

Comparative Analysis of Parotid Doses in Tomotherapy Versus Volumetric Modulated Arc Therapy for Head and Neck Cancer Patients Undergoing Bilateral Neck Irradiation: A Non-Randomized, Prospective, Dosimetric and Clinical Study

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ABSTRACT:

Background and Objectives: Xerostomia, a common side effect of head and neck radiation therapy, significantly impacts subjective well-being and quality of life. Its severity depends on the radiation dosage received by the parotids. Advanced techniques like Volumetric Modulated Arc Therapy (VMAT) and Tomotherapy offer improved parotid sparing. This prospective, non-randomized, double arm, dosimetric, and clinical study aims to compare parotid dosages between Tomotherapy and VMAT (Rapid Arc) in head and neck cancer patients undergoing bilateral neck irradiation.

Methods: Fifty-two eligible patients were included, with 26 treated by Tomotherapy and 26 by VMAT. Plans were cross planned between the two techniques while maintaining similar Planning Target Volume (PTV) coverage. Bilateral parotid dosages were evaluated, and clinical xerostomia assessment utilized the Xerostomia Questionnaire (XQ) and Radiation Therapy Oncology Group (RTOG) scoring criteria. Statistical analysis employed the paired t-test.

Results: Both right and left parotids received significantly lower mean doses on Tomotherapy ($21.23\text{Gy} \pm 4.429$) compared to VMAT ($23.26\text{Gy} \pm 4.531$) ($p < 0.001$). XQ scores and RTOG scores did not show statistically significant differences between the two arms at both follow-ups. Tomotherapy demonstrated better parotid sparing, translating into reduced acute salivary gland morbidities.

Conclusion: This study highlights Tomotherapy's superiority in parotid sparing over Rapid Arc (VMAT), leading to clinically relevant reductions in xerostomia. Notably, oral cavity cancer patients exhibited higher xerostomia scores, emphasizing the importance of minor salivary glands. Long-term follow-up, extending to at least 2 years post-radiotherapy, is crucial for a comprehensive assessment of the technique's advantage in reducing xerostomia and improving quality of life.

KEYWORDS: Head and neck cancers, Tomotherapy, VMAT, Xerostomia, Parotids

INTRODUCTION:

Head and neck cancer, a pervasive global health challenge, has been a focal point of medical attention for decades, particularly in Southeast Asia, necessitating diverse treatment approaches, ranging from surgery to radiotherapy. Treatment strategies, ranging from surgery to radiotherapy, have evolved over time. As early as 1911, the French pathologist Bergorie described the phenomenon of radiation-induced salivary gland injury (1). Since then, numerous studies have delved into the relative radiosensitivity of these tissues, employing both animal and human models.

Historically, standard radiotherapy (RT) for head and neck cancer (HNC) involved treating major salivary glands within the radiation fields, resulting in a full dose. This approach, while effective in treating cancer, has been associated with significant consequences for salivary gland function. In the initial days of treatment, up to a 50% reduction in parotid gland function is observed. Over time, there is a substantial decline, with less than 10% of saliva flow preserved, and minimal long-term functional recovery (2). Modern radiation therapy techniques, such as Intensity Modulated Radiation Therapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT), aim to address these challenges by minimizing the impact on salivary glands. This study specifically concentrates on the comparative impact of VMAT and Tomotherapy on parotid doses, recognizing the pivotal role of parotids in oral function and the historical challenges associated with traditional radiotherapy. The objective is to contribute insights for future decision-making, emphasizing the importance of preserving salivary gland function for enhanced patient quality of life.

MATERIALS AND METHODS:

Ethical Statement: This study adheres to the principles outlined in the Declaration of Helsinki. Approval was obtained from the Ethics Committee of Basavatarakam Indo American Cancer Hospital and Research Institute, with reference no: IEC/2018/136, dated 10.09.2018.

Informed Consent: Informed consent was secured from all individual participants enrolled in the study.

