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Effect of 1mm and 2mm alteration in field size on target dose distribution for head and neck cancers in neutron therapy

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Abstract

Purpose: To investigate the effect of 1 (one) and 2 (two) millimetre (mm) changes in field sizes on a target volume and normal surrounding tissue's dose distribution during treatment planning of the planning target volume (PTV) of head and neck cancers.

Methods and materials: Eleven (n=11) previously treated head and neck (H&N) patients' plans were modified by 1 and 2mm. These simulated plans were calculated and the dose volume histograms (DVH) were analysed. The target dose and the organs at risk (OAR) maximum doses of the original treatment plans were compared with the newly generated plans. *Spearman's correlation coefficients* were calculated and analysed.

Results: The most prominent change observed was the mean dose difference in the target of -1.4% with a standard deviation of 3.611% ($p = 0.227$) if the field size was increased by both 1 and 2mm. The organ at risk (OAR) most affected by the field size changes was the left optic nerve with a median dose increase of 0.2% with a quartile range of 0.4% ($p < 0.001$) if field sizes were increased by 2mm. The organs at risk's biggest decrease in percentage dose was when the field size was decreased by 2mm, to the spinal cord, left lens, and the left and right optic nerves of 0.1% with a quartile range of 0.4, 0.5, 0.3 and 0.4 and these findings were all statistically significant with $p = 0.008$, 0.004, respectively and $p < 0.0001$ for both optic nerves.

Conclusion: Changes to the dose distribution were observed with changes in field size. It is therefore important that geometric uncertainties are considered during the treatment planning process. Furthermore protocols to simulate for field size changes in individual patients should be considered as a standard pre-treatment verification procedure for head and neck cancer patients. One should keep in mind that a 1.4 % dose influence to the PTV that was noted is for a neutron dose. Thus in photon terms it is at least 3 times more.

Keywords

Field size uncertainties, planning simulation

Introduction

Cancers of the head and neck (H&N) which include cancers of the buccal cavity, head and neck subset, larynx, pharynx, thyroid, salivary glands, and nose/nasal passages, account for 6% of all malignancies in the United States of America [1]. H&N cancers represent 5% of all malignancies in South Africa and are the fourth most common cancer in men [2]. The mouth is the most common site, followed by the larynx and the pharynx. In South Africa H&N cancers are usually squamous cell cancers [2]. From September 1988 to June 2009, 1610 cancer patients, 812 of them with H&N malignancies, were treated on the Neutron Therapy Unit at the iThemba LABS (Laboratory for Accelerated Based Sciences), previously known as the National Accelerator Centre. This is more than three new patients a month in the past 20 years at one institution in the Western Cape [3]. Treatment for these malignancies is primarily radiation therapy, surgery or chemotherapy; in most cases it is a combination of these modalities. Aggressive multimodality treatment has improved the local control rate and overall survival in H & N cancer patients [4]. The anatomy of the head and neck region is irregular and the tissue separation varies considerably in different parts of the treatment field. This makes the choice of correct prescription depth difficult in the planning target volume (PTV) and results in dose inhomogeneity within the treatment volume [4].

Planning is essential before radiation treatment can commence. This allows the full benefit of radiation therapy to PTV and minimal radiation to normal tissue adjacent to the PTV. Positioning is extremely important in radiation therapy [5]. Accuracy and reproducibility of patient treatment setup are keys to satisfactory radiation therapy. The use of immobilisation devices to reduce random setup errors can also reduce the amount of normal tissue irradiated and ensure adequate coverage of the clinical target volume (CTV) [5].

The entire treatment planning process involves beam data acquisition and entry into the computerized treatment planning system (TPS), patient data acquisition, treatment plan generation and the final transfer of data to the treatment machine. Successive improvements in treatment planning hardware and software have been most notable in the graphics, calculation and optimization aspects of current systems [6]. However an on-going quality assurance (QA) program is fundamental to accurate treatment delivery. Apart from the head and neck anatomy being so diverse in density, sources of error in radiation therapy may derive from deficiencies in tumour localisation, patient immobilisation, field placement, daily patient setup and dose calculation, as well as from equipment problems. Acceptable limits of the individual QA checks are documented in a quality control program at iThemba LABS together with their respective tolerances according to the South African Medical Physics Society (SAMPS) guidelines. Radiation field size verification is performed quarterly and allows for a tolerance up to 2mm [7]. Previous studies have shown a change in distribution due to daily patient setup, dose calculations and patient movement. However a change in distribution due to a field placement that

is within QA tolerance is still illusory [8].

