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A prospective study to assess for the prognostic value of tumour volume reduction rate in head and neck cancer, during definitive chemo-radiation in a tertiary care hospital.

SANTHOSHA KULAL [1,*], BHASKAR VISHWANATHAN [2] and GEETA SN [2]

[1] *Department of Radiation Oncology Sri Devaraj Urs Academy of Higher Education and Research Tamaka Kolar. Karnataka India.*

[2] *Department of Radiation Oncology, Vydehi Institute of Medical Sciences and Research Centre, Bangalore, Karnataka India.*

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Abstract

Tumour volume (TV) is an important factor influencing Radiation therapy(RT) outcome of patients. Logically, total dose and its fractionation should be tailored to the initial number of tumor cells which strongly correlated with tumor volume (TV) rather than to the tumor diameter or stage T.

Aims and objectives: To assess tumour volume reduction rate weekly in patients with biopsy proven head and neck cancers treated with definitive chemo-radiation ant to correlate with histology haemoglobin and BMI .

Methods and Materials: All oral cavity, oropharyngeal, hypopharyngeal, nasopharyngeal, and laryngeal cancer patients meeting inclusion criteria were included after obtaining informed written consent. All patients received definitive chemoradiation with weekly CT scanning of head and neck for the assessment of tumour and nodal volume response to chemoradiation. Tumour volume was contoured every week on CT scanning images. Tumour volume response rate (TVRR) was calculated.

Results: Fourty patients were recruited. Most tumours were MDSCC accounting for 55%. Phase 1 TVRR was marginal which steeply increase 3rd week onwards during chemoradiation. In the phase 2, TVRR increased markedly. The mean TVRR on week 7 for WDSCC, MDSCC and PDSCC were 14.38 ± 7.01%, 15.01 ± 7.95% and 19.82 ± 10.44% respectively. The maximum TVRR was observed on the 7 th week of treatment which is the last week of treatment period. Patients with PDSCC had higher TVRR .

Conclusion: Our study demonstrated TVVR increased markedly third week onwards and it was found to be maximum at 7th week .

Keywords: Tumour Volume; Tumour Volume Response Rate; TVRR; HNSCC; Chemoradiation; Adaptive Planning

1. Introduction

Head and neck cancer (HNC) is a heterogeneous tumor at various anatomic sites and one of the most common cancers in India[1]. The commonly used TNM classification system for HNC does not reflect tumour volume (TV). Compared to other known tumour response predictors, the TV appears to be specific and relatively easy to obtain. Higher dose is needed to sterilize a higher number of tumour cells in larger tumours. it is reported that for given tumour clonogen

* Corresponding author: SANTHOSHA KULAL

number increases linearly with the tumour volume (TV)[2,3,4] . With improvement in segmentation algorithms and advances in computer technology occurred, giving the possibility for routine TV assessment.

TV seems to be one of non-anatomical factors representing properties of the tumour and showing significant impact on radiotherapy outcome**.** Because a direct relationship exists among the clonogen number, tumour volume, and radiation dose, the tumour volume could also be predictive of the treatment outcome[5, 6]. The measurements of tumour volume, however, could better reflect the actual tumour burden than the conventional 2-dimensional methods. Meanwhile, the evaluation and assignment of response is performed only after the completion of an RT course. This, in turn, means that the realization of early and timely therapeutic modification, necessary for the patients at high risk of recurrence, is often difficult. The earlier prediction of the prognosis based on the volumetric parameters than the conventional ways could lead to better disease control by providing a basis for the early application of an individualized therapeutic modification.

The adverse effects of increasing tumour burden on local control using radiotherapy (RT) are important. Thus, outcome variations among studies may be partly influenced by unaccounted differences in the tumour volume. Pre-treatment computed tomography (CT) with volumetric analysis has been shown to be an effective predictor of local control in many head-and-neck tumors treated with RT [7-10]. However, most reports investigating volumetric analysis have not evaluated the clinical implications of the volume reduction rate (VRR) during RT.

Several methods for assessing tumor response during irradiation have been applied; the most easily used is the value of the VRR. In clinical practice, this value can be obtained when adaptive radiation planning has been arranged. From the radiobiologic point of view, VRR during irradiation might relate to many factors, such as intrinsic radiosensitivity, tumour kinetics, capacity for tumor repopulation, and proportion of normal tissue in the tumor. Despite recent advances in the response to RT in head-and-neck cancer, implementation of individualized therapy is limited by a lack of comprehensive knowledge about individual response to a given RT until treatment has been completed. If the prognostic value of the VRR for a certain tumor can be understood, radiation oncologists might be able to assess the feasibility of salvage surgery or conduct a dose escalation scheme earlier for those who have great probability of local failure. It has been established that there is direct relationship between various factors like body mass index (BMI), haemoglobin, histopathology pattern and site of tumour to chemoradiotherapy/ radiotherapy in the outcome of treatment.

We hypothesis that, in a considerable number of radiotherapeutic situations, radio-biologically based dose corrections for tumor volume effects could be made before the completion of definitive RT. Such an approach may contribute toward optimized radiotherapy. Also, there is very limited study on tumor volume worldwide as well as in India. Hence our study.

Objectives of the study

- To assess tumour volume reduction rate (TVRR) weekly in patients with biopsy proven head and neck cancers treated with definitive chemo-radiation.
- To assess correlation of various tumour factors like body mass index (BMI), haemoglobin, histopathology pattern, site of tumour, and volume of tumour to chemoradiotherapy/ radiotherapy.

2. Material and methods

It was a Hospital based prospective study. Patients presented with biopsy proven squamous cell carcinoma of head and neck patients planned for definitive radiotherapy with or without chemotherapy to the department of Radiation Oncology, Vydehi Institute of Medical Sciences & Research Centre, Bangalore **during** Jan 2020 to June 2021 . The following patients were **Included in the study (a)**Age more than 18yrs and less than 70 yrs, (b) Eastern Cooperative Oncology Group (ECOG) performance status: 0-2, (c) Histologically proven, un-resectable squamous cell carcinoma of the head and neck (d) no distant metastasis at the time of initial diagnosis. Patients with reccurence or prior surgery were excluded. With 95% confidence interval and 90% power the calculated sample size was **40.**

After obtaining approval from institutional Ethics Committee clearance and obtaining informed written consent from each patient who fulfilled the inclusion criteria, patients are recruited. Pre-treatment evaluation including complete medical history taking and physical examination, routine blood tests, direct flexible fiberoptic endoscopic examination, histopathological examination, computed tomography (CT) scans or magnetic resonance image of the head-and-neck region, were performed in all patients. Patients were staged according to the TNM staging system- American Joint Committee on Cancer cancer staging manual 8th edition.