Study Design: This prospective, non-randomized, double-arm observational study evaluated dosimetry and clinical outcomes in 52 patients with head and neck carcinoma. Patients meeting inclusion criteria for radical, or adjuvant intent underwent treatment with either Volumetric Modulated Arc Therapy (VMAT) or Tomotherapy.

Patient Selection: Patients with biopsy-proven head and neck carcinoma within specified subsites were included, while those with distant metastasis, second primary cancers post-curative therapy, or specific exclusion criteria were excluded. The cohort comprised 26 patients each for VMAT and Tomotherapy arms.

Simulation and Imaging: All patients were immobilized using thermoplastic masks, and contrast-enhanced CT scans were performed with 3 mm slice thickness. Target volumes (GTV, CTV low/intermediate/high risk, and PTV) and organs at risk were contoured based on RTOG guidelines.

Treatment Techniques: Radical intent received 66-70Gy in 33-35 fractions, while adjuvant intent received 60-63.6Gy in 30 fractions. Treatment employed simultaneous integrated boost or sequential phases. Dose constraints for parotid glands were defined.

Planning and Dosimetric Comparison: Planning was conducted on both Tomotherapy and VMAT. Cross-planning between Tomotherapy and Rapid Arc was done. Inverse planning techniques were

employed, with iterative optimization for Tomotherapy plans. Dosimetric parameters were compared, ensuring PTV coverage and dose constraints.

Parotid Dosimetry Comparison: Parotid dosages were compared for both techniques, encompassing D mean, D median, V15, V30, and V50 for right and left parotids, as well as combined parotids' V20.

Concurrent Chemotherapy Plan: Patients undergoing radical intent received weekly cisplatin at a dose of 40 mg/m² or 3-weekly cisplatin at a dose of 100 mg/m². In the adjuvant setting, chemoradiation was administered selectively to patients with positive margins and extra nodal extension. A few patients did not receive any chemotherapy, a decision based on individual patient considerations.

Clinical Evaluation of Patients on Follow-ups: Patients treated with Tomotherapy and VMAT were clinically evaluated at the first and second follow-ups. Evaluation included both patient-reported xerostomia questionnaire (XQ) and observer-reported Radiation Therapy Oncology Group (RTOG) scoring criteria (3).

Xerostomia Questionnaire (XQ): A literature search informed the selection of questions for the XQ, incorporating xerostomia-specific and general head and neck cancer quality of life instruments. The questionnaire, adapted from the Eisbruch xerostomia questionnaire (4), consisted of 8 items assessing dryness while eating or chewing and dryness while not eating or chewing. Patients rated each symptom on an 11-point Likert scale, with scores transformed linearly to produce a final summary score between 0 and 100. Questionnaires were administered at 1st and 2nd follow-ups, 2-3 months, and 5-6 months post-radiotherapy completion for Tomotherapy and VMAT patients, respectively.

Clinical Observations and Toxicity Grading: Patients' medications were recorded at each visit, with restrictions on salivary stimulating or protecting agents during the study. Observer-defined toxicity grading, specifically the RTOG scoring criteria for acute salivary gland morbidities, was employed. This subjective assessment correlated XQ scores and RTOG scores with the treatment technique received.

Table 1: Xerostomia Questionnaire (Adapted from Eisbruch et al)

1. Assess the difficulty you experience in speaking due to dryness.
2. Evaluate the challenge you face in chewing due to dryness.
3. Rate the difficulty you encounter in swallowing solid food because of dryness.
4. Indicate the frequency of sleeping problems attributed to dryness.
5. Evaluate the dryness in your mouth or throat while consuming food.
6. Assess the dryness in your mouth or throat during periods of not eating.
7. Indicate how often you sip liquids to aid in swallowing food.
8. Rate the frequency of sipping liquids for oral comfort during times of not eating.

Table 2: RTOG scoring criteria for acute salivary gland morbidities

- Grade 0: No change over baseline
- Grade 1: Mild dryness of mouth, slightly thickened saliva, slightly altered or metallic taste.
- Grade 2: Moderate to complete dryness, thick sticky saliva, and markedly altered taste.
- Grade 3: Not defined for acute xerostomia.
- Grade 4: Acute salivary gland necrosis.

