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Original Article

Oncology Section

A Systematic Approach to Optimise the Number of Beams for Intensity Modulated Radiotherapy in Pituitary Adenoma using Radiobiological Parameters

RICHA SHARMA[1], SUNIL DUTT SHARMA[2], DEVESH KUMAR AVASTHI[3], ROHIT VERMA[4]

ABSTRACT

Introduction: The number of beams used in a Radiotherapy (RT) plan effects the overall quality of the plan and hence the treatment. The inclusion of radiobiological concepts in finding the optimum number of beams for a particular planning technique has the potential to provide a step ahead of the routine clinical practice where clinical decisions are more dependent on the physical dose parameters.

Aim: To optimise the number of beams for Intensity Modulated Radiotherapy (IMRT) plan based on Tumour Control Probability (TCP) and Normal Tissue Complication Probability (NTCP) biological parameters.

Materials and Methods: This retrospective study was done on 30 patients with pituitary macro-adenoma who underwent radiotherapy with a prescribed dose of 50.4 Gy in 28 fractions in Delhi State Cancer Institutes, Delhi, India from December 2012 to August 2018. The study data was collected and analysed between June 2018 and April 2020. These patients were treated with step and shoot IMRT technique on ONCOR™ Expression linear accelerator (Siemens Healthineers, USA). But, the number of beams used to deliver IMRT plans were different as decided by the medical physicist and hence planner dependent rather than the disease. Being a centrally located disease, a symmetric beam arrangement was adopted for IMRT planning. For dosimetric comparison, three IMRT plans with five, seven, and nine equispaced beams were generated in Monaco treatment planning system for each patient and thus, a total of 90 IMRT plans were created and evaluated. For fair comparison, same IMRT planning parameters were utilised in all three plans of each patient. Monte Carlo (MC) dose calculation algorithm was used for all the plans. Resulting Cumulative Dose Volume Histograms (CDVHs) were exported to MATLAB, where these cDVHs were processed as per Niemierko's radiobiological model to calculate the values of TCP and NTCP based on the Equivalent Uniform Dose (EUD). After this, the analysis of variance, ANOVA test was conducted over the resulting values of EUD, TCP, and NTCP to assess the difference of quality among plans having different beam arrangements at 0.05 level of significance.

Results: The mean tumour control probability (TCP) for IMRT plans with seven and nine beams were found to be 89.0±0.8% and 89.1±0.9% respectively for planning target volume (PTV). These values were not significantly different from each other. However, the mean TCP value for IMRT plans with five beams was found to be 88.4±1.1% for PTV. Further, this TCP value was proved to be significantly lower as compared to IMRT plans with seven and nine beams with a p-value of 0.008 and 0.004, respectively. On the other hand, the mean Normal Tissue Complication Probability (NTCP) was assessed to be less than 1% for all critical organs irrespective of the beam arrangement, indicating almost no probability of radiation induced toxicity in any of the organ.

Conclusion: This study concludes that the plan efficiency can be improved by using optimum number of beams for IMRT planning of pituitary adenoma.

Keywords: Beam number optimisation, Dose escalation, Equivalent uniform dose, Normal tissue complication probability, Tumour control probability

INTRODUCTION

Pituitary adenomas comprise of 10-15% of all intracranial tumours. Although, these adenomas are classified as benign they may be locally invasive and may cause major morbidity and mortality. Initially, surgery was the only modality used for the treatment of pituitary adenoma, but gradually it was found that surgery followed by RT was more effective than surgery alone since in 90% of the cases, only a partial resection can be performed [1]. The goal of RT is to deliver lethal dose to tumour without exceeding the tolerance doses of other neighboring organs.

The RT has improved continuously with time to achieve better Therapeutic Ratio (TR) by means of more conformal planning techniques and better treatment delivery systems, having greater accuracy and precision. Inclusion of radiobiological concepts in routine practice can provide a step forward in the direction of further improvement [2]. Complicated radiobiological calculations are no more cumbersome in today's era due to the availability of high speed computers that are common in RT departments. Although, the radiobiological concepts like EUD, TCP and NTCP are decades old, yet they are underutilised in routine practice. Even though, EUD is being used as an optimisation constraint in many commercial Treatment Planning Systems (TPSs) where the option of radiobiological optimisation is available, the clinical decision still depends on physical dose distribution and physical Dose Volume Histogram (DVH) rather than on the values of TCP and NTCP while selecting one plan over the other [3,4]. Even the dosimetric comparison studies between different planning techniques are based on physical dosimetric parameters [5,6]. The inclusion of radiobiological parameters is required to further improving the clinical practice in RT. As per the International Commission on Radiation Units and Measurements (ICRU) 83, NTCP and EUD are also to be included for level three reporting of IMRT plans [4].