Patients were underwent mould room procedure - immobilization by a thermoplastic mask and simulation CT scan with contrast in supine position (pre-treatment / initial scan) with 2.5 to 5-mm slice thickness. All sets of acquired simulation CT images were imported into the treatment planning system and the gross tumor volumes (GTVs) of the primary tumor and the metastatic lymph nodes were manually contoured according to RTOG guidelines. The delineation of GTV is based on both clinical examination findings as well as all available diagnostic images. Target volume and normal structures were delineated as per departmental protocol. The primary clinical target volume will be generated by expanding the GTV for primary tumour by 1–1.5 cm and additionally all high-risk regions. The high-risk nodal clinical target volume was contoured by expanding the GTV for lymph nodes by 1 cm, and the low-risk nodal CTV included the remaining nodal levels at risk. PTV was generated by giving a 5-mm expansion in all directions to CTVs. The treatment plans were verified and authorized after cross-sectional and dose–volume histogram analysis of the PTV and organs at risk. RT were delivered by 6-MV photon beams on a linear accelerator and technique will be by either 3-dimensional conformal RT (3D-CRT)/ IMRT OR VMAT. Patient alignments were checked online before treatment by using cone-beam CT on the first day of RT and then repeated once every week. Online corrections were applied if there is deviation beyond the threshold limit 5mm. All patients were treated up to conventional dose of 7000 cGy in 35 fractions and with/without concurrent platinum based chemotherapy.

2.1. Measurement of tumour volume (TV) and tumour volume reduction rate (TVRR):

All patients were undergoing CT simulation on every weekly after intiation of radiotherapy with/without concurrent chemotherapy and on 1 month follow up post treatment. Gross tumour volume (GTV) was calculated which were used for generating tumour volume reduction rate. GTV has seen on the re-simulation CT scan were contoured as GTVP1/ GTVPi (GTV of primary on rescan) and GTVN1 (GTV of node on rescan) along with the new shape/location of normal structures relating to any changes in tumour volumes and normal anatomy. By the same method, interval gross tumour volume(iGTV) of the primary and nodes delineated.

The tumour volume reduction rate (TVRR) is defined as the percentage reduction of the GTV in relation to the PRE- RT GTV and calculated by the following equation[4]:

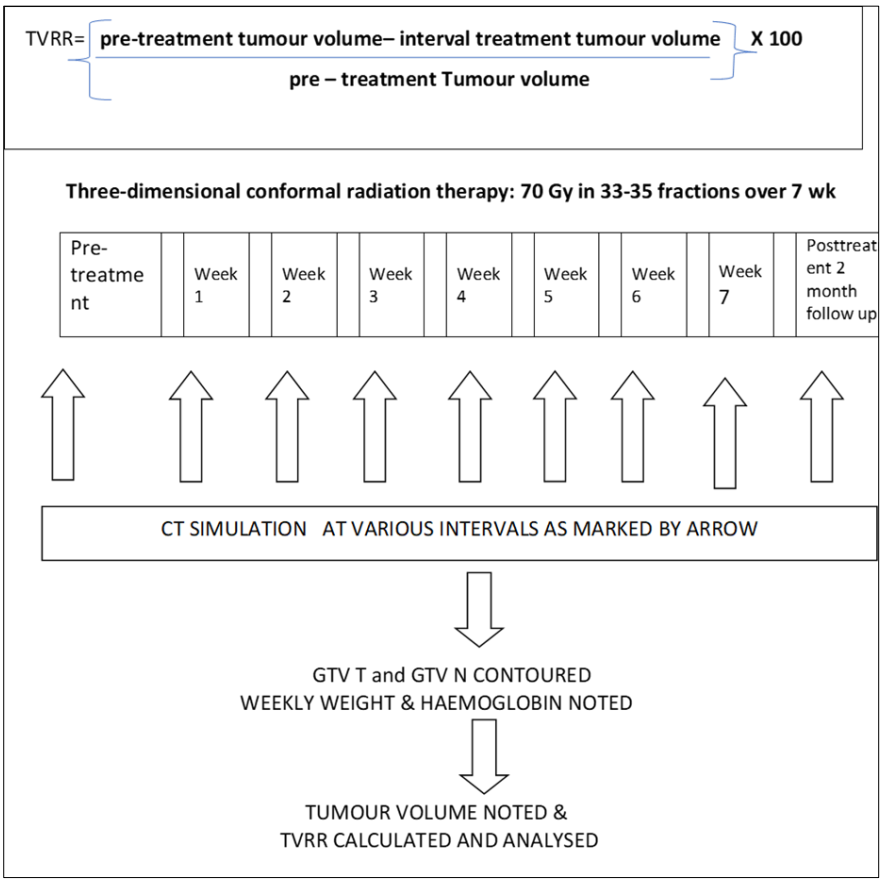

Figure 1 Scheme of tumor volume measurements pre- radiation therapy during and follow up (RT) course. (TVRR-tumour volume reduction rate)

Patients were discharged and called for follow up at 2 months. Tumor response assessment were done on follow up at 2 month with CT simulation scan. After CT simulation with thermoplastic mask, contouring will be done according to RTOG guidelines and analysed. Tumour volumes noted for each week. Tumour volume reduction rate of various tumour and nodes of head and neck cancer derived.

2.2. Chemotherapy

All patients were receiving concurrent platinum-based chemotherapy based on standard guidelines. Chemotherapeutic agents will be administered concurrently with radiation therapy, starting on Day 1 (D1), D8, D15, D22, D29, D36, D43 along with weekly CBC, RFT and serum electrolyte, weight monitoring.

2.3. Statistical analysis

Data were entered and analyzed using SPSS Version 21. Data analysis by Repeated Measure ANOVA were used and performed to see mean GTV and TVRR across different weeks.

3. Result

A total number of 40 patients with oral cavity, nasopharyngeal, oropharyngeal, hypopharyngeal and laryngeal cancers were included, and the various characteristics are shown in the following pages.