RESULTS:

Study Evaluation: Patient Characteristics:

Total Enrolment: A total of 52 patients participated in the study, comprising 12 females and 40 males. In the Tomotherapy arm, there were 25 males and 1 female, while the Rapid Arc arm included 11 females and 15 males (refer to Figure 1).

Age Distribution: Among patients treated with Tomotherapy, 10 were aged between 60-70 years, 8 were under 60 years, and 8 were over 70 years. In the Rapid Arc arm, 14 patients were under 60 years, 8 were between 60-70 years, and 4 were over 70 years old (refer to Figure 2).

Treatment Intent: Most patients underwent treatment with radical intent, with 19 in the Tomotherapy arm and 20 in the Rapid Arc arm. Adjuvant intent was observed in 7 patients in the Tomotherapy arm and 6 in the Rapid Arc arm. Treatment modalities included both simultaneous integrated boost and sequential phases, determined by physician preference (refer to Figure 3).

Diagnosis Distribution: Within the Tomotherapy arm, the predominant diagnoses were oral cavity cancers (7), followed by hypopharynx, oropharynx (6 each), larynx (5), and nasopharynx (2). In the Rapid Arc arm, the majority had hypopharyngeal cancers (8), followed by oral cavity, larynx (7 each), oropharynx (3), and nasopharynx (1) (refer to Figure 4).

Fig 1 showing graphical representation of distribution of gender among techniques.

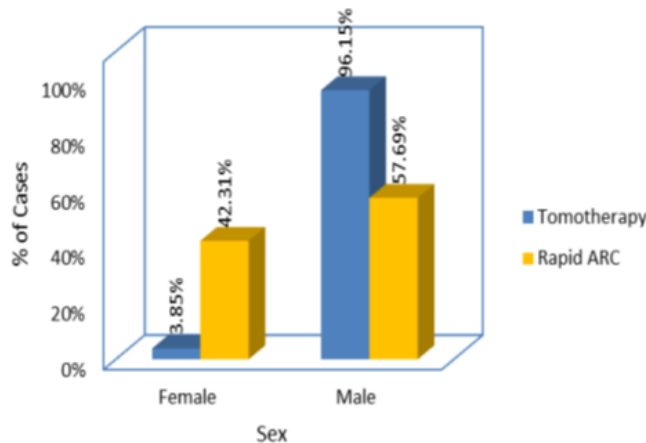


Fig 2 showing graphical representation of age distribution among techniques.

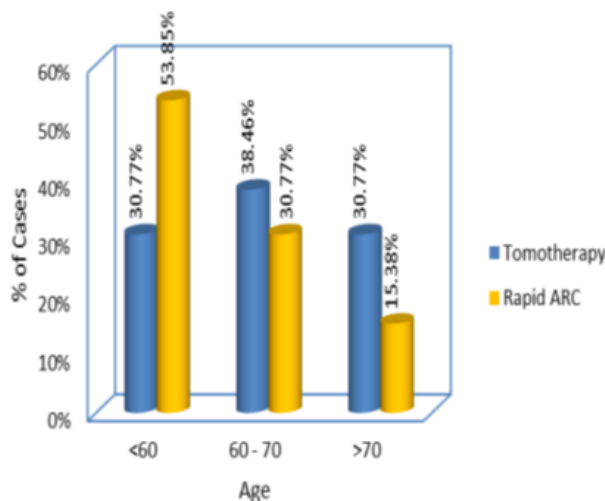


Fig 3 showing graphical representation of distribution of intent to treat among techniques.

