Original Article

Prognosticating Gross Tumor Volume in Head-and-Neck Cancer – Redefining Gross Tumor Volume Beyond Contouring

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Abstract

Purpose: Precision radiotherapy (RT) requires accurate delineation of gross tumor volumes (GTVs) for targeted dose delivery. Volumetric measurement of this GTV can predict the treatment outcomes. This volume has been limited for mere contouring and its potential as the prognostic factor is less explored. **Materials and Methods:** The data of 150 patients with oropharynx, hypopharynx, and larynx cancer undergoing curative intensity-modulated RT and weekly cisplatin between April 2015 and December 2019 were retrospectively evaluated. GTV-P (primary), GTV-N (nodal), and GTV-P+N were defined, and volumetric parameters were generated. Volume thresholds were defined as per the receiver operating characteristics, and the prognostic value of these tumor volumes (TVs) with respect to treatment outcomes was analyzed. **Results:** All patients completed 70 Gy, median chemotherapy cycles were six. Mean GTV-P, GTV-N, and GTV-P+N were 44.5 cc, 13.4 cc, and 57.9 cc, respectively. Oropharynx constituted 45% of cases. Forty-nine percent had Stage III disease. Sixty-six percent had complete response (CR). As per the defined cutoff values, GTV-P <30cc, GTV-N <4 cc, and GTV-P+N <50 cc had better CR rates with $P < 0.05$ (82.6% vs. 51.9%; 74% vs. 58.4% and 81.5% vs. 47.8%, respectively). At median follow-up of 21.4 months, overall survival (OS) was 60% and median OS was 32.3 months. The median OS in patients with GTV-P <30 cc, GTV-N <4 cc, and GTV-P+N <50 cc was better with $P < 0.05$ (59.2 vs. 21.4; 59.2 vs. 22.2, and 59.2 vs. 19.8 months, respectively). **Conclusion:** GTV should not just be limited for contouring but its role as an important prognostic factor has to be recognized.

Keywords: Gross tumor volumes, head-and-neck cancer, intensity-modulated radiotherapy, prognostic factor

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Introduction

Radiotherapy (RT) with or without chemotherapy is the standard of care in the definitive management of squamous cell carcinomas (SCCs) of the pharynx and larynx.[1] Volume-based precision RT techniques such as intensity-modulated RT (IMRT) or image-guided IMRT (IG-IMRT) have become routine in the contemporary RT practice in head-and-neck cancers after the results of parotid-sparing intensity-modulated versus conventional radiotherapy in head-and-neck cancer trial.[2] With these techniques, we not only are able to visualize and delineate the extent of tumor in three dimensions but also measure them volumetrically. Volumetric measurement is just not a geometric data, it gives us valuable information on the tumour burden,[3] number of clonogenic cells in the tumor[4] and extent of hypoxia;[5] all of which have independent bearing on the tumor response to RT and the ultimate clinical outcomes.

Defining the tumor extent accurately is the foremost and crucial part of IMRT planning process. Especially, in the modern day RT as high conformality, dose escalation and dose painting strategies are in practice. This tumor volume can be defined in diagnostic computed tomography (CT) imaging by manual, semiautomated, or automated segmentation process. Slice-by-slice segmentation is considered the current reference method to assess tumor volumes.[6,7] Similar process is followed in defining the tumor volume during RT planning.

Planning CT images are used for defining gross tumor volume (GTV), whereas data from magnetic resonance imaging or positron emission tomography (PET) images can

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be fused for more accurate delineation. This GTV is specific to the patient and precise; most importantly is an integral part of RT planning process, very easy to measure and is a complementary data as we define tumor volumes (TVs) routinely in every single case.

While the prognostic value of traditional factors such as tumor node metastasis (TNM) and stage group has been well recognized,[8] TV as a predictive and prognostic factor in head-and-neck cancers is least explored. Although few published literature across different primary tumor sites exist,[9-14] these were mostly at the time when IMRT was still emerging. In recent times, as IMRT and IG-IMRT have become an indispensable part of RT in head-and-neck cancers, further effort to build on this evidence or an attempt to integrate volumetric data with TNM is lacking. Consequently, the merit of GTV is confined for contouring purpose alone. This study aims to evaluate the prognostic significance of GTV in patients with locally advanced head and neck-SCC, treated with concurrent chemoradiation (CCRT).