Since the advent of RT, the selection of an optimal number of beams for different clinical cases has been dependent either upon the trial and

error process or on the clinical experience of the planner. Although, using an optimal number of beams is an important step of planning which directly affects the quality of a plan but even after decades of practice, planners do not have a case specific and systematic method to define an optimum number of beams in IMRT [7].

Many studies have been done to investigate the optimum number of beams for IMRT and even for conventional planning technique, but all of them were based on concepts like conformity index, homogeneity index, normal tissue integral dose etc. which are ultimately based on physical doses only [7-10]. None of these studies was based on the radiobiological concept. Moreover, these studies were done on a small group of patients (less than or equal to six) and hence their results were more prone to statistical fluctuations. In this article, a systematic method is proposed to find the optimum number of beams for IMRT of pituitary adenoma based on the radiobiological concepts. Although, the method is illustrated via the case of pituitary adenoma treated with IMRT. The proposed method in this study is a generalised one and is applicable to all external beam RT plans irrespective of the treatment site and planning technique e.g. Three Dimensional Conformal Radiotherapy (3DCRT), IMRT, Volume Modulated Arc Therapy (VMAT) etc.

MATERIALS AND METHODS

This retrospective study was performed on data of 30 patients with pituitary adenoma who were treated with step and shoot IMRT technique on ONCOR™ Expression (Siemens Healthineers, USA) linear accelerator (LINAC) machine with a prescribed dose of 50.4 Gy in 28 fractions (i.e., with 1.8 Gy dose per fraction) in Delhi State Cancer Institute, Delhi, India from December 2012 to August 2018. The study data was collected and analysed between June 2018 and April 2020. The number of beams used for IMRT plan were different as decided by the medical physicist and hence was planner dependent rather than the disease. The pituitary adenoma was thought to be an ideal case for demonstrating the proposed method as this case involves many critical organs.

Inclusion criteria: The patients with known primary pituitary macro-adenoma (both secreting and nonsecreting tumours) were included in the study. The postoperated patients with residual disease were also included.

Exclusion criteria: Pituitary micro-adenoma patients were not included in the study. The patients with large macro-adenomas invaded in surrounding Organs At Risk (OARs) e.g. optic nerves were also excluded.

Imaging and Contouring

Computed Tomography (CT) scan of each patient was acquired on Somatom Definition AS+ 128 slice (Siemens Healthineers, USA) CT scan machine in supine position with 3 mm slice thickness. These acquired images were exported in Digital Imaging and Communication in Medicine (DICOM) format to Monaco TPS (version 5.00.04, Elekta Medical Systems, Stockholm, Sweden) where the target and nearby critical organs were contoured on CT images of each patient.

Planning

After contouring, three IMRT plans with five, seven, and nine equispaced beams (starting from 0° gantry angle) were created for each patient in Monaco TPS and hence a total of 90 plans were made and evaluated. Since pituitary adenoma is a centrally located tumour, hence a symmetric beam arrangement was preferred. All plans were made for a prescribed dose of 50.4 Gy in 28 fractions. The planning optimisation constraints for normal organs were based on Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) and the dose was calculated with a constant dose calculation grid size of three mm using MC dose calculation algorithm for each plan [11]. DVHs were generated with a constant dose bin width of 10 Centigray (cGy). Resulting cumulative DVH (cDVH) data was exported in comma separated value (.csv) format from Monaco TPS to MATLAB [2] (version R2015a) software.

MATLAB

The MATLAB is a matrix laboratory developed by The MathWorks, Inc. (Natick, MA). MATLAB was used to create a program that calculates the values of TCP and NTCP as per Niemierko's radiobiological model. At first, this MATLAB (.m) program converts cDVH data into a differential one. Then, it makes use of withers formula to convert physical doses of DVH into biologically equivalent doses for each dose bin [12]. Withers formula is also known as isoeffect formula and is given by

$$EQD_2 = nd\left[\frac{d+\frac{\alpha}{\beta}}{2+\frac{\alpha}{\beta}}\right] \quad (1)$$

where EQD_2 is the biologically equivalent dose in fraction size of 2 Gy, n is the total number of fractions, d is the physical dose per fraction, and α/β is the amount of dose at which type A damage is equal to type B damage according to the Linear Quadratic (LQ) model. α/β is a tissue specific parameter.