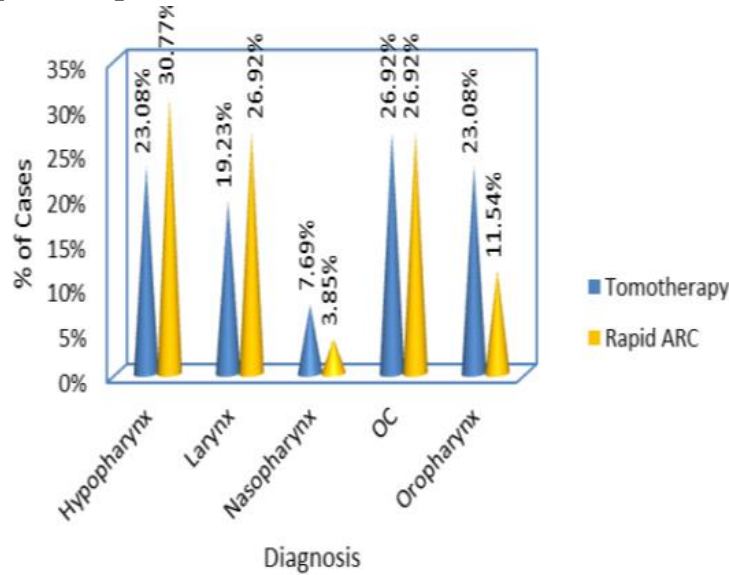
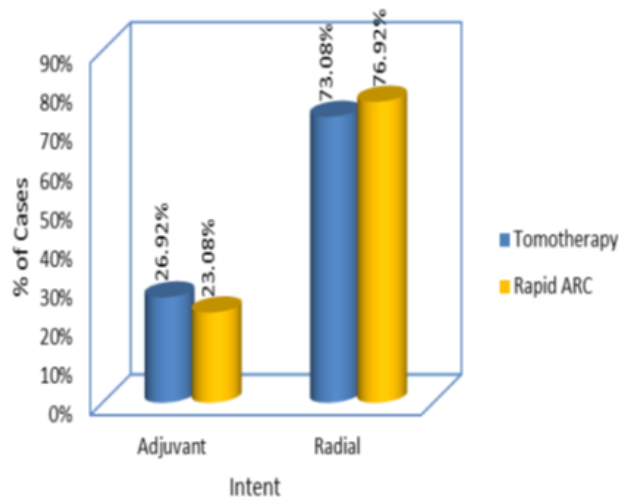


Fig 4 showing graphical distribution of sites treated among techniques.



Total Dose and Number of Fractions: The mean total dose for patients treated with Tomotherapy was 67.26Gy (ranging from 60Gy to 70Gy) with a standard deviation (SD) of 4.09. In the Rapid Arc arm, the mean total dose was 67.345Gy (ranging from 60Gy to 70Gy) with an SD of 3.66. Regarding the number of fractions delivered, the mean in the Tomotherapy arm was 32.04 (ranging from 30 to 35) with an SD of 1.562, and in the Rapid Arc arm, it was 31.88 (ranging from 29 to 35) with an SD of 1.657.

PTV Coverage: For patients treated with Tomotherapy, the mean PTV coverage, representing the dose received by 95% of target volumes, was 65.07Gy (ranging from 57.37Gy to 69.65Gy) with an SD of 4.13 and a standard error (SE) of the mean of 0.81. In the Rapid Arc arm, the mean dose was 65.37Gy (ranging from 57.53Gy to 69.6Gy) with an SD of 3.8.

The mean PTV coverage for Rapid Arc plans executed for patients treated with Tomotherapy was 65.71Gy (ranging from 58.24Gy to 69.45Gy) with an SD of 4.22 and an SE of the mean of 0.82. In Tomotherapy plans executed for patients treated with Rapid Arc, the mean PTV dose was 64.96Gy (ranging from 56.34Gy to 69.06Gy) with an SD of 3.79.

Dose Distribution: The near-maximum dose (D2) ranged from 61.44Gy to 73.3Gy in the Tomotherapy arm (mean 69.11Gy, SD 4.3) and from 61.01Gy to 73.63Gy in the Rapid Arc arm (mean 69.37Gy, SD 3.79). The near-maximum dose (D2) for Rapid Arc plans executed for Tomotherapy-treated patients ranged from 61.22Gy to 75.96Gy (mean 69.17Gy, SD 4.36), and for Tomotherapy plans executed for Rapid Arc-treated patients, it ranged from 61.37Gy to 72.54Gy (mean 69.03Gy, SD 3.57).