Table 1 Patient Characteristics

Patient Characteristics	Number of patients
Age (Years)	
<50	14(35%)
>50	26(65%)
Sex	
Male	28 (70%)
Female	12 (30%)
History of smoking	
Tobacco smoking	25 (62.5%)
Betel nut chewing	03 (7.5%)
No habits	12 (30%)
Clinical T stage	
cT1	05(12.5%)
cT2	03(7.5%)
cT3	11(27.5%)
cT4A	13(32.5%)
cT4B	08(20%)
Clinical N stage	
cN0	07(17.5%)
cN1	10(25%)
cN2A	01(2.5%)
cN2B	03(7.5%))
cN2C	11(27.5%)

cN3A	0
cN3B	08(20%)
Histological Findings	
WDSCC	08 (20%)
MDSCC	22 (55%)
PDSCC	10 (25%)
Body mass index	
Underweight (< 18.5)	15
Normal (18.5 -24.9)	13
Overweight (25-29.9)	09
Obesity (≥30)	03(7.5%)
Hemoglobin	
8 – 10 mg/dl	06
10 - < 12 mg/dl	03(7.5%)
12- <14 mg/dl	11(27.5%)
>/= 14 mg/dl	20(50%)
Primary Site	
CA Oral Cavity	06 (15%)
CA Oropharynx	12 (30%)
Nasopharynx	03 (7.5%)
Hypopharynx	06 (15%)
Glottis	03 (7.5%)
Supraglottic	10 (25%)

Table 2 Bar diagram showing weekly mean tumour volume response rate (TVRR) as per histology during treatment

TVRR (%) / HISTOLOGY	**WEEK1**	**WEEK2**	**WEEK3**	**WEEK4**	**WEEK5**	**WEEK6**	**WEEK7**	**P-value**
WDSCC	2.25 ± 1.64	3.06 ±1.77	12.02 ± 9.71	9.08 ± 3.29	7.97 ±5.57	12.30 ± 4.06	14.38 ± 7.01	<0.0001*
MDSCC	2.19 ± 2.58	3.4 ± 3.09	8.11 ± 7.12	9.03 ± 7.41	11.51 ± 7.68	15.4 ± 9.36	15.01 ± 7.95	<0.0001*
PDSCC	1.5 ± 1.15	3.43 ± 2.28	8.63 ± 5.09	9.7 ± 4.98	18.58 ± 7.38	13.78 ± 7.19	19.82 ± 10.44	<0.0001*
P-value	0.668	0.947	0.430	0.995	0.010*	0.631	0.281	

The mean TVRR on week 1 for WDSCC, MDSCC and PDSCC were 2.25 ± 1.64%, 2.19 ± 2.58%, 1.5 ± 1.15%. The mean TVRR on week 2 for WDSCC, MDSCC and PDSCC were 3.06 ±1.77%, 3.4 ± 3.09%, and 3.43 ± 2.28% **respectively.** The mean TVRR on week 3 for WDSCC, MDSCC and PDSCC were 12.02 ± 9.71%, 8.11 ± 7.12% and 8.63 ± 5.09% **respectively.** The mean TVRR on week 4 for WDSCC, MDSCC and PDSCC were 9.78 ± 3.29%, 9.93 ± 7.41% and 9.7 ± 4.98%

respectively. The mean TVRR on week 5 for WDSCC, MDSCC and PDSCC were 7.97 ±5.57%, 11.51 ± 7.68% and 18.58 ± 7.38% **respectively.** The mean TVRR on week 6 for WDSCC, MDSCC and PDSCC were 12.30 ± 4.06%, 15.4 ± 9.36% and 13.78 ± 7.19% **respectively.** The mean TVRR on week 7 for WDSCC, MDSCC and PDSCC were **14.38 ± 7.01%, 15.01 ± 7.95% and 19.82 ± 10.44% respectively.** With respect to tumour volume reduction rate, the maximum mean reduction was observed in the 7th week for WDSCC, MDSCC and PDSCC were 14.38 ± 7.01%, 15.01 ± 7.95% and 19.82 ± 10.44% respectively. Detains shown in table-2 and and figure-1

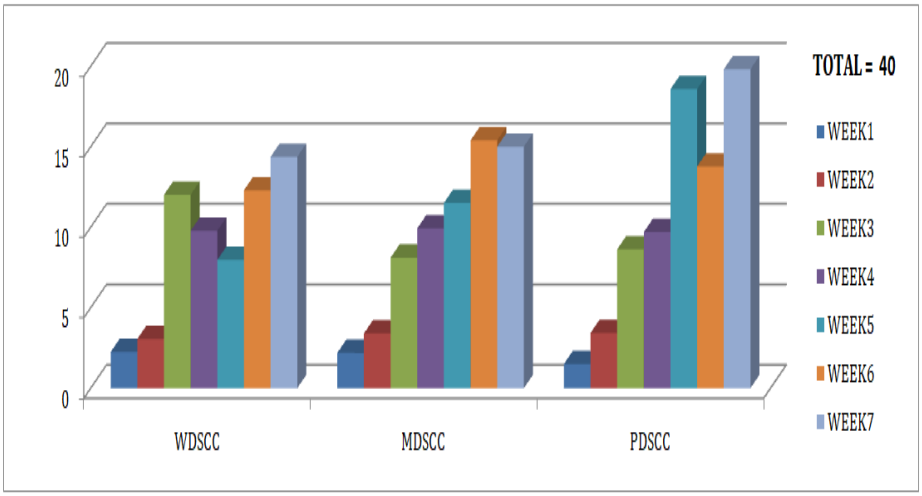

Figure 2 Bar diagram showing weekly mean tumour volume response rate (TVRR) as per histology during treatment (X-axis:histological types , Y-axis: mean TVRR in %age)

The week-wise mean phase-1 and phase- 2 tumour volume reduction rate (TVRR) between different histology groups shown in above table no-3. The week-wise mean phase-1 tumour volume reduction rate in our study for WDSCC, MDSCC, and PDSCC were 8.29 %, 7.16 % and 6.66 % respectively. The week-wise mean phase - 2 tumour volume reduction rate in our study for WDSCC, MDSCC, and PDSCC were 42.84%, 43.72 % and 49.03 % respectively. Upon testing with chi square test, there is a statistically significant difference noted between the week wise phase 1 and phase 2 reduction rates. This implies that the reduction in the phase-2 is much higher compared to the reduction that happened in phase-1. In other words, we can conclude that among patients undergoing chemoradiation, maximum tumour volume reduction is expected in the phase 2. **Among histology, maximum reduction was shown by WDSCC in phase 1 and by PDSCC in phase 2.**

