 cases of adenosquamous carcinoma.
† Include 1 case of adenosquamous carcinoma.

Table 2. Dosimetry for three-dimensional image-guided brachytherapy.

<table>
<thead>
<tr>
<th></th>
<th>Mean dose (EQD2)</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRCTV D90</td>
<td>77.9 Gy</td>
<td>75.1 Gy</td>
<td>77.8 Gy</td>
<td>82.1 Gy</td>
</tr>
<tr>
<td>D2cc rectum</td>
<td>67.4 Gy</td>
<td>67.6 Gy</td>
<td>66.8 Gy</td>
<td>68.5 Gy</td>
</tr>
<tr>
<td>D2cc sigmoid</td>
<td>70.5 Gy</td>
<td>74.6 Gy</td>
<td>71.0 Gy</td>
<td>63.7 Gy</td>
</tr>
<tr>
<td>D2cc bladder</td>
<td>76.9 Gy</td>
<td>76.6 Gy</td>
<td>74.2 Gy</td>
<td>83.4 Gy</td>
</tr>
<tr>
<td>HRCTV V100</td>
<td>91.3%</td>
<td>88.7%</td>
<td>91.6%</td>
<td>94.4%</td>
</tr>
</tbody>
</table>

The two patients who did not have all four brachytherapy treatments planned using 3D IGBT technique were excluded from the following statistical analysis for simplicity.

The HRCTV D90 mean doses in 2014, 2015, and 2016 were 75.1 Gy, 77.8 Gy, and 82.1 Gy, respectively. The corresponding HRCTV V100 values were 88.7%, 91.6%, and 94.4%, respectively. The full course EQD2 of D2cc values of rectum, sigmoid colon, and bladder are shown in Table 2.

The HRCTV D90 mean dose in 2016 was significantly higher than that in 2014. No statistically significant difference in D2cc of rectum was observed over these 2.5 years. The D2cc value of sigmoid colon in 2016 was significantly lower than that in 2014 or 2015. The D2cc value of bladder in 2016 was significantly higher than that in 2015 but still within acceptable limits (Table 3).

Table 3. Dosimetric comparison between 2014, 2015 and 2016.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HRCTV D90</td>
<td>NS (p = 0.0914)</td>
<td>NS (p = 0.0625)</td>
<td>p = 0.0003</td>
</tr>
<tr>
<td>D2cc rectum</td>
<td>NS (p ≥ 0.9999)</td>
<td>NS (p ≥ 0.9999)</td>
<td>NS (p ≥ 0.9999)</td>
</tr>
<tr>
<td>D2cc sigmoid</td>
<td>NS (p = 0.395)</td>
<td>p = 0.0081</td>
<td>p = 0.0002</td>
</tr>
<tr>
<td>D2cc bladder</td>
<td>NS (p ≥ 0.9999)</td>
<td>p = 0.0365</td>
<td>NS (p = 0.2512)</td>
</tr>
<tr>
<td>HRCTV V100</td>
<td>NS (p = 0.0696)</td>
<td>NS (p = 0.1966)</td>
<td>p = 0.0011</td>
</tr>
</tbody>
</table>

Abbreviations: D2cc = minimum dose in the most exposed 2 cm³ volume; EQD2 = 2 Gy equivalent dose; HRCTV D90 = dose delivered to 90% of the high-risk clinical target volume; HRCTV V100 = percentage of HRCTV receiving 100% of the prescribed dose (6.5 Gy); NS = non-significant.

Table 4. Comparison of overall survival rates and local control rates in different studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>3-year</th>
<th>5-year</th>
<th>Local control</th>
<th>Distant control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tan et al.</td>
<td>74%</td>
<td>65%</td>
<td>91%</td>
<td>89%</td>
</tr>
<tr>
<td>French study</td>
<td>77%</td>
<td>69%</td>
<td>80%</td>
<td>78%</td>
</tr>
<tr>
<td>STIC study</td>
<td>78.5%</td>
<td>74%</td>
<td>85%</td>
<td>75%</td>
</tr>
</tbody>
</table>

Abbreviations: D2cc = minimum dose in the most exposed 2 cm³ volume; EQD2 = 2 Gy equivalent dose; HRCTV D90 = dose delivered to 90% of the high-risk clinical target volume; HRCTV V100 = percentage of HRCTV receiving 100% of the prescribed dose (6.5 Gy); NS = non-significant.


