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Determining The Optimal Time To Apply Adaptive Radiotherapy Plan For Head And Neck Cancer Patients

Muntather Habeeb Albosaabar[1] , Rozilawati Binti Ahmad[1,*], Hassan Abouelenein[2], Faizal Mohamed[3], Noorazrul Yahya[1], Dalia O. Mohamed[4] and Mona M Sayed[4]

[1]Programme of Diagnostic Imaging and Radiotherapy, Faculty of Health Sciences, Universiti Kebangsaan Malaysia.
[2]Sohag Oncology Center, Egypt.
[3]Department of Applied Physics, Faculty of Science & Technology, Universiti Kebangsaan Malaysia.
[4]South Egypt Cancer Institute (SECI), Asyut University, El- Mesak St. Asyut.

Corresponding author: Rozilawati Binti Ahmad (e-mail: rozie.ahmad@ukm.edu.my).

Abstract **Background:** Head and neck cancer (HNC) patients may have considerable anatomical alterations with IMRT and VMAT. Maintaining dosage precision and minimizing tissue damage using adaptive radiotherapy (ART) improves patients' quality of life. However, the optimal time to initiate ART in HNC patients remains undetermined. **Objective:** This research aimed to identify the optimal time to start ART in HNC patients using a novel method to evaluate anatomical modifications. **Materials and Methods:** The research included 48 people with HNC who had undergone dynamic IMRT. The size of the patient's PTV was used to divide them into different groups. Both the ER of the original PTV and the ER of the revised PTV were determined. ER differences (dER) were correlated with volume decrease percentage (%dV). Pre-treatment CT images were taken, and then again at fractions 7, 14, and 21 throughout therapy. **Results:** The PTV volume distributions were verified to be expected. Small, medium, and high ER volumes showed statistically significant variations between the first and second phases (p<0.001). Fraction 14 was the optimum time to administer ART in cases with a PTV of less than <100cc, whereas fractions 7 and 21 were best for cases with a PTV of 100cc to 500cc. **Conclusions:** The optimal time to begin PTV-based adaptive radiotherapy in HNC patients has been determined. The ER technique improves the clarity of presenting the gap between the reference isodose volume and the PTV, which is valuable information for ART.

Key Words Head and neck cancer, Adaptive radiotherapy, Volume changes, Intensity-modulated radiotherapy

1. Introduction

Radiation treatment for head and neck cancer (HNC) patients is complicated by the inconsistency of target volumes and the proximity of healthy organs. To guarantee optimum dose conformity to the planned target volume (PTV) and to minimize radiation exposure to organs at risk (OAR), intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) have emerged as favored treatments [1]–[4]. These cutting-edge procedures can potentially improve locoregional control while preserving healthy tissue [5], [6].

Adaptive radiation therapy (ART) is effective in the treatment of HNC using intensity-modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT) [1]–[15]. Adaptive replanning is essential for preserving PTV coverage, decreasing toxicity to vital tissues, and enhancing patients' quality of life, according to the results of this research. Despite this agreement, a considerable divide exists over the most appropriate time to begin adaptive radiation in HNC patients [16]–[18].

Radiation therapy presents a significant difficulty for individuals with HNC because tumor volumes vary so quickly throughout treatment [19], [20]. The treatment of head and neck squamous cell carcinoma (HNSCC) is complicated by inter-fractional variability, primarily attributable to target volume differences [21]–[24]. The necessity for replanning during radiation is underscored by previous studies showing significant volumetric changes in OARs [14], [16], [17], [25]–[27]. There is no agreement on the optimal time to intervene to reduce radiation toxicity and preserve healthy tissues and quality of life; thus, reimaging patients after a certain number of treatment fractions is typically recommended [7]–[9], [11], [12], [15].