Table 3 Bar diagram showing week-wise mean phase 1 and 2 TVRR as per histology during treatment

Histology	**MEAN PHASE 1 WEEKLY TVRR (%) with SD**	**MEAN PHASE 2 WEEKLY TVRR (%) with SD**	**P value**
Well Differentiated SCC	8.29 ± 4.93	42.84 ±15.73	0.00094*
Moderately Differentiated SCC	7.16 ± 5.30	43.72 ± 15.84	<0.00001*
Poorly DifferentiatedSCC	6.66 ± 3.13	49.03 ± 9.16	0.00018*
P Value	0.7666	0.5751	

The week-wise mean phase-1 and phase- 2 nodal volume reduction rate (NVRR) between different histology groups shown in above table no-4. The week-wise mean phase-1 nodal volume reduction rate in our study for WDSCC, MDSCC, and PDSCC were 9.03%, 9.96 % and 11.87 % respectively. The week-wise mean phase-2 nodal volume reduction rate in our study for WDSCC, MDSCC, and PDSCC were 30.69 %, 47.17 % and 458.11 % respectively. Upon testing with Chi square test, there is a statistically significant difference noted between the week-wise phase 1 and phase 2 reduction rates in MDSCC and PDSCC. This implies that the reduction in the phase 2 is much higher compared to the reduction that happened phase 1 for MDSCC and PDSCC. In other words, we can conclude that among patients undergoing

chemoradiation, maximum nodal volume reduction is expected in the phase 2. Among histology, maximum reduction was shown by PDSCC in phase 1 as well as phase 2

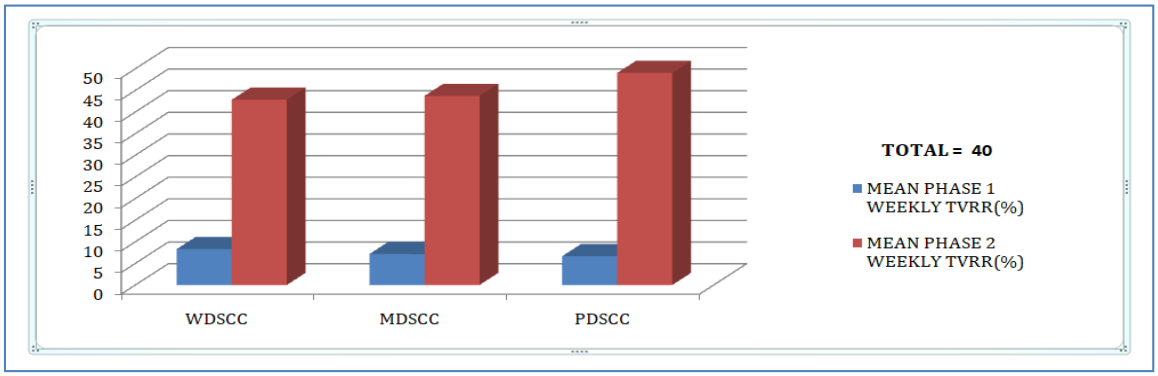

Figure 3 Bar diagram showing week-wise mean phase 1 and 2 TVRR as per histology during treatment

(X-axis:histological types , Y-axis: mean weekly TVRR in %age)

Table 4 Bar diagram showing week-wise mean phase 1 and 2 NVRR as per histology during treatment.

Histology	MEAN PHASE 1 WEEKLY NVRR (%) with SD	MEAN PHASE -2 WEEKLY NVRR (%) with SD	P value
Well Differentiated SCC	9.03 ± 11.85	30.69 ± 33.23	0.42952
Moderately Differentiated SCC	9.96 ± 7.07	47.17 ± 23.37	<0.00001*
Poorly Differentiated SCC	11.87 ±11.03	58.11 ± 28.29	0.00318*
P Value	0.7915	0.1093	

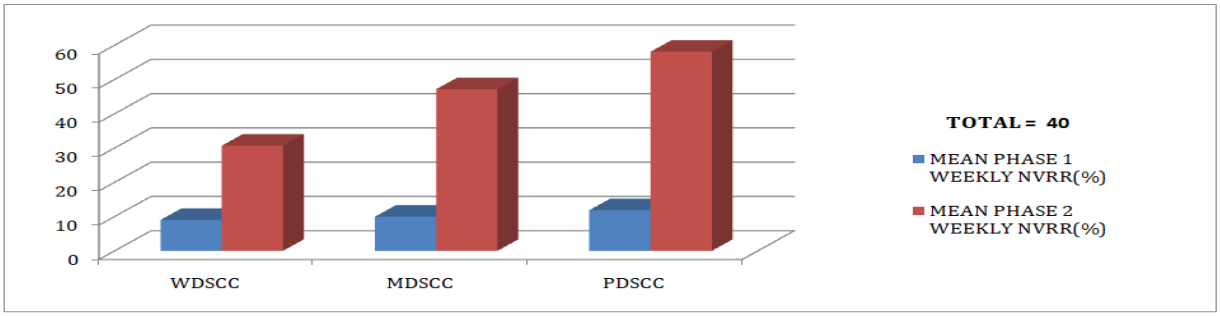

Figure 4 Bar diagram showing week-wise mean phase 1 and 2 NVRR as per histology during treatment

(X-axis: Histological types , Y-axis: mean weekly NVRR in %age)

Table 5 The mean TVRR and NVRR between different body mass index during treatment

BMI	MEAN TVRR (%)	P value	MEAN NVRR (%)	P value
< 18.5 kg/m^2	29.61 ± 7.28	<0.0001*	28.42 ± 17.04	0.136
18.5 - < 24.9 kg/m^2	40.3 ± 7.15		28.6 ± 20.10	
25 – 29.9 kg/m^2	46.38 ± 8.37		38.13 ± 6.22	
>/= 30 kg/m^2	45.93 ± 3.50		54.84 ± 20.42	

The mean TVRR (mean TVRR from week 1-7) and NVRR (mean NVRR from week 1-7) between different **body mass index (BMI)** shown in below table no-5. In our study, the maximum mean TVRR seen in **25 – 29.9 kg/m² BMI** Group (46.38 ± 8.37%) and maximum mean NVRR was seen in **>/= 30 kg/m²** BMI group (54.84 ± 20.42) % respectively. Upon testing with chi square test, there is statistically significant difference in higher BMI vs lower BMI noted. However, there is no statistically significant difference noted between NVRR vs BMI.