After this, MATLAB program computes the equivalent uniform dose (EUD) using the following equation

$$EUD = \left(\sum_{i=1}^{N} v_i (EQD_{2i})^a\right)^{\frac{1}{a}} \quad (2)$$

where i varies from 1 to N dose bins of DVH, v_i is the volume corresponding to the i^{th} dose bin, EQD_{2i} is the biologically equivalent dose corresponding to the i^{th} dose bin, and a is the tissue specific parameter, which is negative for the target structure and positive for OAR [12]. For a=1, EUD is the mean dose and for a=∞, EUD is the maximum dose.

Thereafter, MATLAB program uses EUD value to calculate TCP for the target structure as per Niemierko's radiobiological model using the following equation

$$TCP = \left[1 + \left(\frac{TCD_{50}}{EUD}\right)^{4\gamma_{50}}\right]^{-1} \quad (3)$$

where TCD_{50} (i.e., tumour control dose$_{50}$) is the dose at which there is 50% probability of tumour control, EUD is the equivalent uniform dose, and γ_{50} is the slope of the sigmoidal dose response curve of the tumour at 50% control probability [12]. Radiobiological parameters that were used in MATLAB program to find TCP value of pituitary adenoma are listed in [Table/Fig-1] [13-16].

Parameter	Value	Reference
γ_{50} (%/%)	2	[13]
TCD_{50} (Gy)	38	[14]
a	-8	[15]
α/β (Gy)	3	[16]

[Table/Fig-1]: Radiobiological parameters used in MATLAB program for calculating TCP value of pituitary adenoma [13-16].

Similarly, MATLAB program uses EUD value to calculate *NTCP* for the OAR as per Niemierko's radiobiological model using the following equation

$$NTCP = \left[1 + \left(\frac{TD_{50}}{EUD}\right)^{4\gamma_{50}}\right]^{-1} \quad (4)$$

where TD_{50} is the dose at which there is 50% probability of normal tissue complication, EUD is the equivalent uniform dose, and γ_{50} is the slope of the sigmoidal dose response curve of the normal tissue at 50% complication probability [12]. Oinam AS et al., was referred for a and γ_{50} values of all critical organs [12]. Similarly, the values of TD_{50} and α/β were obtained from Emami B et al., (whole organ value) and Kehwar TS respectively [17,18].

Processing of DVH Data by MATLAB Program

Exported cDVH data of Monaco TPS was imported in MATLAB. MATLAB program processed DVH data of one contoured structure at a time. Hence, the program was made to run several times to evaluate each of the contoured target and organ. Resulting values of EUD, TCP, and NTCP were noted and the average values were calculated for each beam arrangement for all targets and organs.

STATISTICAL ANALYSIS

The data was analysed with ANOVA: single factor and Fisher's Least Significant Difference (FLSD) tests using data analysis tool of Microsoft Excel 16 software package. Moreover, one-tail t-test: two sample assuming unequal variances was also performed using the same software at 0.05 level of significance (α).

Analysis of variance: ANOVA test is used to compare the mean values of several populations [19]. The hypothesis (H_0) for this test is based on the assumption that the mean (μ) values of all populations are the same, i.e.,, $\mu_1=\mu_2=\ldots=\mu_n$ for all n populations that are compared. The alternative hypothesis (H_1) is that at least one of the population has a different μ value. This test was used to verify whether the differences among mean EUD values for different beam arrangements were statistically significant? For this, a hypothesis H_0: All the beam arrangements are equally efficient to deliver the same EUD to the target and an alternative hypothesis H_1: At least one of the beam arrangements is not equally efficient to deliver the same EUD to the target were made and test was performed using the data analysis tool of Microsoft Excel 16 software, at 0.05 level of significance. Similarly, this test was repeated for TCP and NTCP values as well.