This study addresses these flaws in three fundamental ways. To begin, it attempts to settle the ongoing debate about when precisely to intervene in cases of radiation poisoning [7]–[9], [12], [15]. Second, this study uses absolute distance differences, especially the effective radius, as opposed to percentage volumetric changes used in earlier studies. In instances with a broad range of volumes, as is typically found in patients with head and neck cancer [22], [24], [28], this method gives a greater understanding of the influence of volumetric variations on dose conformity, OARs, and healthy tissues around the PTV. Finally, this study intends to investigate the significance of volumetric alterations over a comparatively brief treatment period. Adaptive replanning was conducted after seven fractions of therapy, and it was repeated after fractions 14 and 21 to evaluate the full scope and effect of these modifications to the treatment plan.

Therefore, this research investigates the best time to begin ART, taking into account the changes in initial volume and effective radius. It hopes to provide useful insights that may improve the efficacy and accuracy of radiation treatment for HNC patients.

2. Patients and Methods

A. Study Participants

Patients with head and neck cancer (HNC) made up a group of 48 people treated with intensity-modulated radiation treatment (IMRT). On the basis of the obtained results, the purpose of the study was to determine the optimal timing for implementing adaptive radiotherapy treatment planning (BT-ART) using IMRT to HNC patients.

B. Treatment Planning and Replanning

All patients received treatment with dynamic intensity-modulated radiation therapy (DIMRT) delivered by a linear accelerator. Elkta's Monaco version 5.11.02 (Monaco V 5.11.02) was used to plan treatments. Patients were kept stable during treatment using the head-step shoulder immobilization system and five-point thermoplastic masks. Siemens SOMATOM DEFINITION (ERLANGEN, GERMANY) CT scanners were used to acquire 2mm thick slices for the CT scans. Organs at risk (OAR) and tumor volumes (GTV, CTV, and PTV) were defined by RTOG 1016 recommendations [29].

C. Delineation and Dose Prescriptions

The delineation method includes identifying potentially affected organs and outlining the treatment region. The median dosage per fraction was 2 Gy (range from 1.64-2.12 Gy), with 54Gy prescribed for low-risk, 60Gy for intermediate-risk, and 70Gy/33 fractions for high-risk CTV and GTV. The PTV was determined by increasing the CTV by 3 mm before each treatment portion using pretreatment imaging guidance. Since the PTV sizes within the research group ranged from 20cc to 1055cc, it was decided to rescan, re-delineate, and replan after every seven fractions (fractions 7, 14, and 21). Small PTV volumes (20cc-100cc), medium PTV volumes (>100cc-<280cc), and high PTV volumes (>280cc-<600cc) were used to categorise patients.

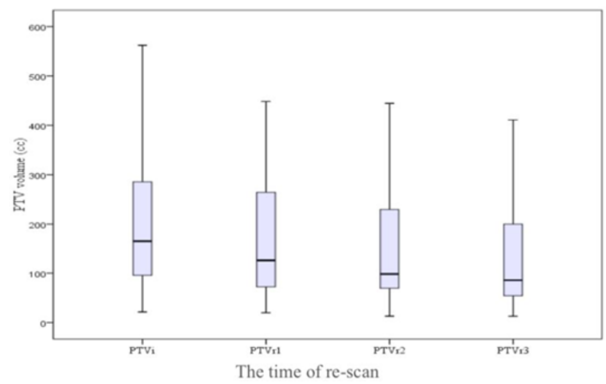

Figure 1: Volumetric changes of PTVs through the first 21 fractions for a whole group of 48 patients between the initial CT (PTVi) and the CT scan at the fractions (7, 14, 21)

D. Effective Radius Calculation

The effective radius (ER) of a sphere of constant volume was determined using Equation 1 [30], allowing for precise evaluation of volumetric changes. In order to comprehend the shifts in PTV volumes, we compared the four CT images for ER changes.

Equation 1:

$$V = \frac{4}{3\pi R^3} \Rightarrow ER = \sqrt[3]{\frac{3V}{4\pi}} \quad (1)$$

E. Criteria for Adaptive Replanning

Previous research informed the selection of 3mm as the threshold for involvement in adaptive replanning. Adaptive replanning was deemed necessary for patients who showed anatomical alterations greater than 3mm on three to four consecutive images.

