



Original Research Article

Dosimetric changes and interfraction anatomical variations during high dose rate brachytherapy of cervical cancers- Can replanning be avoided?

M S Athiyamaan^{1,*}, C H Sridhar¹¹Dept. of Radiation Oncology, Father Muller Medical College, Mangalore, Karnataka, India

ARTICLE INFO

Article history:

Received 12-06-2020

Accepted 20-06-2020

Available online 19-11-2020

Keywords:

Actual plan

High dose rate brachytherapy

Hypothetical plans

Interfraction variation

Replanning

ABSTRACT

Background: Interfraction variations occur due to tumour regression during cervical intracavitary brachytherapy (ICR) requiring replanning with every fraction. This study aimed to determine the correlation of interfraction variations in positioning of applicator and its relationship with relative dosimetry if the dwell time and source positions of the plan of first fraction were applied to other subsequent fractions.

Materials and Methods: This is a retrospective review of the orthogonal radiographs of cervical cancer patients treated from 2013 to 2016 in our institute, receiving ICR with the same dose prescription to point A using a tandem and two ovoids applicators. A hypothetical second and third plan were obtained by applying the same source positions and dwell time as in the first fraction plan. The dose delivered to point A, point B, cervical point, bladder point and rectal point were determined. The actual doses in the treated second and third fractions were compared with these hypothetical plans for any significant change in relative dosimetry. Statistical differences between groups were analysed using 2 tailed paired t test.

Results: There was consistent increase in the doses to the point B, bladder point and rectal point in all the hypothetical plans with statistically significant difference observed for point B ($p=0.001$), rectal point ($p=0.000$) and bladder point ($p=0.041$).

Conclusion: The conception of avoiding the replanning if similar interfraction conditions are achieved looks promising but the significant findings observed in this study warrants strongly to continue as per current recommendation of replanning with every fraction of brachytherapy.

© This is an open access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>) which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

1. Introduction

External beam radiation therapy (EBRT) with concurrent chemosensitizer with cisplatin and intracavitary HDR brachytherapy is the current standard curative treatment of locally advanced cervical carcinoma.¹⁻⁴ Brachytherapy with virtue of its steep gradient of dose distribution, permits not only a higher dose to the target but also confining the normal rectum and bladder tissue within tolerant limits. HDR brachytherapy with fractionation permits an optimal physical dose distribution and shorter treatment duration per fraction. This has also proven to be have better patient comfort with lesser risk of venous thromboembolism. The relative doses the normal tissues at risk and the tumour

volume depend on the patients' pelvic anatomy and the type of applicator placement. The rectum and bladder are very close to the high dose region of brachytherapy. A small distance variation from a particular point to the active sources cause a significant dose difference near the region close to the active sources.^{5,6}

Interfraction variations occur due to tumour volume progression or regression during the course of brachytherapy which warrants the need for replanning with every fraction of brachytherapy and is currently recommended by American Brachytherapy Society (ABS).⁶⁻¹⁰ Garipagaoglu et al. showed a pronounced variation in the interfraction position of applicators accounting for different doses delivered to the bladder and rectal tissues, but with no remarkable

* Corresponding author.

E-mail address: drathiyamaan.ms@gmail.com (M. S. Athiyamaan).

differences in the radiobiological effective doses. It was also noted that the tumour size had no statistical correlation with the discrepancy magnitude among applicator positions, the bladder and rectum points. The possibility of using the original first plan in subsequent fractions might decrease the sedation time for the patients and waiting times for both the patient and the medical personnel time.¹¹

Even in this current era of 3D-image based brachytherapy, these evidences based on orthogonal brachytherapy still remain prominent because despite the increasing usage of 3D image based brachytherapy in high income countries, many low to middle income countries still use the older orthogonal x ray based systems. Jason et al in his recent retrospective review of 29 patients, showed the proof of safely considering the first plan for the subsequent fractions using same source position and dwell time but however do not currently recommend it as a standard of care.¹²

Our study aimed to determine the correlation of interfraction variations in positioning of applicator and its relationship with relative dosimetry if the dwell time and source positions of the plan of first fraction were applied to other subsequent fractions.