The near-minimum dose (D98) ranged from 54.31Gy to 68.9Gy in the Tomotherapy arm (mean 63.94Gy, SD 4.7) and from 51.55Gy to 69.01Gy in the Rapid Arc arm (mean 64.23Gy, SD 4.48). The near-minimum dose (D98) for Rapid Arc plans executed for Tomotherapy-treated patients ranged from 55.14Gy to 68.74Gy (mean 64.41Gy, SD 4.67), and for Tomotherapy plans executed for Rapid Arc-treated patients, it ranged from 55.18Gy to 68.66Gy (mean 61.4Gy, SD 4.15).

Statistical Analysis: In this study, paired t-tests were employed for statistical analysis, considering the dependent nature of the parameters and their normal distribution. The chosen reference p-value (α) was 0.05, with values less than 0.05 considered statistically significant.

"Comparative Analysis of Parotid Dosages":

In assessing parotid dosages, both Tomotherapy and Rapid Arc plans achieved comparable PTV coverages. The key parameters for parotid dosages are detailed below, emphasizing the mean values and their associated standard deviations (SD):

For Tomotherapy Plans:

Mean dose received by 95% of the PTV volume: 65.02Gy +/- SD of 3.929

Mean dose received by 2% of the volume (D2): 69.07Gy + SD of 3.92

Mean dose received by 98% of the volume: 63.83Gy + SD of 4.892

For Rapid Arc Plans:

Mean dose received by 95% of PTV volume: 65.55Gy + SD of 3.98

Mean dose received by 2% of the volume (D2): 69.27Gy + SD of 4.05

Mean dose received by 98% of the volume: 64.32Gy + SD of 4.53

Table 3 provides a comprehensive overview of the mean and SD values for PTV, D2, and D98 across all sites for both Tomotherapy and Rapid Arc techniques.

Table 3: Mean and Standard Deviation of PTV, D2, and D98 for All Sites in Both Techniques		
Parameter	Tomotherapy (52)	Rapid Arc (52)
PTV doses for 95% V	65.02 ± 3.929	65.55 ± 3.981
D2	69.07 ± 3.92	69.27 ± 4.049
D98	63.83 ± 4.892	64.32 ± 4.528

"Dosimetric Analysis of Parotids: Tomotherapy vs. Rapid Arc":

Right Parotids: The mean dose of right parotids in Tomotherapy plans was found to be 21.23Gy with a standard deviation (SD) of 4.429, whereas in Rapid Arc plans, it was 23.26Gy with an SD of 4.531. The statistically significant p-value of < 0.001 indicates that Tomotherapy plans deliver a significantly lower mean dose (D mean) to the right parotids compared to Rapid Arc plans.

Left Parotids: In Tomotherapy plans, the mean dose of left parotids was 22.45Gy with an SD of 7.052, while in Rapid Arc plans, it was 24.75Gy with an SD of 7.642. The observed p-value of < 0.001 suggests that Tomotherapy plans are associated with a significantly lower mean dose (D mean) to the left parotids compared to Rapid Arc plans.

Combined Parotids: The mean average of doses received by 20% of both right and left parotids in Tomotherapy plans was 43.42Gy with an SD of 11.816, whereas in Rapid Arc plans, it was 46.93Gy with an SD of 11.188. The calculated p-value of 0.001 further reinforces that Tomotherapy outperforms Rapid Arc plans in delivering significantly lower doses to the combined parotids.