Previous investigations suggest that treatment target movements of 2.1mm to 10.8mm resulted in treatment dose errors of up to 5% of the prescribed treatment [9-11]. Previous explorations also reported setup errors between 1.2 and 2.5mm when treating H & N cancers [12, 13]. There are reports of some institutions increasing their PTV by 4mm to compensate for these uncertainties or even reducing their prescribed dose [14, 15]. Small movements have been reported of H & N target volumes during treatment; this testifies of impact on dose distribution. Therefore the possibility of small changes in field sizes (1 and 2mm) could have an added effect on the dose distribution. The researcher aimed to profile the tumour dose distribution pattern for field size changes of 1mm and 2mm in the cranio-caudal direction. These changes could then be assessed if significant for both single and multi-isocentric plans. The results of this study should further indicate if the changes seen in target dose distribution are within tolerance with the clinical dose to the tumour and normal surrounding tissue as prescribed for the relevant patient treatment plans.

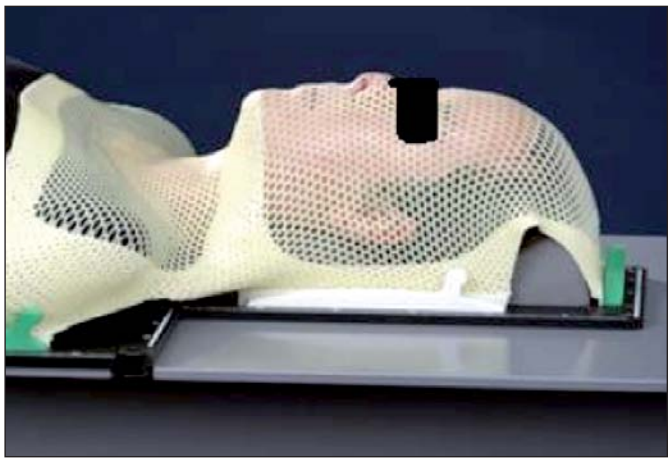


Figure 1: Head and neck immobilisation cast.

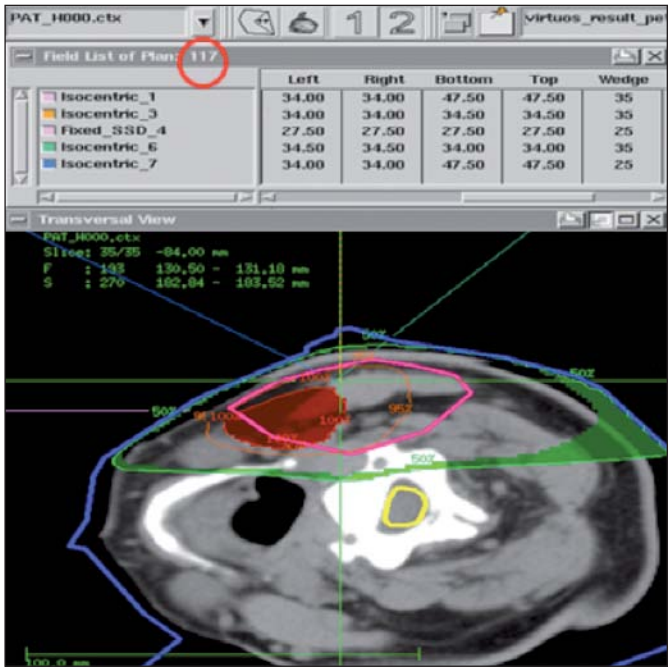


Figure 2: Reference plan 117 for Patient H. The pink irregular shape indicates the target volume and the yellow shape the spinal cord volume.

Methods

For this retrospective study eleven (n=11) patients with H & N cancer were selected. The selection criteria included data of H & N patients that were previously treated to a prescribed dose of 20.4 Neutron Gy (to the 100% isodose) in 15 treatment fractions. The selection included patients that were immobilised using a custom made Klarity® thermoplastic cast (Figure 1) and those that had a computed tomography (CT) scan on the Philips Big Bore CT Scanner using the protocol of 2mm slices 2mm apart.

