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ORIGINAL ARTICLE **CME**

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

RPY Tse, SWK Siu, A Chow, W Chan, F Tang, P Ho, TW Leung, P Kwong

Department of Clinical Oncology, Queen Mary Hospital, Pokfulam, Hong Kong

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 D_{2cc} (minimum dose in the most exposed 2 cm^3 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 D_{2cc} value of sigmoid colon in 2016 was significantly lower than that in 2014 or 2015. The D_{2cc} 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*

Correspondence: *Dr RPY Tse, Department of Clinical Oncology, Queen Mary Hospital, Pokfulam, Hong Kong*
Email: tpy804@ha.org.hk

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中文摘要

宮頸癌的電腦素描引導下近距離放射治療

謝佩楹、蕭偉君、周美君、陳穎樂、鄧年輝、何沛盈、梁道偉、鄺維基

目的：探討宮頸癌近距離放射治療在電腦素描引導下的治療成效。

方法：2014年1月至2016年6月期間共52名患者接受電腦素描引導下近距離放射治療，其中3名患者同時接受組織內針刺近距離放射治療。我們根據歐洲放射腫瘤學會（GEC-ESTRO）指引勾劃出高危靶區（HRCTV）和鄰近器官的體積。記錄的參數包括HRCTV D90（即可傳遞高風險臨床目標體積劑量的90%）平均劑量、HRCTV V100（接受100%處方劑量的HRCTV百分比），以及直腸、乙狀結腸和膀胱的D_{2cc}（即2cc危及器官的最低劑量）。使用Bonferroni對正態分佈數據的多重事後比較檢驗或Dunn多重比較檢驗的單向方差分析評估統計學的顯著差異。

結果：HRCTV D90平均劑量值於2014年、2015年及2016年分別是75.1 Gy、77.8 Gy和82.1 Gy。2016年的HRCTV D90值高於2014年。2016年的乙結腸D_{2cc}值顯著低於2014年及2015年。2016年的膀胱D_{2cc}值顯著高於2015年，但仍於可接受的安全範圍內。沒有患者產生第三或四級急性放射治療副作用。只有1位患者在放射治療後仍被檢測有腫瘤，另有3名患者有遠程轉移，另有1名患者同時有局部及遠程轉移。

結論：宮頸癌在電腦素描引導下作近距離放射治療及輔以組織內針刺是可行的。在三維圖像引導下作近距離放射治療宮頸癌，HRCTV D90有可能予以更高劑量，另一方面能保持鄰近器官劑量在安全值內。

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 ≤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 >6 cm at 0-1 cm from cervical os and/or tumour width >4 cm at ≥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.[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 (ie 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 D_{2cc} (the minimum dose in the most exposed 2 cm^3 volume) of rectum, sigmoid colon, and bladder in each brachytherapy dosimetry plan.[5,6] We aimed to achieve at least 6.5 Gy per fraction in the HRCTV D90 while limiting the D_{2cc} 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 Gy_{EQD2}, and above).[6] Tanderup et al[7] 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 Gy_{EQD2} for bladder and 70 Gy_{EQD2} for rectum and sigmoid colon.[6]

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 – D_{2cc} of bladder; Dunn's multiple comparisons tests otherwise – HRCTV D90 mean dose, D_{2cc} of rectum / sigmoid, HRCTV V100) was used to determine whether there are any statistically significant differences in HRCTV D90 mean dose, HRCTV V100, or D_{2cc} 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.

FIGO stage	No. of patients	Histology		Positive LNs	Relapse		
		Adenocarcinoma	Squamous cell carcinoma		Local	Distant	Both
IB	10	4*	6	4	0	0	1 (Adenosquamous carcinoma)
IIA/B	24	7	17	11	1 (Adenocarcinoma)	1 (Squamous cell carcinoma)	0
IIIA/B	18	4†	14	8	0	2 (1 Adenocarcinoma, 1 squamous cell carcinoma)	0

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.

	Mean dose (EQD2)			
	All	2014	2015	2016
HRCTV D90	77.9 Gy	75.1 Gy	77.8 Gy	82.1 Gy
D_{2cc} rectum	67.4 Gy	67.6 Gy	66.8 Gy	68.5 Gy
D_{2cc} sigmoid	70.5 Gy	74.6 Gy	71.0 Gy	63.7 Gy
D_{2cc} bladder	76.9 Gy	76.6 Gy	74.2 Gy	83.4 Gy
HRCTV V100	91.3%	88.7%	91.6%	94.4%

Abbreviations: D_{2cc} = minimum dose in the most exposed 2 cm^3 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).

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

	2014 vs. 2015	2015 vs. 2016	2014 vs. 2016
HRCTV D90	NS (p = 0.0914)	NS (p = 0.0625)	p = 0.0003
D_{2cc} rectum	NS (p ≥ 0.9999)	NS (p ≥ 0.9999)	NS (p ≥ 0.9999)
D_{2cc} sigmoid	NS (p = 0.395)	p = 0.0081	p = 0.0002
D_{2cc} bladder	NS (p ≥ 0.9999)	p = 0.0365	NS (p = 0.2512)
HRCTV V100	NS (p = 0.0696)	NS (p = 0.1996)	p = 0.0011

Abbreviations: D_{2cc} = minimum dose in the most exposed 2 cm^3 volume; 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.

needle insertion ranged from 6 cm to 8.5 cm. Twenty-three (44%) patients had pelvic lymph node involvement. None of the patients had para-aortic lymph node involvement. None of the 52 patients developed grade 3-4 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 (Table 1).

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 D_{2cc} 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 D_{2cc} of rectum was observed over these 2.5 years. The D_{2cc} value of sigmoid colon in 2016 was significantly lower than that in 2014 or 2015. The D_{2cc} value of bladder in 2016 was significantly higher than that in 2015 but still within acceptable limits (Table 3).

DISCUSSION

Previously, Tan et al[8] reported that 3-year and 5-year local control rates were both 89% and 3-year and 5-year overall survival rates were 77% and 69%, respectively. The RetroEMBRACE study reported 3-year and 5-year local control rates of 91% and 89%, respectively, and 3-year and 5-year overall survival rates of 74% and 65%, respectively.[9] The French STIC study reported a local relapse-free survival rate at 24 months of 78.5% and overall survival rate at 24 months of 74%.[10]

Our dosimetry data are compared with those of Tan et al,[8] the RetroEMBRACE study,[9] and the French STIC study[10] in Table 4. The apparently smaller HRCTV D90 mean dose value of our data may be due to our larger

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

	Mean dose (EQD2)			
	Present study	Tan et al[8]	Retro-EMBRACE[9]	French STIC[10] †
HRCTV D90	77.9 Gy	84 Gy	87 Gy	73.1 Gy
Mean HRCTV volume	49.1 cc*	20.5 cc	37 cc	35.2 cc
D_{2cc} rectum	67.4 Gy	58.5 Gy	64 Gy	61.0 Gy
D_{2cc} sigmoid	70.5 Gy	69.1 Gy	66 Gy	58.1 Gy
D_{2cc} bladder	76.9 Gy	75.5 Gy	81 Gy	69.5 Gy

Abbreviations: D_{2cc} = minimum dose in the most exposed 2 cm^3 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 al[11] 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 D_{2cc} value of sigmoid colon was also improved in 2016 compared with either the 2014 or 2015 data. The D_{2cc} values of rectum and bladder showed no significant differences between 2014 and 2016. The D_{2cc} 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 al[12] 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.

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