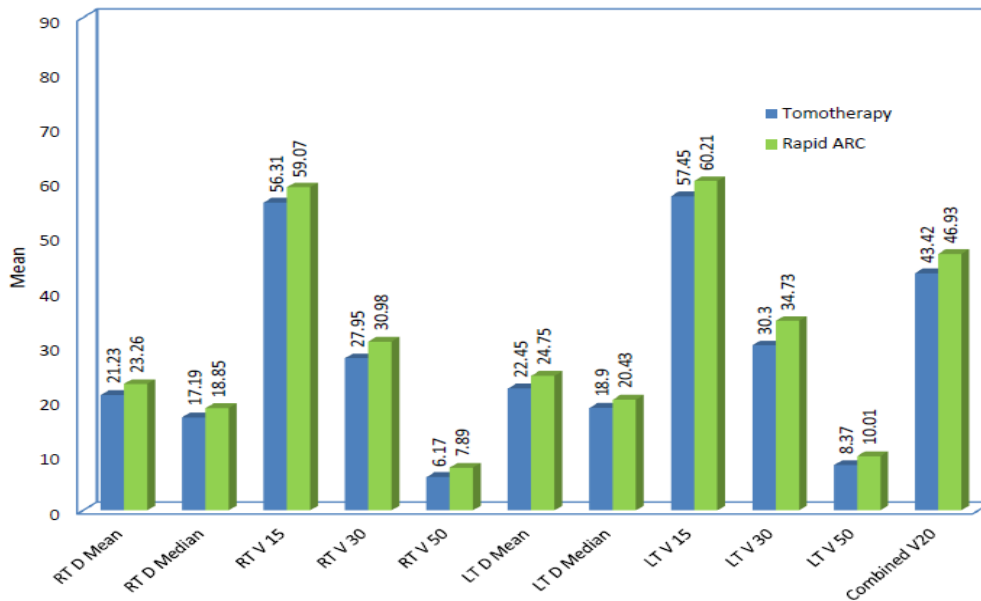
Table 4 provides a comprehensive statistical analysis of dose parameters for left, right, and combined parotids, highlighting the superiority of Tomotherapy over Rapid Arc in minimizing radiation doses to these critical structures.

Table 4: Statistical Analysis of Dose Parameters for Left, Right, and Combined Parotids Among Both Techniques			
Parameter	Tomotherapy	Rapid Arc	P Value
RT Parotid D Mean	21.23 ± 4.429	23.26 ± 4.531	<0.001
RT D Median	17.19 ± 5.723	18.85 ± 6.097	<0.001
RT V 15	56.31 ± 12.914	59.07 ± 12.838	0.002
RT V 30	27.95 ± 8.47	30.98 ± 9.765	<0.001
RT V 50	6.17 ± 6.917	7.89 ± 7.837	<0.001
LT Parotid D Mean	22.45 ± 7.052	24.75 ± 7.642	<0.001
LT D Median	18.9 ± 8.696	20.43 ± 8.918	0.004
LT V 15	57.45 ± 15.099	60.21 ± 14.272	0.004
LT V 30	30.3 ± 15.673	34.73 ± 15.135	<0.001
LT V 50	8.37 ± 11.765	10.01 ± 13.38	0.005
Combined V20	43.42 ± 11.816	46.93 ± 11.188	0.001

"Statistical Significance of Parotid Parameters: Tomotherapy vs. Rapid Arc": The t-Test conducted for all parotid parameters, including D mean, D median, V15, V30, V50, and combined V20, for both right and left parotids revealed a noteworthy finding. The obtained p-values for these datasets were consistently lower than < 0.05. This statistical significance suggests that a meaningful difference exists in the given observations, highlighting the superiority of one treatment technique over the other in terms of parotid dosages.

Graphical Representation: The statistical significance is visually depicted in a graphical representation in Figure 5. This figure serves as a powerful visualization tool, illustrating the distinct and statistically significant differences in parotid parameters between Tomotherapy and Rapid Arc plans.

Fig 5 shows a graphical representation of various dose parameters for right parotids, left parotids, and combined parotids among both techniques.