2. Materials and Methods

This is a retrospective review of the orthogonal radiographs of patients with carcinoma cervix receiving intracavitary brachytherapy with the same dose prescription to point A using a tandem and two ovoid applicators treated from 2013 to 2015 in the Department of Radiotherapy, Father Muller Medical College, Mangalore. The eligible cases were the histologically proven nonmetastatic cervical cancer patients treated with curative intent definitive chemoradiation with EBRT of 46-50Gy in 23-25 fractions by 4 field box technique followed by 3 fractions of HDR brachytherapy each receiving 7.5 Gy to point A using Fletcher suit Williamson applicator.

Brachytherapy procedure - The HDR brachytherapy procedure was done in accordance of ABS guidelines.¹³ All patients had at least 10 hours of fasting with use of laxatives for rectal elimination of matters, use of 7cc of contrast into the balloon of Foleys catheter which was kept throughout the procedure and placement of rectal markers. All patients received the same procedure of sedation and analgesia during all the fractions of brachytherapy procedure. The Fletcher suit Williamson applicator consisting of an intrauterine tandem and two lateral ovoids. The degree of tandem curvature selection depended on the treating oncologist. Adequate vaginal packing was done to move away rectum and bladder from the applicators.

Orthogonal X-ray films using lateral and antero posterior view were taken for each fraction after applicator placement. The dosimetric planning after digitization of

the images were done by the medical physicist using the Elekta Microselectron V2 brachytherapy planning software. ICRU 38 principles were followed for dose prescription, optimization and the monitoring points - Point A, Point B, Bladder Point and Rectal Point. The cervical point is elucidated as 1cm lateral and superior to the central flange/cervical os. A dose of 7.5 Gy was delivered at point A for in all the patients using Iridium 192 Nucletron afterloader machine.

A hypothetical second and third plan were calculated using the previous recorded digitized orthogonal films by applying the same source positions and dwell time as in the treated first fraction plan. The dose delivered to point A, point B, rectal point, bladder point and cervical points were determined. The actual doses obtained in the treated second and third fractions were compared with this hypothetical plans for any remarkable change in relative dosimetry.

2.1. Statistical analysis

Descriptive statistics (mean and standard deviation) were used to summarize demographic data, analyses of differences between groups was done using 2 tailed paired t test. P values < 0.05 were considered significant.

3. Results

During the period from January 2013 to December 2016, a total of 159 patients with cervical cancer were treated with curative chemoradiation consisting of whole pelvic EBRT followed by HDR brachytherapy. The review of radiation charts excluded 26 patients as they received less than 3 fractions of brachytherapy and a total of 133 patients were eligible for the final analysis. The demographic data with tumour and patient characteristics are depicted in the Tables 1 and 2.

The comparison of dose points (point A, point B, cervix point, bladder point, rectum point) of the actual plan and the hypothetical plan was done (Table 3).

The cervix doses for the actual plan were 17.19 ± 2.43 Gy, 17.69 ± 3.83 Gy and 17.56 ± 3.52 Gy for the first, second and third plan respectively. The cervix doses observed for the hypothetical plan were 17.24 ± 4.23 Gy and 17.16 ± 3.84 Gy for the subsequent second and third plan respectively. There was a consistent decrease in the doses measured in the cervical points of all the hypothetical plans in comparison to the actual plans and the same pattern was observed during both the subsequent second and third brachytherapy plans. However this did not amount to significant difference ($P > 0.05$). Even though the cervix doses in the actual three treatment plans did not show any distinct pattern, an increase in the cervix doses were recorded in the second and third actual plan when compared to the first plan.

The bladder doses measured for the actual plan were 3.32 ± 1.15 Gy, 3.26 ± 1.06 Gy and 3.39 ± 1.14 Gy for the first, second and third respectively. The bladder doses obtained for the hypothetical plan were 3.34 ± 1.14 Gy and 3.48 ± 1.21 Gy for second and third plan respectively. There was a consistent increase in the doses to the bladder points measured in the hypothetical plans in comparison to the recorded actual plans and the same pattern was observed during both the second and third brachytherapy plans with statistically significant difference observed for the second plan ($P=0.041$). The bladder dose for both actual and hypothetical plans were more for third brachytherapy plan when compared to the first two plans.