3. Results

A. Planning Target Volume Changes

This research used anticipated CT scans and rigorous redefining and re-delineation of tumor volumes under the supervision of a consistent radiation oncologist to systematically analyze volumetric changes in 48 individuals diagnosed with head and neck cancer. Figure 1 provides a visual representation of these changes in volume. Surprisingly, in the three CT scans that followed the original one, the planning target volumes (PTVs) shrank by 10%, 25%, and 35%, respectively.

A normal distribution analysis and statistical computations were performed using the DATA Tabe calculator to evaluate the significance of these shifts. After just 7 fractions of treatment, the data revealed extremely significant volumetric differences between PTVi and PTVr1, PTVr2, and PTVr3, with p-values < 0.001.

B. Volumetric and Radius Changes For Group1 (Small Volumes)

A comparison of planning target volume (PTV) alterations across four CT scans revealed considerable percentage differences: 17% between PTVi and PTVr1, 35% between PTVi and PTVr2, and 37% between PTVi and PTVr3. The PTV radius was significantly smaller ($p<0.001$) when volumetric changes were factored in using Equation 1. In particular, the PTV radius reduced from 2.46 cm for PTVi to 2.33 cm for PTVr1, 2.15 cm for PTVr2, and 2.04 cm for PTVr3 (Table 1). The significant decrease in radius 3 mm after 14 fractions of radiation emphasizes the need for prompt action to improve reference isodose conformity to the PTV and dose sparing for adjacent vital structures.

C. Volumetric and Radius Changes For Group2 (Medium Volumes)

The study found significant volumetric changes across the four CT scans for medium planning target volumes (PTVs) between 100cc and 280cc, with percentage differences of 24%, 41%, and 48% between the initial scan (CTi) and the subsequent scans (CTr1, CTr2, and CTr3, respectively; $p<0.002$). The results for the medium volume group, including volume changes, effective radius, variations in effective radius, and p-values, are shown in Table 2.

The research found significant changes in the PTV effective radius (ER) when using Equation 1 to compute the PTV radius owing to volume variations. The observed effective radii for PTVi, PTVr1, PTVr2, and PTVr3 are 3,4, 3,3, and 2,8 centimeters, respectively (Table 2). Changes in medium volume had an even more pronounced effect on conformance than those in small volume, where a 24% drop in PTV volume resulted in a shift of more than 3 mm in radius. These results show that medium-volume modifications may have a significant impact, perhaps affecting conformance by more than 10%.

D. Volumetric and radius changes for group 3 (large volumes)

Patients with large planned target volumes (PTVs) between 280cc and 600cc were studied by comparing volumetric changes across four CT images to determine the best time to use adaptive radiation treatment (ART). The findings revealed statistically significant ($p<0.001$) percentage differences of 8%, 20%, and 24% between the first scan (PTVi) and the two repetitions (PTVr1 and PTVr2, respectively). By using equation 1, we were able to determine the significance of volume variations on PTV radius. PTVi had a radius of 4.3 cm, PTVr1 was 4.01 cm, PTVr2 was 3.9 cm, and PTVr3 was 3.7 cm, as can be seen in Table 3.

Notably, the 8% volumetric change shown between the baseline CT scan and CTr1 appeared to be less than what was seen in the preceding two groups. This difference highlighted the limits of using volumetric changes alone. Specifically, it showed how difficult it is to use this method to pinpoint the ideal moment to begin adaptive radiation treatment (ART).