"Clinical Evaluation of Xerostomia on Follow-up":

Grading Xerostomia (XQ): On the first follow-up, the mean XQ was 41.35 (range, 32 to 54) + SD of 6.331 for patients treated with Tomotherapy and 41.5 (range 32 to 56) + SD 7.77 for patients treated with Rapid Arc. The p-value was 1, indicating no statistically significant difference between the two techniques. On the second follow-up, the mean XQ was 32.65 (range, 26 to 42) + SD of 5.344 for patients treated with Tomotherapy, which was slightly lower than the mean XQ for patients treated with Rapid Arc, 33.42 (range, 24 to 44) + SD 6.357. However, the p-value was 0.639, suggesting that this difference was statistically insignificant. Notably, XQ scores were observed to be lower in the second follow-up compared to the first follow-up for both treatment techniques, as tabulated in Table 5.

Follow-up	Technique Treated	Mean XQ ± SD	p-Value
1st F/U	Tomotherapy	41.35 ± 6.331	1
	Rapid Arc	41.5 ± 7.777	
2nd F/U	Tomotherapy	32.65 ± 5.344	0.639
	Rapid Arc	33.42 ± 6.357	

"RTOG Scoring for Xerostomia at Follow-ups":

RTOG Scoring Overview: At the first follow-up, most patients experienced grade 1 or grade 2 xerostomia in both Tomotherapy and Rapid Arc. The mean RTOG score was 1.38 + 0.496 in the Tomotherapy arm and 1.5 ± 0.51 in the Rapid Arc arm, with an insignificant p-value.

At the second follow-up, the mean RTOG scores were 1.08 ± 0.272 for Tomotherapy and 1.04 ± 0.196 for Rapid Arc. Although the p-value remained less than 0.05, indicating statistical significance, the scores were relatively lower at the second follow-up compared to the first, aligning with the trend observed in XQ scores. The detailed statistical analysis is presented in Table 6.

Table 6: Statistical Analysis of RTOG Scores at First and Second Follow-ups Among Both Techniques Treated

RTOG Score	Technique Treated	Mean ± SD	P-Value
1st F/U	Tomotherapy	1.38 ± 0.496	0.412
	Rapid Arc	1.5 ± 0.51	
2nd F/U	Tomotherapy	1.08 ± 0.272	0.561
	Rapid Arc	1.04 ± 0.196	

DISCUSSION:

DVH Utilization in Clinical Practice: Dose-volume histograms (DVH) emerged as a valuable tool in radiotherapy, offering a comprehensive assessment of delivered dose distribution. Unlike reference point reporting, DVH, as recommended by the International Commission on Radiation Units and Measurements (ICRU) in Report 83, focuses on organ-at-risk (OAR) sparing and target volume coverage (5). Our study adhered to ICRU guidelines, reporting parameters such as D95, D2, and D98 for target volumes.

Parotid Dose Considerations: The significance of sparing salivary glands, particularly the parotids, is well-established in radiotherapy. Literature supports the notion that minimizing the mean dose to parotids is crucial in reducing the risk of xerostomia. Eisbruch et al. (2001) proposed a mean dose threshold of 24–26Gy for severe parotid injury, emphasizing the exponential relationship between mean dose and saliva output (6).

Comparative Analysis: In our study, we compared dose parameters between helical tomotherapy and rapid arc, showcasing their ability to outperform intensity-modulated radiation therapy (IMRT) in terms of target coverage. Wiezorek et al. demonstrated that helical tomotherapy (HT) and volumetric-modulated arc therapy (VMAT), such as rapid arc, provided superior target dose homogeneity and organ-at-risk protection (7). Van Gestel et al. conducted a dosimetric study emphasizing the favourable outcomes of HT in oropharyngeal carcinoma cases (8).

Parotid Dose-Volume Relationships: Salivary glands, acting as parallel-responding tissues, exhibit dose-volume-response relationships. QUANTEC (Quantitative Analyses of Normal Tissue Effects in the Clinic) and Milano et al. recommended controlling the parotid D mean below 25Gy or 26Gy, respectively, to mitigate xerostomia risk (9,10). Our study maintained parotid dosages below these thresholds in both techniques, aligning with the literature suggesting that sparing at least 20 ccs of parotid tissue from doses exceeding 20Gy is crucial for retaining significant saliva production.