Ethics approval to use patient data for this retrospective study was granted by the Faculty of Health and Wellness Sciences at Cape Peninsula University of Technology and by the South African Medical Association Ethics Committee. The selected patient data were transferred to the VIRTUOS (version 3.1) treatment planning system for radiotherapy planning in a different directory from the one used for clinical planning. Data were anonymized by editing the XML files that act as the header for the binary files of each patient and contain patients' name, surname and other demographic data, as well as all the necessary geometrical data related to the CT study. All the patient-specific information was replaced with anonymous labels. For example, name: Patient A.

The original treatment plan for each of the eleven patients was copied and used as the reference plan for analysis (Figure 2). Each beam's field size was then increased by both 1mm and then 2mm respectively in order to simulate geometric uncertainties likely to be encountered in clinical radiotherapy. Each new plan was saved under the specific patient file (Figure 3a and b).

The reference plan was reloaded and field size adjustments of 1mm and 2mm decreases were also done respectively and received new plan numbers (Figure 3(c) and (d). Each patient would then have five plans for this assessment. The CT data with the original volumes of interest remained unchanged. The organs at risk outlined for each patient were brain, spinal cord, left and right lenses, left and right optic nerves, left and right lungs. Plans generated with changes in field sizes kept the original normalisation percentage at the same point compared as the reference plans. The new plans were calculated and dose volume histograms (DVHs) calculated and the values entered into a spreadsheet. DVHs were also calculated for the reference plans and imported into a spreadsheet for analysis (Table 1 and Figure 4). The same cycle to calculate the DVHs was repeated for each four remaining plans for each patient and imported into a spreadsheet.

For the OAR the maximum doses were captured in a spreadsheet and plotted to demonstrate the maximum dose to the organ for each plan for each patient. Figure 4 demonstrates the brain as organ at risk plotted for each patient showing the five different plans. This procedure was then repeated for each organ at risk.

Descriptive studies on different data sets (by using basic stats function in Statistica 9) first had to check what the data distribution was for the different percentage dose distributions of different volumes of interest. If the data distribution were skew, it would indicate a significant distribution of the data and a median would be used because it is unaffected by extreme values. The other case (normal distribution) would be a non-significant data distribution and a mean would be used (as this data is affected by extreme values).

With the normal data distribution the mean and standard deviation (STD) and p-value, General ANOVA/MANOVA (one way ANOVA) with Bonferoni (significant testing) was used. With a skew distribution the median with ± quartile range was used for