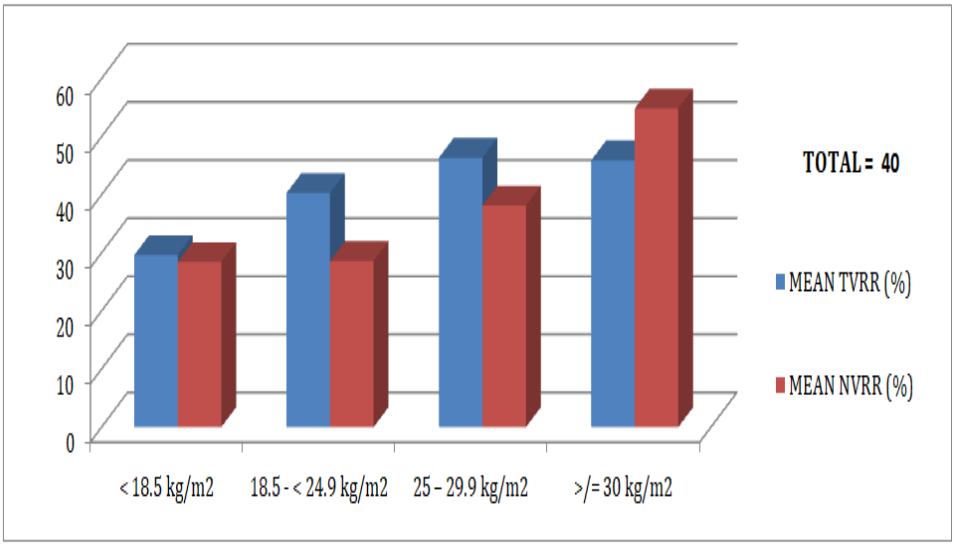

Figure 4 Bar diagram showing the mean TVRR and NVRR between different body mass index during treatment

(X-axis:Body Mass Index , Y-axis: mean TVRR and NVRR in %age)

The mean TVRR (mean TVRR from week 1-7) and NVRR (mean NVRR from week 1-7) between different **haemoglobin group** shown in above table no-6. In our study, the maximum mean TVRR seen in **>/= 14 mg/dL** haemoglobin Group (44.06 ± 7.26%). Upon testing with chi square test, there is statistically significant difference in higher haemoglobin and TVRR noted.

Table 6 The mean TVRR and NVRR between different haemoglobin category during treatment

HAEMOGLOBIN	MEAN TVRR (%)	P value	MEAN NVRR (%)	P value
8- <10 mg/dL	24.18 ± 6.98		35.32 ± 11.33	
10 - < 12 mg/dL	32.76 ± 2.51		21.58 ± 20.45	
12 - <14 mg/dL	35.23 ± 6.92		27.31 ± 19.82	
>/= 14 mg/dL	44.06 ± 7.26	<0.0001*	34.64 ± 17.68	0.494

The residual disease at 2 months between histology shown in above table no-7. In the study, total of 13 patients were had residual disease at 2 months. Most of the residual disease seen in WDSCC group However it was not statistically significant.

Table 7 Incidence of residual disease at 2 months as per histology in the study

HISTOLOGY	NUMBER	RESIDUAL DISEASE	p value
WD	8	3 (37.5%)	0.1243
MD	22	7 (31.81%)	
PD	10	3 (30%)	
Total	40	13	

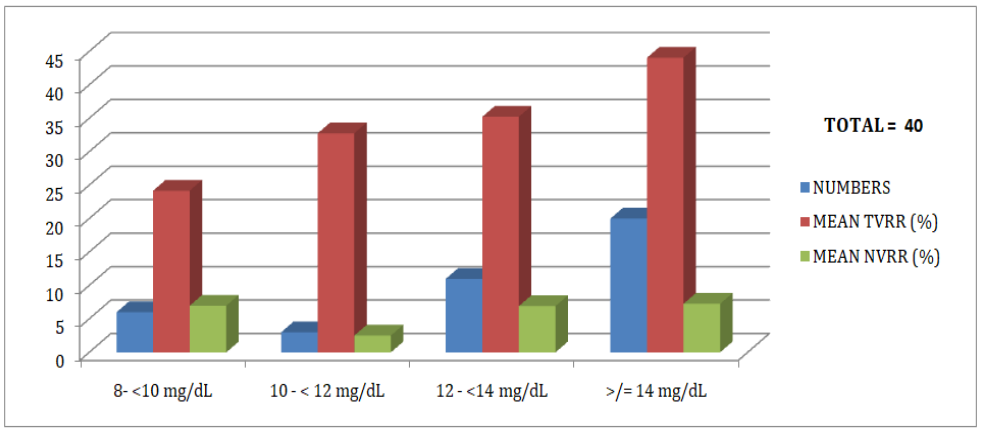

Figure 5 Bar diagram showing the mean TVRR and NVRR between different haemoglobin category during treatment.