The ideal time for adaptive radiation treatment (ART) across the three patient groups was determined by using Equation 1, which reveals a linear association between changes in volume and effective radius. Homogeneous volumes between 100cc and 1000cc were separated into ten

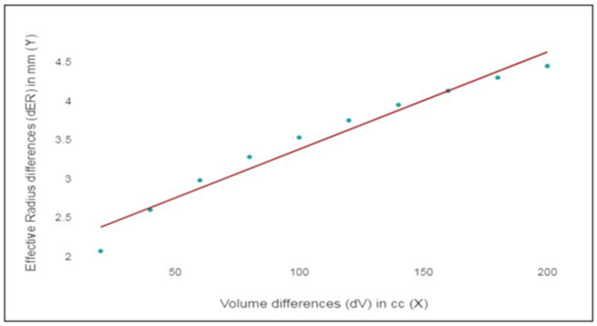

Figure 2: The linear connection between dER and dV. Effective Radius changes (dER). Volumetric change (dV)

groups to verify the notion of the effective radius's applicability. Table 4 shows the resulting effective radii for a 20% decrease in volume for each of these classes. Equation 2 demonstrates a significant linear correlation between dER and dV, with dV being a strong predictor of dER and accounting for 96.09% of the variance ($R2 = 0.96$). Significantly different from zero was the impact that was actually seen ($F = 196.83$, p .001).

$$Y = mx + b \tag{2}$$

A change of 3 mm in radius was used as the intervention goal for treatment plan modification, as suggested by Equation 3 ($dER = 0.01\ dV + 2.13$) generated from the regression model. According to the findings, a reduction of 60cc in volume translates to a 3 mm shrinkage in effective radius. Specifically, the effect of volume changes on effective radius was shown to be a 25% decrease in medium-volume instances and a significant 60% decrease in small-volume cases. The impact was more noticeable for larger volumes; a 15% drop in volume resulted in an equal reduction in effective radius. Figure 2 is a scatter plot that graphically displays these results, demonstrating the linear connection between dER and dV.

$$dER(Y) = 0.01 \times dV(X) + 2.13 \tag{3}$$

4. Discussion

A. Conformity Index and Quality of treatment plans

The Conformity Index (CI) emphasizes the balance between dose conformity and spatial alignment in assessing radiation treatment plans. Volumetric disparities have dominated previous CI formulas, overlooking spatial differences between the tumor and reference isodose line. Advanced CI formulae with volumetric and spatial conformance address this problem [31]–[36].

This research examines the effective radius (ER) parameter for calculating Adaptive Radiation Therapy (ART) scheduling. This technique improves treatment plan quality evaluation by assessing the geographical differences between the Planning Target Volume (PTV) and the reference isodose line. The study's intervention point is a 3mm decrease in the

Patients#	PTVi CC	PTVr1 CC	PTVr2 CC	PTVr3 CC	ERi cm	ER1 cm	ER2 cm	ER3 cm	ERi-ER1cm	ERi-ER2 cm	ERi-ER3 cm
1	21.39	19.79	12.93	12.76	1.72	1.68	1.46	1.45	0.04	0.27	0.27
2	30.22	28.69	15.68	14.64	1.93	1.90	1.55	1.52	0.03	0.38	0.41
3	33.55	30.79	20.36	19.65	2.00	1.95	1.70	1.68	0.06	0.31	0.33
4	40.86	40.35	21.68	19.25	2.14	2.13	1.73	1.66	0.01	0.41	0.47
5	50.27	48.26	27.54	25.76	2.29	2.26	1.87	1.83	0.03	0.42	0.46
6	64.42	65.38	49.78	41.12	2.49	2.50	2.28	2.14	-0.01	0.20	0.35
7	89.48	52.28	45.51	40.32	2.78	2.32	2.22	2.13	0.46	0.56	0.65
8	64.56	36.88	31.66	26.14	2.49	2.07	1.96	1.84	0.42	0.53	0.65
9	96.91	76.01	72.76	54.08	2.85	2.63	2.59	2.35	0.22	0.26	0.50
10	95.04	90.77	75.85	70.29	2.83	2.79	2.63	2.56	0.04	0.21	0.27
11	98.41	76.51	73.26	54.58	2.86	2.63	2.60	2.35	0.23	0.27	0.51
12	96.21	75.31	72.06	53.38	2.84	2.62	2.58	2.34	0.22	0.26	0.51
13	63.72	64.68	49.08	40.42	2.48	2.49	2.27	2.13	-0.01	0.21	0.35
14	71.24	53.76	42.19	35.30	2.57	2.34	2.16	2.04	0.23	0.41	0.54
15	88.97	84.61	82.27	77.87	2.77	2.72	2.70	2.65	0.05	0.07	0.12
Average	67.02	56.27	46.17	39.04	2.47	2.33	2.15	2.04	0.13	0.32	0.43
P-Value	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001