Fisher's Least Significant Difference (FLSD): Once H_0 is rejected, one is confident that at least one of the populations has a different mean value. However, ANOVA test does not tell which of the mean value is different, i.e., if $\mu_1 \neq \mu_2$ or $\mu_2 \neq \mu_3$ or … $\mu_{n-1} \neq \mu_n$. In such condition, post hoc test such as FSLD is used to identify which of the mean value is different from others [20]. For those cases where H_0 was rejected, FLSD test was used to identify the beam arrangement which has a significantly different mean value compared to other beam arrangements.

RESULTS

It can be observed that all three beam arrangements deliver approximately the same EUD to target structures [Table/Fig-2]. Further evaluation of EUD data with ANOVA and FLSD tests indicated insignificant difference in mean EUD values and hence equal efficiencies of seven and nine beam plans as indicated by the high p-value (p>0.05) as showed in [Table/Fig-3]. It also indicates a significantly lower efficiency of five beam plans as shown by p-value (<0.05), when compared to plans having seven and nine beams. Similar results were obtained for mean TCP values [Table/Fig-4].

Target	Mean EUD (Gy)		
	5 Beams	7 Beams	9 Beams
GTV	49.6±0.7	49.9±0.6	50.0±0.6
CTV	49.6±0.5	50.0±0.4	50.0±0.4
PTV	49.0±0.6	49.4±0.5	49.4±0.6

[Table/Fig-2]: Mean values of equivalent uniform dose (EUD) of target structures for all beam arrangements.
GTV: Gross tumour volume; CTV: Clinical target volume; PTV: Planning target volume

Target structure	p-value			
	ANOVA test	FLSD test		
	All beam arrangements	5 beams vs 7 beams	7 beams vs 9 beams	5 beams vs 9 beams
GTV	0.049	0.036	0.317	0.012
CTV	0.006	0.005	0.383	0.004
PTV	0.008	0.008	0.308	0.004

[Table/Fig-3]: p-values of analysis of variation (ANOVA) and Fisher's least significant difference (FLSD) tests at 0.05 level of significance for mean EUD values of target structures.
GTV: Gross tumour volume; CTV: Clinical target volume; PTV: Planning target volume

Equal efficiency of plans with seven and nine beams while showing significantly lower efficiency of plans having 5 beams is demonstrated in [Table/Fig-5].

Moreover, we can see from that NTCP value <1% for all critical organs irrespective of the beam arrangement, indicating almost no probability of radiation-induced toxicity in any of the organ [Table/Fig-6].

Target	Mean TCP (%)		
	5 Beams	7 Beams	9 Beams
GTV	89.3±1.0	89.8±0.9	90.0±0.9
CTV	89.4±0.8	89.9±0.6	90.0±0.7
PTV	88.4±1.1	89.0±0.8	89.1±0.9

[Table/Fig-4]: Mean values of Tumour Control Probability (TCP) of target structures for all beam arrangements.
GTV: Gross tumour volume; CTV: Clinical target volume; PTV: Planning target volume

Target structure	p-value			
	ANOVA test	FLSD test		
	All beam arrangements	5 beams vs 7 beams	7 beams vs 9 beams	5 beams vs 9 beams
GTV	0.048	0.036	0.313	0.012
CTV	0.006	0.005	0.398	0.004
PTV	0.008	0.008	0.325	0.004

[Table/Fig-5]: p-values of analysis of variation (ANOVA) and Fisher's least significant difference (FLSD) tests at 0.05 level of significance for mean TCP values of target structures.
GTV: Gross tumour volume; CTV: Clinical target volume; PTV: Planning target volume

OAR	Mean NTCP (%)		
	5 Beams	7 Beams	9 Beams
Brain	0.2	0.2	0.2
Brainstem	0.5	0.5	0.5
Left eye	0.0	0.0	0.0
Right eye	0.2	0.0	0.0
Left lens	0.0	0.0	0.0
Right lens	0.0	0.0	0.0
Left optic nerve	0.7	0.6	0.7
Right optic nerve	0.6	0.6	0.7

[Table/Fig-6]: Mean values of Normal Tissue Complication Probability (NTCP) of organs at risk for all beam arrangements.

DISCUSSION

The selection of optimum number of beams has been a topic of interest not only for advanced planning techniques like IMRT but for conventional plans as well [10]. Now-a-days, various beam angle optimisation algorithms are available to provide an optimised number of beams with corresponding angles for a plan [7,8]. However, the selection of an appropriate number of beams is still an important step since many of such algorithms need an adequate number of beams as an input [7].