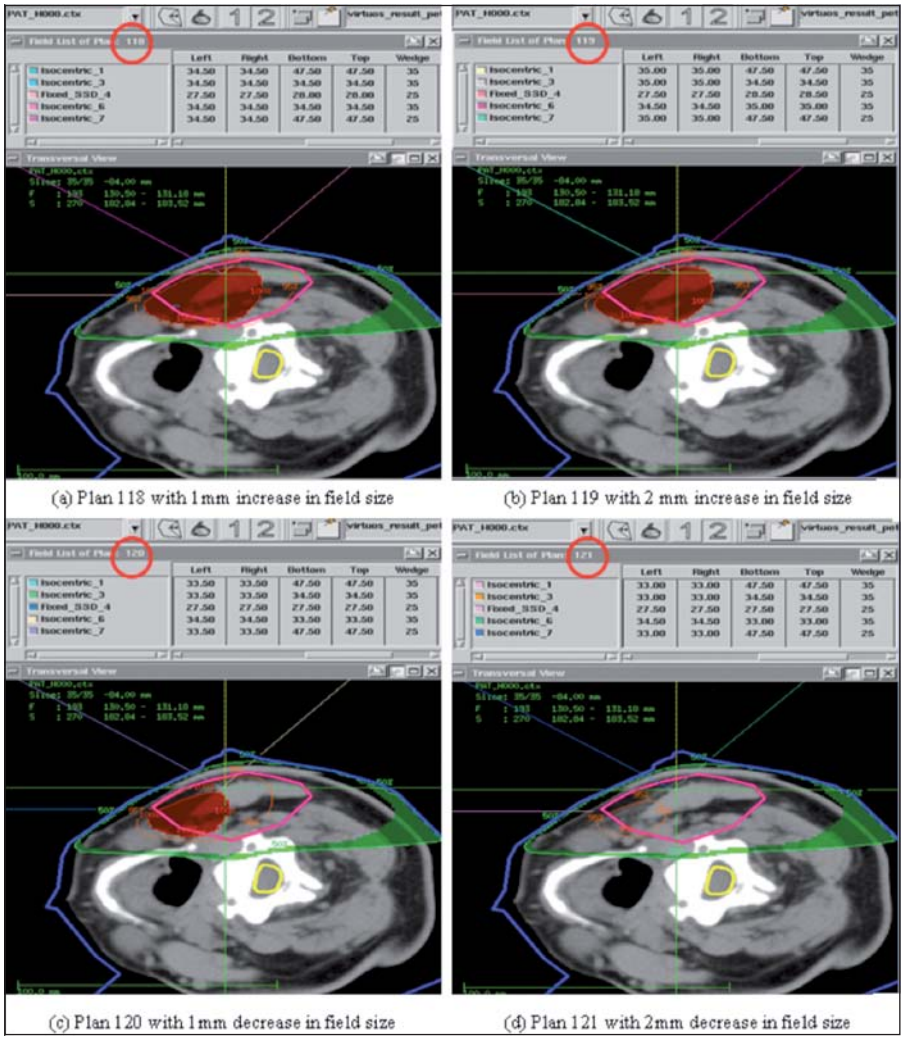


Figure 3: Plans 118 to 121 ((a) to (d)), illustrating distribution on the same CT-slice with 1 and 2mm field size increase; followed by a 1 and 2 mm field size decrease compared to the reference plan for Patient H respectively. Note how the 100% isodose coverage changes when field size is altered with.

nonparametric statistics comparing two independent samples (groups). The Mann-Whitney U test for p-values was used. To summarise the strength between different percentage distributions and the effect caused by field size changes, two different correlation coefficients were considered: Pearson's correlation coefficient and Spearman's rank correlation coefficient. The former requires both variables to be measured on an interval or ratio scale and the calculation is based on the actual values. Pearson correlation coefficient was used if the distribution was normal and not skewed. Spearman's rank correlation coefficient is used as a measure of linear relationship between two sets of ranked data, that is, it measures how tightly the ranked data clusters around a straight line. In this study the Spearman correlation coefficient was used for skewed (not normal) distribution and if either of the variables had a skewed distribution.