**CC is cubic centimeters. PTVi is the initial planning target volume.
PTVr1 is the first replanning. PTVr2 is the second repplanning.
PTVr3 is the third replanning. ERi, ER1, ER2 and ER3 are the effective radii at the four treatment planning phases.
The Shapiro-Wilk test is a method used to determine if a random sample is drawn from a normal distribution.

Table 1: PTV volumetric changes, effective radius changes and p-value for the small volume group

Patients#	PTVi CC	PTVr1 CC	PTVr2 CC	PTVr3 CC	ERi cm	ER1 cm	ER2 cm	ER3 cm	ERi-ER1 cm	ERi-ER2 cm	ERi-ER3 cm
1	148.91	118.65	89.37	56.69	3.29	3.05	2.78	2.38	0.24	0.51	0.91
2	151.58	124.05	109.58	86.15	3.31	3.10	2.97	2.74	0.21	0.34	0.57
3	203.47	173.87	107.74	88.54	3.65	3.46	2.95	2.77	0.19	0.70	0.88
4	187.86	184.48	179.86	170.59	3.56	3.53	3.50	3.44	0.02	0.05	0.11
5	164.40	68.13	65.66	63.27	3.40	2.54	2.50	2.47	0.87	0.90	0.93
6	205.83	164.35	156.74	152.16	3.67	3.40	3.35	3.31	0.26	0.32	0.35
7	204.17	174.57	108.44	89.24	3.66	3.47	2.96	2.77	0.19	0.70	0.88
8	128.25	111.00	100.00	95.00	3.13	2.98	2.88	2.83	0.15	0.25	0.30
9	147.71	128.12	92.24	85.45	3.28	3.13	2.80	2.73	0.15	0.48	0.55
10	168.40	152.87	96.38	63.79	3.43	3.32	2.85	2.48	0.11	0.58	0.95
11	112.51	90.63	73.01	67.56	3.00	2.79	2.59	2.53	0.21	0.40	0.47
12	209.85	164.37	156.76	152.18	3.69	3.40	3.35	3.31	0.29	0.34	0.37
13	170.28	69.01	66.54	64.15	3.44	2.55	2.52	2.49	0.89	0.93	0.96
14	100.99	91.72	76.80	71.24	2.89	2.80	2.64	2.57	0.09	0.25	0.32
15	138.69	125.16	88.83	77.13	3.21	3.11	2.77	2.64	0.11	0.44	0.57
16	166.51	131.46	128.37	125.19	3.42	3.16	3.13	3.11	0.26	0.28	0.31
17	129.53	108.24	91.03	75.37	3.14	2.96	2.79	2.62	0.18	0.35	0.52
Average	161.11	128.27	105.14	93.16	3.36	3.10	2.90	2.78	0.26	0.46	0.58
P-Value	0.002	0.002	0.002	0.002	0.001	0.001	0.001	0.001	0.001	0.001	0.001

**CC is cubic centimeters.
PTVi is the initial planning target volume.
PTVr1 is the first replanning.
PTVr2 is the second replanning.
PTVr3 is the third replanning. ERi, ER1, ER2 and ER3 are the effective radii at the four treatment planning phases.

Table 2: PTV volumetric changes, effective radius changes and p-value for medium volume group

PTV's effective radius to reduce radiation exposure to Organs at Risk (OARs) and improve patient quality of life.