Table 4. Dosimetry for three-dimensional image-guided brachytherapy at our centre and comparison with other studies.8-10

<table>
<thead>
<tr>
<th>Mean dose (EQD2)</th>
<th>Present study</th>
<th>Tan et al4</th>
<th>RetroEMBRACE5</th>
<th>French STIC6†</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRCTV D90</td>
<td>77.9 Gy</td>
<td>84 Gy</td>
<td>87 Gy</td>
<td>73.1 Gy</td>
</tr>
<tr>
<td>Mean HRCTV</td>
<td>49.1 cc</td>
<td>20.5 cc</td>
<td>37 cc</td>
<td>35.2 cc</td>
</tr>
<tr>
<td>D2cc rectum</td>
<td>67.4 Gy</td>
<td>58.5 Gy</td>
<td>64 Gy</td>
<td>61.0 Gy</td>
</tr>
<tr>
<td>D2cc sigmoid</td>
<td>70.5 Gy</td>
<td>69.1 Gy</td>
<td>66 Gy</td>
<td>58.1 Gy</td>
</tr>
<tr>
<td>D2cc bladder</td>
<td>76.9 Gy</td>
<td>75.5 Gy</td>
<td>81 Gy</td>
<td>69.5 Gy</td>
</tr>
</tbody>
</table>

Abbreviations: D2cc = minimum dose in the most exposed 2 cm3 volume; EQD2 = 2 Gy equivalent dose; HRCTV D90 = dose delivered to 90% of the high-risk clinical target volume.

* Only the first fraction from every patient was evaluated.
† Only showing the data from their Group 3. Patients from their Groups 1 and 2 received surgery. The treatment regimen for patients in their Group 3 consisted of external beam radiotherapy concurrent with chemotherapy, followed by brachytherapy; hence, it is the same as that received by our included patients.

mean HRCTV. In the RetroEMBRACE study, 80.9% of the patients underwent 3D IGBT based on MRI guidance. Hegazy et al11 suggested that the volumes of CT-based HRCTVs were significantly larger than the volumes of MRI-based HRCTVs. Hence, it is possible that our tumour sizes were overestimated, leading to an apparently lower HRCTV D90 mean dose. Moreover, 14 out of 40 (35%) patients in Tan et al had tumours > 5 cm, while in our centre, 23 (44%) patients had tumours in that size range. In the RetroEMBRACE study, 262 (45.1%) patients had tumours ≥5 cm. (The French STIC study did not include tumour width in their published data.)

There was a significant improvement in our HRCTV D90 mean dose in 2016 compared with that in 2014. The D2cc value of sigmoid colon was also improved in 2016 compared with either the 2014 or 2015 data. The D2cc values of rectum and bladder showed no significant differences between 2014 and 2016. The D2cc value of bladder in 2016 was significantly higher than that in 2015, but it was still within acceptable limits. Hence, tumour coverage was not simply improved at the expenses of the dosage received by the organs at risk.

The improvement in our HRCTV D90 mean dose is likely due to partial contributions from experience accumulated over the past 2.5 years and implementation of interstitial needle insertion since December 2015. Fokdal et al12 showed that the combined use of intracavitary and interstitial applicators can improve the therapeutic ratio compared with use of intracavitary applicators alone. They showed that the HRCTV D90 value was improved from 83 Gy to 92 Gy (p < 0.01) with no differences in doses to organs at risk found. They also showed that the 3-year local control rate in patients with HRCTV ≥30 cc was 10% higher (p = 0.02) in the group using combined intracavitary and interstitial applicators.

In addition to the 3D IGBT planning technique, there are other means to improve dosimetry, such as bladder volume control. Bladder volume control may potentially improve bladder volume consistency.13 This may result in reduced radiation dose to the surrounding bowel while not affecting the dose to the HRCTV, thus potentially reduce toxicity without compromising treatment outcomes.

Other modalities for image-based brachytherapy have emerged, such as MRI, CT-MRI hybrid, and ultrasound, with respective benefits and outcomes data available.14-19 Owing to resource and manpower limitations, MRI and ultrasound machines are not available in our department for brachytherapy treatment planning. If resources allow, however, 3D IGBT planning with MRI and applicator insertion with ultrasound guidance may further improve accuracy in target volume localisation and dosimetry, thus potentially lead to improvement in treatment outcomes.

The primary limitation of this retrospective study is that data were limited and collected from only a single centre. We suggest that future work could include patients from more centres in Hong Kong and with a longer follow-up, or even compare data between CT-guided brachytherapy versus MRI-guided brachytherapy if the latter treatment modality becomes available in more local centres in future.

CONCLUSION

CT-based 3D IGBT for cancer of the cervix uteri, with or without interstitial needle insertion, is feasible in the local setting. There is the potential to administer a higher dose to the HRCTV by the 3D IGBT technique, and the doses to organs at risk can be limited to acceptable levels. Studies with a longer follow-up and larger sample size are required to better define the clinical benefits of 3D IGBT in comparison with conventional 2D planning.

REFERENCES