The rectal doses recorded for the actual plan were 2.86 ± 0.90 Gy, 2.77 ± 0.88 Gy and 2.75 ± 0.83 Gy for the first, second and third respectively. The rectal doses obtained for the hypothetical plan were 2.94 ± 1.05 Gy and 2.91 ± 0.93 Gy for second and third plan respectively. There was again a consistent increase in the doses to the rectal points measured in the hypothetical plans in comparison to recorded actual plans in both the second and third brachytherapy plans with statistically significant difference observed in both the plans ($P=0.000$). The rectal dose in actual plan were more for first brachytherapy plan when compared to the second and third actual plans which accounts for the statistically significant high doses for both the hypothetical plans.

The point B doses for the actual plan were 1.80 ± 0.13 Gy, 1.79 ± 0.13 Gy and 1.80 ± 0.12 Gy for the three plans respectively. The point B doses for the hypothetical plans were 1.83 ± 0.18 Gy and 1.87 ± 0.2 Gy for the subsequent second and third plan respectively. There was also a consistent increase in the doses to point B in the hypothetical plans in comparison to the actual plans in both the second and third brachytherapy plans with statistically significant difference observed in both ($P=0.001$ vs $P=0.000$). The point B dose for actual plan were marginally more for first brachytherapy plan when compared to the second and third actual plans.

Table 1:

Variable	Mean	Standard deviation (range)
AGE, years	54.19	+/- 9.20
Variable	Number	Percentage (%)
EBRT DOSE – 46 Gy	68	51.12
50 Gy	65	48.87

4. Discussion

The result of the study tries to provide an answer to the question whether replanning is necessary for subsequent fractions of brachytherapy or use the implemented first

Table 2:

Variable	Number	Percentage (%)
Histology		
Squamous cell carcinoma	122	92.48
Adenocarcinoma	10	7.52
	133	100.00
Stage (FIGO)		
IB	3	2.3
IIA	2	1.5
IIB	48	32.3
IIIA	8	6.0
IIIB	71	53.4
IVA	6	4.5
	133	100.0

plan to the subsequent sessions. Previous studies showed a varied opinion for the need of replanning. Garipagaoglu et al showed a significant variation in the interfraction position of applicators accounting for different doses delivered to the bladder and rectal tissues, but with no remarkable differences in the radiobiological effective doses¹¹ whereas the study by Jason et al in his recent retrospective review of 29 patients, showed evidence of the safely considering the first plan using the same source position and dwell time for the subsequent fractions but however do not currently recommend it as a standard of care.¹²

This study with a sample size of 133 patients, convey that when the source position and dwell time of the first implemented fraction plan when applied to the subsequent second and third brachytherapy applications, there is a statistically significant difference between the doses received to the point B, rectum and bladder points, which necessitates replanning for every session of brachytherapy. The results of this study is in accordance to the current American Brachytherapy Society recommendation for replanning with every fraction.¹³

The planning with orthogonal x ray films uses dose points rather than volumes, thus the maximum dose may not be always determined and there is also a three times overdosage of rectal dose. The use of nonoptimized plans also results in overdosage at rectum, bladder and vaginal surface thereby necessitates the use of optimized replans.¹⁴ This significant results from the study recommends a routine replanning for every fraction of brachytherapy.

There are two important factors which determine the need for replanning namely the tumour regression and the operator dependant differences in applicator insertion and vaginal packing. There is a continuous regression in the tumour size during the entire course of EBRT and also during brachytherapy sessions. Bahena et al¹⁵ reports a correlation between the degree of regression with the applicator positions. This tumour regression may demand the use of varied tandem curvature or a different applicator

Table 3: Doses in Gy in Hypothetical Plan vs Actual Plan (mean \pm -standard deviation)