Table 4 computations highlight the importance of this 3mm decrease. The effective radius decreased by 3mm for an average PTV capacity of 300cc, resulting in a CI of 1.25, which was about 25%, deviating from the ideal value of 1. This deviation from the conformal design shows how regional differences affect treatment effectiveness. Even with larger PTVs with tiny percentage variances, a 10% volume shift reduced the effective radius by 3mm, demonstrating the importance of spatial precision.

The research showed that small PTV volumes had substantial benefits with minor volumetric changes. The effective radius decreased by 1mm due to 24% volumetric changes between identical treatment periods. Expressing volume changes as radius changes helped identify geographical discrepancies and guide OAR modifications. A 3mm calculation grid was a reliable criterion for PTV radius modifications of 3mm or more. Timing adaptive replanning was essential for accurate and successful radiation treatment at this level.

B. IMRT and Steep Dose Gradients

Modern radiotherapy techniques like IMRT, VMAT, SRS, and SBRT aim for steep dose gradients outside the Planning Target Volume (PTV) while minimizing radiation doses to Organs at Risk. Radiosensitive tumors like Head and Neck Cancer (HNC) need Adaptive Radiation Therapy (ART). HNC patients should start ART during the first week, according to prior research [1]–[15]. In HNC situations, permissible dosage distributions typically differ due to the target volume's uneven shape and the closeness to OARs like the spinal cord.

Patients#	PTVi CC	PTVr1 CC	PTVr2 CC	PTVr3 CC	ERi cm	ER1 cm	ER2 cm	ER3 cm	ERi-ER1 cm	ERi-ER2 cm	ERi-ER3 cm
1	280.25	262.73	176.53	168.66	4.06	3.98	3.48	3.43	0.09	0.58	0.63
2	352.29	310.39	297.32	257.3	4.38	4.2	4.14	3.95	0.18	0.24	0.44
3	280.67	262.44	233.64	201	4.06	3.97	3.82	3.64	0.09	0.24	0.43
4	330.55	240.14	235.36	225.36	4.29	3.86	3.83	3.78	0.43	0.46	0.51
5	284.66	262.43	233.63	200.99	4.08	3.97	3.82	3.64	0.11	0.26	0.45
6	403.27	300.87	297.32	257.3	4.59	4.16	4.14	3.95	0.43	0.44	0.64
7	303.55	250.14	240.36	225.36	4.17	3.91	3.86	3.78	0.26	0.31	0.39
8	285.51	245.25	233.86	199.64	4.09	3.89	3.82	3.63	0.2	0.26	0.46
9	360.27	322.87	297.32	257.3	4.42	4.26	4.14	3.95	0.16	0.27	0.47
10	290.67	231.35	210.59	200.64	4.11	3.81	3.69	3.63	0.3	0.42	0.48
11	285.76	237.7	225.78	180.35	4.09	3.85	3.78	3.51	0.24	0.31	0.58
12	428.01	393.49	280.48	244.74	4.68	4.55	4.06	3.88	0.13	0.61	0.8
13	292.55	222.26	205.64	196.25	4.12	3.76	3.66	3.61	0.36	0.46	0.51
14	457.28	413.27	412.7	411	4.78	4.62	4.62	4.62	0.16	0.16	0.17
15	328.99	263.14	237.36	225.36	4.29	3.98	3.84	3.78	0.31	0.45	0.51
16	562.01	448.35	444.48	400.01	5.12	4.75	4.74	4.57	0.37	0.39	0.55
Average	345.49	291.67	266.4	240.7	4.33	4.1	3.97	3.83	0.24	0.37	0.50
P-Value	0.001	0.002	0.002	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001

**CC is cubic centimeters.
PTVi is the initial planning target volume.
PTVr1 is the first replanning.
PTVr2 is the second replanning.
PTVr3 is the third replanning. ERi, ER1, ER2 and ER3 are the effective radii at the four treatment planning phases.