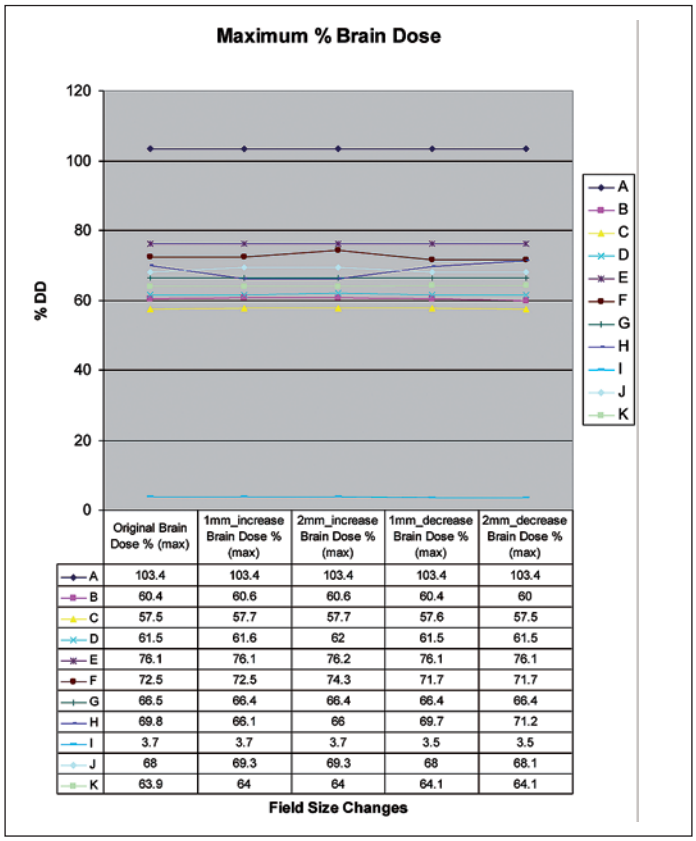
Results

The changes made to the field sizes did have an effect on the dose distribution to the target. Table 2 shows the median changes to the target's minimum, mean and maximum doses with the quartile ranges. The distribution of the data captured from the DVHs caused by the field sizes was normal except for the mean dose difference with 2mm decrease in field size. The mean difference in percentage dose to the target with a 2mm decrease in field size was -0.136% with a standard deviation (SD) of 0.70%. The minimum mean percentage change due to a 2mm decrease in field size was -1.3% and the maximum +1.4%. However this was not significant as the significant testing (Bonferoni) p-value was 0.534. There were no statistically significant changes observed (Table 2) to the percentage dose to the target for any of the patients. However, the biggest change observed (not statistically significant) was the minimum dose that decreased by a mean of 1.4% with a SD of 3.61% when field sizes increased with 1mm and also a decrease of 1.4% with a SD of 3.63% when field sizes increased with 2mm.

The Spearman correlation coefficient, however, indicated a strong linear relationship between the reference plan percentage doses to the target and the altered field size plan percentage dose to the target. The strongest correlation was for the 1 and 2mm increase that showed an $R = 0.986$ with a $p = < 0.0001$, for the maximum dose to the target, thus indicating a strong positive relationship. This correlation states that the increase in the maximum target dose could be explained by the increase in the field size.

The biggest percentage dose difference was observed for one patient that was planned with two isocentres at the slice where the fields abutted each other (Figure 5). Figure 5a clearly indicates the 100% dose coverage to the target and then with an increase of 2mm the 100% coverage is significantly smaller (Figure 5b). The reduction in the percentage mean dose to the target is illustrated by the DVH in Figure 5c. The significant change on the DVH for plan 117 (Figure 5a) and plan 119 (Figure 5b) could clearly be seen and the mean percentage dose to the target changed from 97.5% ± 11.0% to 92.9% ± 10.6%, a reduction to the mean target dose of 4.6% ± 0.4% when the field sizes were increased by 2mm.

The changes made to field sizes did show a statistically significant outcome to the overall changes to the organs at risk (OAR) for most plans irrespective of the change made to the field size. The OAR however, that did not show a statistically significant result when 1mm decrease in field sizes (spinal cord, right lens, and right optic nerve) and 1mm increase in field sizes (left optic nerve) changes were made is summarised in Table 3. The Bonferoni significant test showed p values to above mentioned organs at risk to be $p = 0.153$, 0.106, 0.137 and 0.324, respectively. The highest increase in percentage dose was the maximum dose to the left optic nerve with a median dose increase of 0.2% with a quartile range of 0.4%; this was statistically significant with $p < 0.001$. When the fields were decreased by 2mm the spinal cord, left lens and the left and right optic nerves showed a 0.1% decrease with a quartile range of 0.4, 0.5, 0.3 and 0.4 re-



	Original Brain Dose % (max)	1mm_increase Brain Dose % (max)	2mm_increase Brain Dose % (max)	1mm_decrease Brain Dose % (max)	2mm_decrease Brain Dose % (max)
A	103.4	103.4	103.4	103.4	103.4
B	60.4	60.6	60.6	60.4	60
C	57.5	57.7	57.7	57.6	57.5
D	61.5	61.6	62	61.5	61.5
E	76.1	76.1	76.2	76.1	76.1
F	72.5	72.5	74.3	71.7	71.7
G	66.5	66.4	66.4	66.4	66.4
H	69.8	66.1	66	69.7	71.2
I	3.7	3.7	3.7	3.5	3.5
J	68	69.3	69.3	68	68.1
K	63.9	64	64	64.1	64.1

Figure 4: Maximum percentage dose to the brain for each patient with the respective plans of altered field sizes.

spectively. These results were statistically significant with $p = 0.008$ for the spinal cord, $p = 0.038$ for the left lens and $p < 0.005$ for both optic nerves. The Spearman correlation coefficient indicated a strong linear relationship between the reference plan maximum percentage doses to the brain and left lens with 2mm increase and 2mm decrease respectively. The strongest correlation was with a 2mm increase in field size for the brain and signified a correlation coefficient of $R = 0.973$ with a $p = <0.0001$, for the maximum dose to the brain indicating a strong positive relationship. This correlation states that the increase in the maximum brain dose could be explained by the increase in the field size. The strongest negative correlation was between the reference plan and the 2mm decrease in field size plans, where the right lens showed a correlation coefficient of $R = -0.991$ and $p <0.0001$. This correlation states the decrease in maximum dose to the right lens could be explained by the decrease in field size.