Clinical Implications: Our findings not only corroborate existing literature but also extend support for the importance of dose-volume relationships in salivary glands. The optimization of radiation techniques, exemplified by our study's emphasis on DVH and dose thresholds, holds promise in significantly enhancing post-radiation saliva production, reducing xerostomia, and ultimately improving patients' quality of life.

Clinical Correlation of Dosimetric Analysis: Our study extends beyond a mere dosimetric analysis, encompassing a clinical evaluation of xerostomia, aiming to discern the advantages of one technique over another in mitigating salivary gland morbidity. The attempt to correlate dosimetric parameters with clinical outcomes represents a holistic approach to treatment assessment.

Comparative Clinical Outcomes: Boning Cai et al (11) noted a lower incidence of Grade 2 xerostomia with helical tomotherapy (HT) compared to Rapid Arc (RA). Our findings align with the literature, revealing a milder score at the 2nd follow-up in tomotherapy-treated patients. Despite the lack of statistical

significance, both techniques exhibited reduced xerostomia at the second follow-up, suggesting an overall improvement in salivation. Smet et al. (12) reported superior target coverage and lower acute toxicity with rapid arc compared to sliding window IMRT. Our study, while not directly comparing these techniques, contributes to the broader understanding of treatment outcomes by incorporating both dosimetric and clinical perspectives.

Xerostomia Assessment Methods: Accurate measurement of xerostomia is imperative for comprehensive evaluation. We utilized a combination of functional imaging, salivary output measurements, observer-assessed toxicity grading, and patient-reported evaluations. This multifaceted approach enhances the reliability and validity of our findings.

Short-Term Evaluation and Recovery Considerations: Our study evaluated only the first two follow-ups, acknowledging the limited timeframe to comment on xerostomia recovery. Literature supports the notion that the degree of recovery is dose-dependent, with minimal improvement observed at doses exceeding 50–60Gy. Roesink et al. (13) and Eisbruch et al. (6) reported recovery trends in irradiated parotid glands, underscoring the importance of prolonged monitoring.

Treatment Technique Selection: Our anticipation, drawn from the study, suggests that the recent advancements in intensity-modulated radiotherapy (IMRT) techniques, such as helical tomotherapy, offer a feasible strategy for minimizing salivary gland doses in bilateral neck irradiation. Tomotherapy, with demonstrated advantages in delivering lower dosages to parotids, emerges as a favourable choice for head and neck cancer patients undergoing bilateral neck radiation.

Limitations and Future Considerations: While our study provides valuable insights, limitations exist. The subjective nature of patient-reported outcomes and the exclusion of submandibular glands as an organ-at-risk (OAR) are acknowledged. Future studies could explore submandibular gland sparing and extend the follow-up period for a more comprehensive assessment of xerostomia recovery.

CONCLUSION:

In conclusion, our study delves into the intricate interplay of dosimetric precision and clinical outcomes in head and neck cancer treatment, specifically focusing on helical tomotherapy and volumetric modulated arc therapy (VMAT). Both modalities effectively safeguard parotid glands during bilateral neck irradiation, yet helical tomotherapy demonstrates superior dosimetric outcomes by delivering lower dosages to parotids. Interestingly, the observed dosimetric advantages did not uniformly correlate with the incidence of xerostomia, prompting a nuanced understanding of clinical outcomes. Our findings underscore the ongoing advancements in radiation therapy, particularly with helical tomotherapy, and emphasize the need for standardized evaluation metrics for xerostomia. Radiation-induced xerostomia, a significant concern in head and neck cancer treatment, continues to be mitigated by evolving radiation delivery techniques. This study contributes valuable insights to the optimization of radiation therapy, positioning helical tomotherapy as a promising avenue for refining patient outcomes and minimizing treatment-related morbidities.

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