(X-axis - Hemoglobin Level , Y-axis - mean TVRR and NVRR in %age)

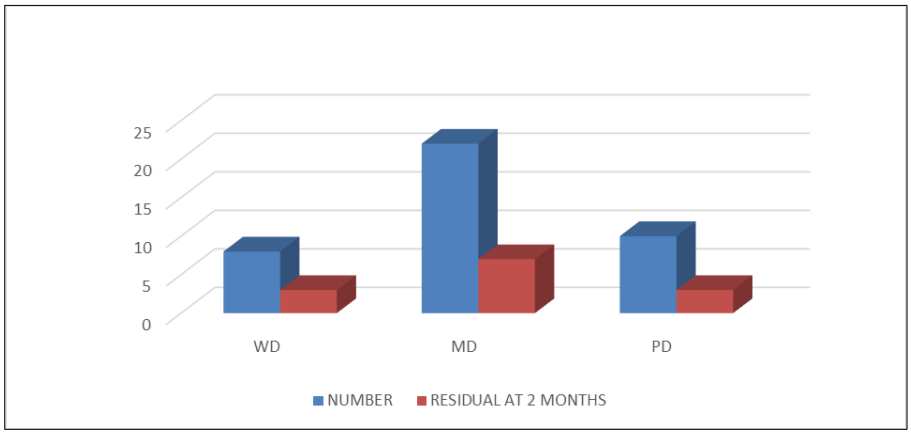

Figure 6 Bar diagram showing Incidence of Residual Disease At 2 Months as Per Histology

(X-axis – Histological types, Y-axis – number of residual disease at 2 months)

The comparison of tumour and nodal parameters among residual and no-residual disease group at 2 months shown in table no-8. The mean BMI between residual and no-residual disease group were 16.96 ± 2.95 Kg/m2 and 22.84 ± 4.34 Kg/m2 respectively. The mean TVRR between residual and no-residual disease group were 25.56 ± 11.22% and 36.45 ± 10.66 % respectively. Upon testing with chi square test, there is statistically significant difference between the groups noted. This implies that the reduction is much higher in no residual group who had higher BMI compared to the reduction that happened residual disease group who had lower BMI. In other words, we can conclude that among patients undergoing chemoradiation, maximum tumour volume reduction is expected in the higher BMI group.

The mean haemoglobin between residual and no-residual disease group at 2 months were 11.27 ± 2.14mg/dl and 13.7 ±1.51 mg/dl respectively. The mean TVRR between residual and no-residual group at 2 months were 25.56 ± 11.22% and 36.45 ± 10.66 % respectively. Upon testing with chi square test, there is statistically significant difference between the groups noted. This implies that the reduction is much higher in no residual group who had higher haemoglobin compared to the reduction that happened residual disease group who had lower haemoglobin. In other words, we can conclude that among patients undergoing chemoradiation, maximum tumour volume reduction is expected in the higher haemoglobin group.

The mean pre-treatment tumour volume between residual and no-residual group at 2 months were 63.46 ± 51.16 cc and 28.54 ± 15.41 cc respectively. The mean TVRR between residual and no-residual disease group were 25.56 ± 11.22% and 36.45 ± 10.66 % respectively. Upon testing with chi square test, there is statistically significant difference

between the groups noted. This implies that the reduction is much higher in no residual group who had lower tumour volume compared to the reduction that happened residual disease group who had higher tumour volume. In other words, we can conclude that among patients undergoing chemoradiation, maximum tumour volume reduction is expected in the lower tumour volume group.

The mean pre-treatment nodal volume between residual and no-residual disease group at 2 months were 37.86 ± 44.01 cc and 10.26 ± 14.45 cc respectively. The mean NVRR between residual and no-residual group at 2 months were 33.08 ± 21.85 % and 38.72 ± 23.79% respectively.

Table 8 Comparing tumour and nodal parameters between residual and no-residual disease group at 2 months

MEAN ± SD	RESIDUAL DISEASE GROUP	NO-RESIDUAL DISEASE GROUP	P VALUE
BODY MASS INDEX(Kg/m2)	16.96 ± 2.95	22.84 ± 4.34	0.00018*
HAEMOGLOBIN (mg/dL)	11.27 ± 2.14	13.70 ± 1.52	0.00052*
TVPW0(cc)	63.46 ± 51.16	28.54 ± 15.41	0.00114*
MEAN TVRR (%)	25.56 ± 11.22	36.45 ± 10.66	0.0004*
NVW0(cc)	37.86 ± 44.01	10.26 ± 14.46	0.0784*
MEAN NVRR (%)	33.08 ± 21.85	38.72 ± 23.79	0.475

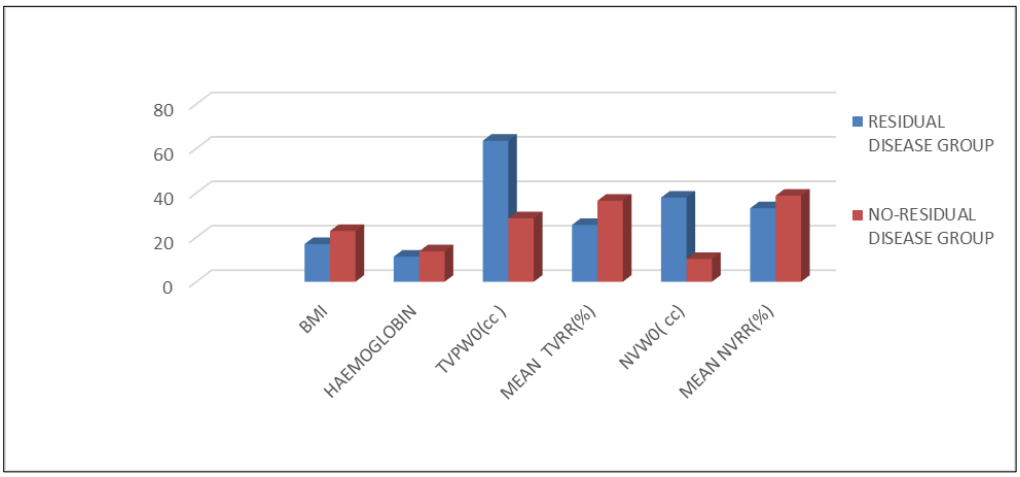

Figure 7 Bar diagram showing comparison of tumour and nodal parameters between residual and no-residual disease group at 2 months. (X-axis - tumour and nodal parameters between residual and no-residual disease**,** Y-axis– quantitative numbers with respective units)

4. Discussion

Several authors have noted that TV is even better predictor of treatment outcome than TNM system or AJCC clinical stage [11]. Head and neck malignant tumours subsites are T-classified with the consideration of tumour dimension. In these cases the classification is based on a single dimensional measurement only. Such surrogate for TV seems to be not adequate. Traditionally, tumour and nodal categorization as part of TNM staging have used unidimensional thresholds. Such categorization makes an assumption of tumours being spherical and such measurements are assumed to be a surrogate for tumor burden. Staging based on single dimension measurement may be insufficient due to various clinical appearance of the tumour.