Dose point	First plan		Second plan		P	Third plan		P
	Actual dose	Actual dose	Hypo- Thetical dose	Hypo- Thetical dose		Actual dose	Hypo- Thetical dose	
A	7.50	7.50	7.50	7.50		7.50	7.50	
B	1.80 \pm 0.13	1.79 \pm 0.13	1.83 \pm 0.18	1.83 \pm 0.18	.001	1.80 \pm 0.12	1.87 \pm 0.2	.000
CERVIX	17.19 \pm 2.43	17.69 \pm 3.83	17.24 \pm 4.23	17.24 \pm 4.23	.087	17.56 \pm 3.52	17.16 \pm 3.84	.114
BLADDER	3.32 \pm 1.15	3.26 \pm 1.06	3.34 \pm 1.14	3.34 \pm 1.14	.041	3.39 \pm 1.14	3.48 \pm 1.21	.077
RECTUM	2.86 \pm 0.90	2.77 \pm 0.88	2.94 \pm 1.05	2.94 \pm 1.05	.000	2.75 \pm 0.83	2.91 \pm 0.93	.000

during each fraction taking account of the patients' anatomy. Robert Kimet al⁸ observed the adequacy of vaginal packing to be better in the first application than in the last one and also mentions that the major geometric variations between applications occurred more commonly in colpostats placement than in tandem placement. The variation in the degree of vaginal packing and applicator insertion along with the tumour regression during each subsequent brachytherapy sessions results in the significant differences in the dose received to the various points and organs at risk.^{16,17} The fact that cervical dose showed a consistent decrease in subsequent hypothetical plans when compared to the actual plans, proves that the anatomical variation occurred primarily due to the tumour regression and to an extent due to the differences in tandem and ovoid insertions.

3D image guided brachytherapy using MRI or CT imaging facilities is the current trend used in the planning of HDR brachytherapy. The American Brachytherapy Society (ABS) conducted an updated survey in the United States of America which highlighted that for dose specification to the target, 95% respondents always used CT and 34% always used MRI. However, the interesting finding noted was that 46% still used point A for dose specification to the target,¹⁸ suggesting that regardless of economic and financial status, dose prescription to point A is still followed throughout all parts of the world. With cervical cancer being more pronounced in developing and less developed countries, the International Federation of Gynaecology and Obstetrics (FIGO) has been adopting a clinical staging incorporating limited diagnostics, taking into consideration that advanced modern facilities may not be easily available. Hence our findings is still valid to all the centres that use orthogonal x ray based planning for treating cervical cancer with intracavitary brachytherapy. Until similar analysis are done using CT-based three dimensional software to prove waiving off the replanning, the current concept of replanning for every fraction of brachytherapy should continue as a standard of care.

The retrospective study has a few limitations. Even though it had a large sample size and considered the standard International Commission on Radiation Units and Measurements (ICRU) definitions for various point systems, it lacked strict inclusion criteria with respect

to the differences observed due to usage of varied tandem curvature and the uterine dilatation length between fractions. The study being retrospective in nature, the use of radio opaque rectal wire marker for the prescription of the rectal point could not be controlled as a variable and also the usage of this rectal marker may not be the recommended standard in all institutions.

5. Conclusion

The results of this study is in similar lines as with the current concept of replanning with every fraction of intracavitary brachytherapy for cervical cancers as recommended by ABS. The conception of avoiding the replanning if similar inter fractions conditions are achieved may appear as an interesting concept, the statistically significant findings observed in this study warrants strongly to continue as per current recommendation of replanning with every fraction of brachytherapy.

6. Source of Funding

None.

7. Conflict of Interest

The authors declare that there is no conflict of interest.

References

- Lanciano R. Optimizing radiation parameters for cervical cancer. *Semin Radiat Oncol.* 2000;10(1):36–43.
- Nori D, Dasari N, Allbright RM. Gynaecologic Brachytherapy I: Proper incorporation of brachytherapy into the current multimodality management of carcinoma of the cervix. *Semin Radiat Oncol.* 2002;12:40–52.
- Logsdon MD, Eifel PJ. FIGO IIIB squamous cell carcinoma of the cervix: an analysis of prognostic factors emphasizing the balance between external beam and intracavitary radiation therapy. *Int J Radiat Oncol Biol Phys.* 1999;43(4):763–75.
- Green JA, Kirwan JM, Tierney JF, Symonds P, Fresco L, Collingwood M, et al. Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis. *Lancet.* 2001;358(9284):781–6.
- Thomadsen BR, Shahabi S, Stitt JA, Buchler DA, Fowler JF, Paliwal BR. High dose rate intracavitary brachytherapy for carcinoma of the cervix: the madison system: II. Procedural and physical considerations. *Int J Radiat Oncol Biol Phys.* 1992;24(2):349–57.
- King GC, Bloomer WD, Kalnicki S, Faul CM, Gooding WE, Stockstill TF, et al. Point dose variations with time during