Discussion

A sample error of 13% out of a very small population of H & N patients referred for neutron therapy was used [16, 17]. Eleven patients for a study of this magnitude failed to produce sufficient evidence to incorporate a standard protocol to be put in place to accommodate field size uncertainties. It must also be recognised that studies with smaller sample sizes did however conclude sturdy outcomes on distribution changes due to geometrical uncertainties [9]. Support to such effects was also greatly due to the geometrical uncertainties observed between 2.1mm to 10.8mm, which showed a significant change in distribution [9, 15].

The current study however, was a planning exercise and not an error reproduction investigation where the need to change the monitor units would used along with the normalisation or field out-

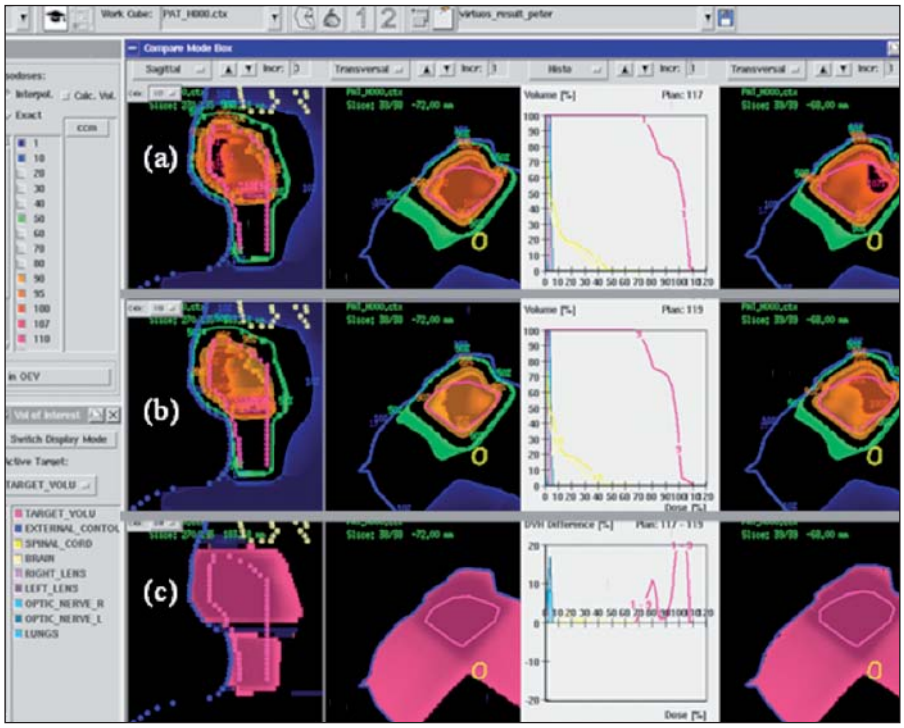


Figure 5: Displaying the reference plan dose distribution (a), compared with the dose distribution for the same patient with field sizes increased by 2mm (b) and also displaying the dose distribution of the difference of the 2 plans (c) on the same slice.

Table 1: Summary of patients target dose histogram statistics of reference plans.

Patient	Number of Treatment Fields	Number of isocentres	Maximum % dose to Target	Dose in Neutron Gray	Mean % Dose to Target	Dose in Neutron Gray	Minimum % Dose to Target	Dose in Neutron Gray
A	4	2	110.30	22.50	96.60	19.71	39.90	8.14
B	2	1	109.80	22.40	101.40	20.69	65.00	13.26
C	4	2	111.40	22.73	96.20	19.62	56.60	11.55
D	4	3	109.90	22.42	95.20	19.42	45.60	9.30
E	3	1	111.00	22.64	104.50	21.32	64.10	13.08
F	3	1	110.50	22.54	102.60	20.93	77.10	15.73
G	3	1	110.30	22.50	103.80	21.18	72.70	14.83
H	5	2	111.50	22.75	97.50	19.89	66.40	13.55
I	5	3	109.20	22.28	101.50	20.71	75.20	15.34
J	4	1	110.50	22.54	103.60	21.13	88.20	17.99
K	4	2	110.10	22.46	87.70	17.89	44.50	9.08
Median % Dose to Target			110.30	22.50	101.40	20.69	65.00	13.26
P-value			0.81		0.11		0.72	
Quartile Range			1.10	0.22	7.40	1.51	29.60	6.04