Of 40 patients most of the patients were belonged to oropharyngeal region (30%) and were moderately differentiated squamous cell carcinomas histology (55%). In this study, phase 1 volume response rate was marginal which steeply

increase 3rd week onwards during chemoradiation. In the phase 2, VRR increased markedly. So, this implies that ideal time for the adaptive planning/aggressive treatment strategy can be done in those set of patients who are at risk for locoregional failure in the phase 2 of treatment during chemoradiation. Accelerated repopulation which is rapid multiplication of surviving clonogens during a course of irradiation may contribute to local failure. since growth characteristics of a specific tumour may change during a course of irradiation, the optimal fractionation scheme may also vary during treatment. Recognition of this possibility is very important since accelerated hyper-fractionation is being used with increased frequency for many disease sites throughout the body Most accelerated hyper-fractionation trials have used a uniform fractionation scheme throughout treatment[12] and therefore do not compensate for changes in tumor growth characteristics that may occur during treatment. Accelerated repopulation of tumor clonogens late in radio- therapy is an insidious threat to the efficacy of radiotherapy. Awareness of the potential of tumors for accelerated regrowth should not be obscured by the apparent continuing regression of the macroscopic tumor mass. If treatments are interrupted, the radiotherapist should aim to make up lost time through administration of more than 1 fraction/ day if such treatments would be tolerated by the mucosa.[13]

Accelerated dose delivery at the start of therapy may not be advantageous since many of the tumor cells are likely to be hypoxic (non-cycling cells) and therefore relatively radioresistant. Conversely, accelerated dose delivery later in treatment (after tumor shrinkage and accelerated repopulation of clonogens has occurred) may be more useful[12,14]. Most tumour volume changes occur after the second week of treatment[14-17]. This means that the appropriate time for either adaptive interventions or assessment of tumour regression might be more than 2 weeks after the beginning of irradiation. If adaptive planning is done in the late phase of an irradiation course, its advantages might be restricted because of the limited response time. The mean TVRR on week 1 for WDSCC, MDSCC and PDSCC were 2.25 ± 1.64%, 2.19 ± 2.58%, 1.5 ± 1.15%. The mean TVRR on week 2 for WDSCC, MDSCC and PDSCC were 3.06 ±1.77%, 3.4 ± 3.09%, and 3.43 ± 2.28% respectively. The mean TVRR on week 3 for WDSCC, MDSCC and PDSCC were 12.02 ± 9.71%, 8.11 ± 7.12% and 8.63 ± 5.09% respectively. The mean TVRR on week 4 for WDSCC, MDSCC and PDSCC were 9.78 ± 3.29%, 9.93 ± 7.41% and 9.7 ± 4.98% respectively. The mean TVRR on week 5 for WDSCC, MDSCC and PDSCC were 7.97 ±5.57%, 11.51 ± 7.68% and 18.58 ± 7.38% respectively. The mean TVRR on week 6 for WDSCC, MDSCC and PDSCC were 12.30 ± 4.06%, 15.4 ± 9.36% and 13.78 ± 7.19% respectively. The mean TVRR on week 7 for WDSCC, MDSCC and PDSCC were 14.38 ± 7.01%, 15.01 ± 7.95% and 19.82 ± 10.44% respectively. Upon performing statistical tests, to find whether there was difference between the week wise reduction rate, above results are noted. Upon testing with Chi Square test, there is a statistically significant difference noted between the week-wise reduction values. As seen in the graph, reduction rate in the initial two weeks were very minimal which markedly increased third week onwards. This increase in reduction rate was maximum in 7th week. This implies that the reduction rate in the 7th week is much higher compared to the reduction that happened in the other weeks. In other words, we can conclude from our study that among patients undergoing chemoradiation, maximum tumour volume reduction is expected in the 7th week. Among histology, similar findings observed. However, PDSCC had higher reduction rate as compared to other histology groups. As observed in our study, the maximum TVRR was observed on the 7th week of treatment which is the last week of treatment period.

Despite the limitations, such as the small sample size, the lack of a uniform combination of chemotherapeutic agents, primary sites, tumour staging, nodal staging, stage group and total radiation dose and fractionation schedule, this study provides a novel volumetric marker for head-and-neck cancer. Of course, actual oncologic outcomes do not depend simply on volumetric factors alone. The VRR value itself might represent a combination outcome of several biologic parameters. Based on our data, we recommend using VRR during adaptive imaging as a parameter for assessing local control in some head- and-neck cancers. For the best treatment modification in simultaneous integrated boost technique, adaptive image at 4 to 5 weeks might be relevant. In other words, daily fraction size could be increased in the second course of IMRT if a dose-escalation scheme needs to be done without prolongation of treatment time. Nonetheless, the best timing of adaptive planning might be earlier and need further investigation for optimizing a dose-escalating scheme. As seen in our study data, 7th week will be too late for adaptive planning. Considering all these facts, we recommend appropriate time for either adaptive interventions or assessment of tumour regression might be planned around 3-5 weeks after the beginning of irradiation if the desired TVRR was not met in the relatively radio-resistant tumour histopathology types.

In our study, the maximum mean TVRR and maximum mean NVRR was seen in PDSCC Groups (39.63 ± 6.29 % and 37.73 ± 18.57 respectively). Upon testing with chi square test, there was statistically significant difference noted (p value = 0.00018*).

Although there is evidence that tumour hypoxia adversely affects locoregional tumour control and survival in HNC patients it is still not well established how hypoxic fraction of the tumor could be measured. Results of some studies suggest that TV may, in some way, predict effectiveness of RT both, reflecting status of tumor oxygenation and correlating with hemoglobin (Hb) concentration.

Haemoglobin concentration is well recognized prognostic factor for HNC patients treated with RT. Among other assumptions, it has been proposed that Hb is a surrogate marker for tumor hypoxia[16] but still few data exist to test this hypothesis. In our study, the mean haemoglobin between residual and no-residual group were 11.27 ± 2.14mg/dl and 13.7 ±1.51 mg/dl respectively. Upon testing with chi square test, there is statistically significant difference between the groups noted. This implies that the reduction is much higher in no residual group who had higher haemoglobin compared to the reduction that happened residual disease group who had lower haemoglobin. In other words, we can conclude that among patients undergoing chemoradiation, maximum tumour volume reduction is expected in the higher haemoglobin group.