Table 3: PTV volumetric changes, effective radius changes and p-value for large volume group

Volume differences (dV) in cc (X)	Effective Radius differences (dER) in mm (Y)	m*X	b	(dER) in cm	%dV for the same decrease in ER
20	2.06547258	0.2504046	1.815067969	0.2065473	60
40	2.60233238	0.5008092	2.101523157	0.2602332	30
60	2.97892694	0.7512138	2.227713106	0.2978927	20
80	3.27873334	1.0016184	2.277114895	0.3278733	15
100	3.53190843	1.2520231	2.279885374	0.3531908	12
120	3.75321276	1.5024277	2.250785092	0.3753213	10
140	3.9511069	1.7528323	2.198274621	0.3951107	8.5
160	4.13094516	2.0032369	2.12770827	0.4130945	7.5
180	4.2963561	2.2536415	2.042714599	0.4296356	6.6
200	4.44992577	2.5040461	1.945879657	0.4449926	6
		AVER.	2.126666674		
SLOPE (m)	0.012520231	±SD	0.154313184		

*Y are the effective Radius changes (dER), m the slope x is the volumetric changes dV and b is the constant.

Table 4: Parameters used to validate linearity between dER and dv and %dV, which produce a 3mm shift in ER

IMRT is extremely sensitive to positional errors and anatomical alterations due to the pronounced dose gradients that are a hallmark of the therapy. Researchers found that HNC radiation reduces tumor volume [37]. The Planning Target Volume (PTV) decreased 13.16% after four weeks of radiation. IMRT gradients from PTV surfaces are based on separation distance from neighboring OARs, not volume. For a maximum dosage gradient of less than 1% volume, the PTV and OAR must be separated by more than 2 mm, the calculation grid used in this investigation [38]–[40].

C. Determination Of Optimum Time To Apply ART

The analysis of volumetric changes (%dV) depicted in Table 4 demonstrates a direct relationship between the reduction in Effective Radius (ER) and the timing of treatment fractions, as demonstrated by the findings of this study. Group 1, which had small-volume alterations, had a 3 mm ER decrease at treatment fraction 14 (CTr2). The conceptual assumption is supported by this temporal alignment and a 47% %dV for tiny Planning Target Volumes. In Group 2, medium-volume modifications, a 2.6 mm ER alteration resulted in a 30% %dV at treatment fraction 7 (CTr1), a statistically significant result (p=0.001). The research found that the best time for the first Adaptive Radiation Therapy (ART) intervention in the third group of PTV volumes from 280cc to 500cc was fraction number 7 (CTr1). A sustained 3 mm drop in the effective radius between CTr1 and CTr3 necessitated surgery at CTr3.

These optimum timing findings demonstrate the benefits of early replanning, especially in parotid gland sparing for oropharyngeal cancer patients. Mulder et al. [22] have noted that head and neck cancer patients may experience worse quality of life and treatment results due to normal tissue toxicities. The importance of Adaptive Radiation Therapy (ART) in addressing acute toxicities, including xerostomia and dysphagia, was validated by Weppler and Han investigations [28], [40].

5. Conclusion

In conclusion, the effective radius approach, beyond percentage volume reduction, is crucial to adaptive radiotherapy planning time. This research identified intervention points for different PTV volumes. Start adaptive radiation (ART) at fraction 14 (PTVr2) for modest PTV volumes. Medium and large PTV volumes need ART at fractions 7 and 21 (PTVr1 and PTVr3). This research's precise timings, driven by radius reductions, offer improved treatment accuracy and fewer toxicities, highlighting its therapeutic value.

Future studies should examine inter-fractional variability in radiation doses to risk organs. This research supported the notion of a 3mm decrease in effective radius, allowing nuanced treatment methods to enhance results and quality of life for head and neck cancer radiation patients. This research improves adaptive radiation and emphasizes the need for individualized, data-driven treatments in cancer treatment.

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Conflict of interest

The authors declare no conflict of interests. All authors read and approved final version of the paper.

Authors Contribution

All authors contributed equally in this paper.

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