The present study has have tested the proposed method for just three equispaced beam arrangements having five, seven, and nine beams. The reason behind not testing for lower or higher number of beams was the observation from previous studies which have shown that plans with less than five or more than nine beams are of inferior quality compared to other equispaced beam plans [7-9]. These studies have shown that an IMRT plan with three beams has the least value of conformity index and conformal index and has the highest value of inhomogeneity index, mean non target dose, average MU/segment, sensitivity of objective function, and objective function value. Similarly, for a plan with 11 or more beams, the values of conformity index and conformal index are lower compared to a plan with five beams. Furthermore, such high beam number plan has the highest number of Monitor Units (MUs), segments and mean non target dose due to increased overlapping of low dose regions. However, being in the saturation region, only slight changes in inhomogeneity index, objective function value, sensitivity of objective function, and average MU/segment are present for such plans.

Past studies on IMRT beam number comparison have been done with fewer number of patients [7-10]. Moreover, some of these studies incorporated patients of different sites as well. On the other hand, the present study included thirty patients with the same

disease (i.e., pituitary adenoma) and therefore results are less prone to statistical fluctuations compared to the past studies. However, the present study's results are in correlation with the past studies. In addition, the present study proved that an IMRT plan with seven or nine beams has significantly better efficiency than an IMRT plan with five beams in terms of tumour control. The results also indicate an insignificant difference between efficiencies of seven and nine beam IMRT plans.

Previous studies have reported that escalating the number of beams in a plan beyond a particular point does not improve the quality of plan [7-9]. Since such unnecessary addition in the number of beams leads to more radiation leakage and hence increased normal tissue dose. Moreover, it results in an increased number of segments and MUs with a decrease in mean MU/beam that may further add to uncertainty in the delivery of treatment even for dynamic IMRT [7,8]. Higher MUs implies greater risk of secondary cancer because of irradiation to low dose and a longer treatment time that leads to more intrafraction motion of tumour as well as lesser patient comfort [5]. It is also recommended to use the minimum possible number of beams that are essential to produce a good quality plan in order to reduce the overall time required for treatment delivery and dosimetric verification [8]. Hence, this study indicates planning with seven equispaced beams to be the optimum choice for coplanar IMRT of pituitary adenoma.

The maximum limit of prescription dose is set by the tolerance dose of OARs since the aim of RT is not just the treatment of cancer, but the quality of life should also be high. This study suggests the possibility of dose escalation in case of pituitary adenoma. The proposed method can be used for virtually testing the same. For this, the prescription dose of pituitary adenoma can be increased while keeping an eye over NTCP values of normal organs. It means to test for the possibility of dose escalation, one can do replanning for old patients with higher doses and can use the proposed method to look for related improvements in TCP values together with the increased values of NTCP. If NTCP values are still under set limits, the virtual test accomplishes its task. Although, this study is demonstrated via the case of IMRT planning for pituitary adenoma, the proposed method can also be applied to other sites and planning techniques. More radiobiological studies for different types of tumour should be performed to generate more such data so as to facilitate the use of radiobiological dosimetric parameters in routine clinical practice.

Limitation(s)

The main limitation of the proposed method is the scarcity of radiobiological parameter data availability in literature. Most of the literature data is old and has to be collected from different studies.

CONCLUSION(S)

The present study concludes that the plan efficiency can be improved by using optimum number of beams. Moreover, the use of radiobiological parameters for plan evaluation also indicates the scope of radiation dose escalation and therefore better tumour control without causing more damage to surrounding organs.

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PARTICULARS OF CONTRIBUTORS:
1. Research Scholar, Department of Applied Physics, Amity Institute of Applied Sciences, Amity University, Noida, Uttar Pradesh, India.
2. Head, Medical Physics Section, Radiological Physics and Advisory Division, Bhabha Atomic Research Centre, Mumbai, Maharastra, India.
3. Dean, Research and Development, School of Engineering, University of Petroleum and Energy Studies, Dehradun, Uttarakhand, India.
4. Assistant Professor, Department of Applied Physics, Amity Institute of Applied Sciences, Amity University, Noida, Uttar Pradesh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Richa Sharma,
Research Scholar, Department of Applied Physics, Amity Institute of Applied Sciences, Amity University, Noida, Uttar Pradesh, India.
E-mail: richa035@gmail.com

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