Our data shows higher haemoglobin group had better TVRR and NVRR as compared to lower lower haemoglobin group. Nordsmark et al. found both, Hb and tumor hypoxia as significant but independent prognostic factors for locoregional tumor control for HNC patients after RT, and Hb concentration was not a surrogate marker of tumor hypoxia [16]. Rutkowski et al. described significant negative correlation between TV and Hb concentration both, before and after RT in 160 patients with T2 laryngeal cancer [17]. Stadler et al. tried to reevaluate the prognostic significance of hypoxic fraction, percentage of pO_2, median pO_2. In this study significant correlation between Hb concentration and TV was also found[18]. We recommend prompt correction of anemia and adequate nutrition counseling before the initiation of treatment and regular monitoring.

In this study the mean BMI in residual disease at 2 months group was 16.96Kg/m^2 whereas for no residual group had much higher mean BMI (22.83Kg/m2) group . The mean pre-treatment tumour volume between residual and no-residual group at 2 months were 63.46 ± 51.16 cc and 28.54 ± 15.41 cc respectively. The mean TVRR between residual and no-residual disease group were 25.56 ± 11.22% and 36.45 ± 10.66 % respectively. Our data shows higher BMI group had better TVRR and NVRR as compare to lower BMI group. Obesity, however, has not been shown to increase risk or worsen prognosis in HNSCC. In fact, lower BMI is associated with increased incidence of HNSCC, independent of tobacco and alcohol use 19-22. First, obesity may act as a "buffer" from weight loss due to treatment-related side effects such as dysphagia, mucositis, and poor appetite, which impacts survival27 . The existing data has also suggested that high BMI is associated with improved prognosis in HNSCC patients23-26 with the exception of one study of oral tongue SCC showing lower survival rates in obese patients 26. We recommend detailed counselling and adequate nutrition care before the initiation of treatment and regular monitoring of weight during treatment.

In our study, the mean pre-treatment primary tumour volume between residual and no-residual group at 2 months were 63.46 ± 51.16 cc and 28.54 ± 15.41 cc respectively. The mean TVRR between residual and no-residual disease group were 25.56 ± 11.22% and 36.45 ± 10.66 % respectively. Upon testing with chi square test, there is statistically significant difference between the groups noted. This implies that the tumour volume reduction rate was higher in no-residual disease group as compared to residual disease group.

In our study, we have divided T1T2 as early stage disease(8 patients (20%)) and T3T4 as locally advanced disease(32 patients (80%)). The mean T1, T2 TVRR in residual and no-residual disease group were 34.64 ± 0.89 % and 44.02 ± 13.30 % respectively. The mean T3,T4 TVRR in residual and no-residual disease group were 23.91 ± 11.46% and 34.28 ± 9.02% respectively. Though it is evident that T1T2 showing higher tumour volume reduction rate it can't be generalised as majority of study population consisted of locally advanced disease (T3T4). In our study, locally advanced (T3, T4) disease residual disease group had larger pre-treatment tumour volume (71.57 ± 51.59 cc) with lower TVRR (23.91 ± 11.46%) in contrast to no-residual disease group having pre-treatment tumour volume of 31.49 ± 15.01 cc and of TVRR of 34.28 ± 9.02%.

We also analysed if the residual disease status post treatment had any bearing on initial tumour volume. **volume. Among** residual disease, those patients with lesser tumour volume had lower haemoglobin (<12 mg/d/L), lower BMI (<18.5mg/kg2) and of well differentiated histology which could be the reason for lesser TVRR. Remaining 27 patients had no residual disease at 2 months. Among No-residual disease, those patients with larger tumour volume in this group had higher haemoglobin (> 12 mg/d/L), higher BMI (> 18.5mg/kg2) that could be the reason for higher TVRR. Due to precise estimation, TV may be used predictor for the choice between more and less aggressive treatment strategy.

However, we also analysed whether all the residual disease group , patient had larger initial tumour volume in our study. We found that one patient having initial tumour volume of 12.15cc belonged to T2 stage had residual disease group at 2 months follow up period. On reviewing the patient data, we found that patient had advanced nodal stage (N3b), lesser haemoglobin and of well differentiated histology which were potential causes for the residual disease.

In our study the mean pre-treatment nodal volume between residual and no-residual group at 2 months were 37.86 ± 44.01 cc and 10.26 ± 14.45 cc respectively. The mean NVRR between residual and no-residual group at 2 months were

33.08 ± 21.85 % and 38.72 ± 23.79% respectively. Upon testing with chi square test, there is no statistically significant difference between the groups noted. This could be because of heterogenous data, smaller sample size and shorter follow up period. From our study data, mean primary tumour volume of 63.46 ± 51.16 cc and mean tumour volume reduction rate of 25.56 ± 11.22 % will predict the higher possibility of having residual disease at 2 months. Similarly, mean tumour volume of 28.54 ± 15.41 cc and mean tumour reduction rate of 36.45 ± 10.66 % will predict the lesser possibility of having residual disease at 2 months. This was correlated with TVRR which found statistically significant (p value- 0.0012)

In our study, we have divided N0N1 as early nodal disease and N2N3 as advanced nodal disease. We could observe a trend in our study population in which those patients who had persistent primary residual disease , advanced nodal disease (N2N3) showed higher TVRR of 28.23 ± 11.95% compared to early nodal disease(N0N1) which showed TVRR of 19.55 ± 7.28%. Similarly those patients who had no-residual primary disease at 2 months, advanced nodal disease (N2N3) showed higher TVRR of 37.37 ± 8.51 % compared to early nodal disease (N0N1) which showed TVRR OF 35.59 ± 12.60 % . However further analysis to be done to correlate radio-biologically.

5. Conclusion

We would conclude that, in a considerable number of radiotherapeutic situations, radio-biologically based dose corrections for tumor volume effects could be made, both for the treatment, and from fraction to fraction. Such an approach may contribute toward optimized radiotherapy. A primary GTV threshold may assist in risk stratification to help identify patients at high risk of failure who might benefit from various strategies of treatment intensification using TVRR and combined modality therapy. Finally, we would recommend a clinical trial with a larger sample size and longer follow up to validate our findings which was limited by its small sample size and shorter follow up.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors have no conflicts of interest to declare.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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