put factor due to shielding. If the need to see what the clinical implications could be, the above mentioned factors should be considered. Statistically significant findings of this work could be erroneous due to the sample size used and the small field size uncertainties chosen for this line of investigation. It was observed that the findings proved a definite change in distribution even with such small uncertainties and emphasised that the maximum effect was at an overall mean dose distribution when more than one isocentric plan was implemented for treatment (4.6% ± 0.4% caused by a 2mm increase in field size). With normal tissue adjacent to the target volume, such as optic nerves, the researcher reports a maximum change of 0.6%. The change in percentage dose may not have been significant but one should consider that the patients used in this investigation were planned to receive neutron radiation and at the energy for p (66)/Be neutron beam has a radiobiological effectiveness value (RBE) of three [18, 19].

Clinically, studies have shown that 3-5% dose changes affect both tumour response and complication risk [20-25]. The above statement encourages revision of previous literature, such as the ICRU report 62 guidelines that suggest that a dose variation between +7% and -5% is acceptable in the PTV [26]. Further investigations are fundamental using a larger number of patients' data and additional geometrical parameters should be considered. An overall representation on dose distribution due to geometrical uncertainties could only benefit any department irrespective of particle or photon treatment.

Conclusion

The significance of this investigation is vague. However changes to the dose distribution were observed therefore the null hypothesis could be rejected. Findings of any investigation around this theme would still be based on a clinical decision whether an individual patient plan needs to be considered for the simulation of geometrical uncertainties before radiation treatment commences. In the author opinion it is recommended that such protocols be considered as a standard pre-treatment verification procedure for head-and-neck cancer patients. In fact one should keep in mind that a 1.4% dose influence to the PTV that was noted is for a neutron dose. Thus in photon terms it is at least 3 times more.

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Table 2: Summary of patients target dose percentage difference from histogram statistics.

Variable	Valid N	Mean	Median	Minimum	Maximum	Quartile Range	Std.Dev.	p value
1mm _increase Target Dose % difference (min)	11	-1.40000	0.000000	-11.8000	0.200000	0.700000	3.611094	0.227476
1mm _increase Target Dose % difference (mean)	11	-0.43636	0.000000	-4.4000	1.200000	0.400000	1.433369	0.336451
1mm _increase Target Dose % difference (max)	11	0.01818	0.000000	0.0000	0.200000	0.000000	0.060302	0.340893
2mm _increase Target Dose % difference (min)	11	-1.40000	0.100000	-11.8000	0.300000	0.700000	3.631529	0.229914
2mm _increase Target Dose % difference (mean)	11	-0.38182	0.000000	-4.6000	1.000000	0.500000	1.502543	0.419040
2mm _increase Target Dose % difference (max)	11	0.02727	0.000000	0.0000	0.200000	0.000000	0.064667	0.192127
1mm _decrease Target Dose % difference (min)	11	-1.18182	-0.100000	-11.9000	0.100000	0.300000	3.559443	0.296610
1mm _decrease Target Dose % difference (mean)	11	-0.16364	0.000000	-1.3000	0.100000	0.300000	0.405642	0.210548
1mm _decrease Target Dose % difference (max)	11	0.00000	0.000000	-0.1000	0.100000	0.000000	0.044721	1.000000
2mm _decrease Target Dose % difference (min)	11	-1.07273	-0.100000	-11.9000	1.300000	0.300000	3.619417	0.348799
2mm _decrease Target Dose % difference (mean)	11	-0.13636	-0.100000	-1.3000	1.400000	0.500000	0.703239	0.534615
2mm _decrease Target Dose % difference (max)	11	0.00909	0.000000	0.0000	0.100000	0.000000	0.030151	0.340893

Table 3. Summary of organs at risk maximum percentage dose difference.