- traditional brachytherapy for cervical carcinoma. *Med Dosimetry*. 2000;25(2):77–80.
7. Eng TY, Fuller CD, Cavanaugh SX, Blough MM, Sadeghi A, Herman T. Significant rectal and bladder dose reduction via utilization of foley balloon catheters in high-dose-rate tandem and ovoid intracavitary brachytherapy of the uterine cervix. *Int J Radiat Oncol Biol Phys*. 2004;59(1):174–8.
 8. Kim RY, Meyer JT, Plott WE, Spencer SA, Meredith RF, Jennelle RL, et al. Major geometric variations between multiple high-dose-rate applications of brachytherapy in cancer of the cervix: frequency and types of variation. *Radiol*. 1995;195(2):419–22.
 9. Zubizarreta EH, Fidarova E, Healy B, Rosenblatt E. Need for Radiotherapy in Low and Middle Income Countries – The Silent Crisis Continues. *Clin Oncol*. 2015;27(2):107–14.
 10. National Comprehensive Cancer Network: Cervical Cancer; 2015. Available from: https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf.
 11. Garipağaoğlu M, Tunçel N, Dalmaz MG, Gülkesen H, Toy A, Kizildağ AÜ, et al. Changes in applicator positions and dose distribution between high dose rate brachytherapy fractions in cervix carcinoma patients receiving definitive radiotherapy. *Br J Radiol*. 2006;79(942):504–9.
 12. Co JL, Bojador MR, Mejia MBA, Ortin TTS, Ganzon DE. Interfraction Variation and Dosimetric Changes in Patients With Cervical Cancer Treated With Intracavitary Brachytherapy. *J Glob Oncol*. 2018;4(4):1–7. doi:10.1200/jgo.2016.008557.
 13. 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 I: General principles. *Brachyther*. 2012;11:33–46.
 14. Noyes WR, Peters NE, Thomadsen BR, Fowler JF, Buchler DA, Stitt JA, et al. Impact of “optimized” treatment planning for tandem and ring, and tandem and ovoids, using high dose rate brachytherapy for cervical cancer. *Int J Radiat Oncol Biol Phys*. 1995;31(1):79–86.
 15. Bahena JH, Martinez A, Yan D, Mele E, Edmunson G, Brown D, et al. Spatial Reproducibility of the Ring and Tandem High-Dose Rate Cervix Applicator. *Int J Radiat Oncol Biol Phys*. 1998;41(1):13–9.
 16. Hoskin PJ, Cook M, Bouscale D, Cansdale J. Changes in applicator position with fractionated high dose rate gynaecological brachytherapy. *Radiother Oncol*. 1996;40(1):59–62.
 17. Hellebust TP, Dale E, Skjønberg A, Olsen DR. Inter fraction variations in rectum and bladder volumes and dose distributions during high dose rate brachytherapy treatment of the uterine cervix investigated by repetitive CT-examinations. *Radiother Oncol*. 2001;60(3):273–80.
 18. Grover S, Harkenrider MM, Cho LP, Erickson B, Small C, Small W, et al. Image Guided Cervical Brachytherapy: 2014 Survey of the American Brachytherapy Society. *Int J Radiat Oncol Biol Phys*. 2016;94(3):598–604.

Author biography

M S Athiyamaan, Associate Professor

C H Sridhar, Medical Physicist

Cite this article: Athiyamaan MS, Sridhar CH. Dosimetric changes and interfraction anatomical variations during high dose rate brachytherapy of cervical cancers- Can replanning be avoided?. *Indian J Pathol Oncol* 2020;7(4):631-635.