Variable	% Valid obs.	Mean	p-value	Median	Quartile Range	Std.Dev.
1mm _increase Brain Dose % difference (max)	84.61538	-0.172727	0.000083	0.000000	0.200000	1.231333
2mm _increase Brain Dose % difference (max)	84.61538	0.027273	0.001481	0.100000	0.500000	1.404344
1mm _decrease Brain Dose % difference (max)	84.61538	-0.081818	0.000827	0.000000	0.100000	0.260070
2mm _decrease Brain Dose % difference (max)	84.61538	0.018182	0.008124	0.000000	0.300000	0.534450
1mm _increase Cord Dose % difference (max)	84.61538	-0.200000	0.000003	0.000000	0.100000	0.814862
2mm _increase Cord Dose % difference (max)	84.61538	-0.190909	0.000002	0.100000	0.100000	0.850241
1mm _decrease Cord Dose % difference (max)	84.61538	-0.018182	0.153781	0.000000	0.200000	0.177866
2mm _decrease Cord Dose % difference (max)	84.61538	0.000000	0.008412	-0.100000	0.400000	0.387298
1mm _increase Rt Lens Dose % difference (max)	84.61538	0.381818	0.000000	0.000000	0.100000	1.204839
2mm _increase Rt Lens Dose % difference (max)	84.61538	0.409091	0.000000	0.000000	0.200000	1.196206
1mm _decrease Rt Lens Dose % difference (max)	84.61538	-0.018182	0.106047	0.000000	0.100000	0.098165
2mm _decrease Rt Lens Dose % difference (max)	84.61538	-0.345455	0.000000	0.000000	0.200000	0.950120
1mm _increase Lt Lens Dose % difference (max)	84.61538	0.363636	0.002648	0.100000	0.300000	0.721488
2mm _increase Lt Lens Dose % difference (max)	84.61538	0.436364	0.005447	0.200000	0.700000	0.710314
1mm _decrease Lt Lens Dose % difference (max)	84.61538	-0.018182	0.031964	0.000000	0.000000	0.075076
2mm _decrease Lt Lens Dose % difference (max)	84.61538	-0.372727	0.037626	-0.100000	0.500000	0.595132
1mm _increase Lt Optic Nerve Dose % difference (max)	84.61538	0.263636	0.137714	0.100000	0.400000	0.365416
2mm _increase Lt Optic Nerve Dose % difference (max)	84.61538	0.545455	0.000003	0.200000	0.400000	1.174192
1mm _decrease Lt Optic Nerve Dose % difference (max)	84.61538	-0.236364	0.000000	0.000000	0.000000	0.818868
2mm _decrease Lt Optic Nerve Dose % difference (max)	84.61538	-0.472727	0.000000	-0.100000	0.300000	1.152468
1mm _increase Rt Optic Nerve Dose % difference (max)	84.61538	0.572727	0.000000	0.000000	0.200000	1.805043
2mm _increase Rt Optic Nerve Dose % difference (max)	84.61538	0.581818	0.000000	0.100000	0.200000	1.801010
1mm _decrease Rt Optic Nerve Dose % difference (max)	84.61538	-0.027273	0.324036	0.000000	0.100000	0.064667
2mm _decrease Rt Optic Nerve Dose % difference (max)	84.61538	-0.863636	0.000043	-0.100000	0.400000	2.022510
1mm _increase Lt Lung Dose % difference (max)	84.61538	-0.018182	0.000069	0.000000	0.000000	0.098165
2mm _increase Lt Lung Dose % difference (max)	84.61538	-0.009091	0.000538	0.000000	0.000000	0.104447
1mm _decrease Lt Lung Dose % difference (max)	84.61538	-0.009091	0.000000	0.000000	0.000000	0.030151
2mm _decrease Lt Lung Dose % difference (max)	84.61538	-0.027273	0.003122	0.000000	0.000000	0.064667
1mm _increase Rt Lung Dose % difference (max)	84.61538	-0.018182	0.000069	0.000000	0.000000	0.098165
2mm _increase Rt Lung Dose % difference (max)	84.61538	-0.009091	0.000538	0.000000	0.000000	0.104447
1mm _decrease Rt Lung Dose % difference (max)	84.61538	-0.009091	0.000000	0.000000	0.000000	0.030151
2mm _decrease Rt Lung Dose % difference (max)	84.61538	-0.027273	0.003122	0.000000	0.000000	0.064667

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