Materials and Methods

TV parameters of 150 consecutive patients with Locally advanced head and neck squamous cell carcinoma (LA-HNSCC) treated from April 2015 to December 2019 in a single unit were retrospectively reviewed and analyzed. LA-HNSCC of oropharynx, larynx, and hypopharynx treated with curative intent chemoradiation with simultaneous integrated boost (SIB)-IMRT and weekly cisplatin were included in this study. Details are shown in Table 1.

The treatment compliance, survival outcomes, and prognostic factors affecting the outcome of these patients were earlier published in April 2022.[15]

Radiotherapy

On the contrast-enhanced simulation CT scan images with 2.5 mm slice thickness, GTV was defined for the primary (GTV-P) and node (GTV-N). GTV was delineated based on clinical assessment (physical examination and endoscopic evaluation) and simulation images on all relevant axial slices as per the standard guidelines.[16] The volumetric measurement of GTV-P and GTV-N was calculated separately using the volume measurement algorithm on Varian Treatment Planning system-Eclipse Version 11. A separate volume GTV-P+N was defined, which was the sum of GTV-P and GTV-N, to represent the total tumor burden.

Around these GTV, clinical target volumes-high (70 Gy), intermediate (59.4 Gy), low risk (54–56 Gy) were defined and final planning target volumes (PTV) - PTV-high risk, PTV-intermediate risk and PTV-low risk were generated with 5mm margin. Organs at risks were contoured and constraints were defined. Treatment was planned with seven or nine field SIB-IMRT technique, to a total dose of 70 Gy in 33 or 35 fractions at a dose of 2.12 Gy or 2 Gy per fraction over 6.5–7 weeks.

Table 1: Demography, tumor, and treatment characteristics

Characteristic	*n*=150, *n* (%)
Age (years), median (range)	58.5 (29-81)
Sex	
Male/female	109/41 (73/27)
KPS	
>70	150 (100)
Site of primary	
Oropharynx	68 (45)
Hypopharynx	54 (36)
Larynx	28 (19)
Tumor stage	
T2/T3	24/93 (16/62)
T4a/T4b	30/3 (20/2)
Nodal stage	
N0	48 (32)
N1/N2/N3	35/62/5 (23/41/3)
Stage group	
III	73 (49)
IVA	67 (45)
IVB	10 (06)
Radiotherapy	
70 Gy	150 (100)
Chemotherapy	
Cisplatin	118 (78.6)
Carboplatin	32 (21.3)
Chemotherapy (cycles)	
Median (IQR)	6 (5-6)
5 cycles or more (>200 mg/m^2)	125 (83.2)
OTT (days), median (IQR)	50 (48-54)

IQR: Interquartile range, OTT: Overall treatment time, KPS: Karnofsky performance status

Statistics

All statistical analyses were done using the SPSS software version 16. Descriptive statistics were used to analyze the demographic and tumor characteristics. Time to event was defined from the start of RT. Kaplan − Meier estimates were performed to calculate the overall survival (OS) and locoregional control (LRC).

The GTV values were analyzed using the measures of central tendencies-mean and median. Receiver operating characteristics (ROC) curves were constructed for OS endpoint and a volumetric threshold was defined which corresponded to 30 cc for GTV-P, 4 cc for GTV-N, and 50cc for GTV-P+N at area under curve-0.66, respectively. Analysis of variance was conducted to assess the association between GTV and various descriptive characteristics (primary tumor site, T status, stage group, and complete response [CR] rates) and disease outcomes. Univariate and multivariate analysis was done on them using log-rank test to study the correlation to survival. $P < 0.05$ was considered statistically significant, throughout the analyses.

Results

Tumor volume parameters

Among 150 patients, 49% had Stage III disease and 45% had oropharyngeal primary. All patients completed planned RT 70 Gy in 33–35#. Median chemotherapy cycles were 6.

For the total patient population, the mean GTV-P, GTV-N, and GTV-P+N were 44.5 cc (range 2.4–169.3 cc), 13.4 cc (range 0–156.1 cc), and 57.9 cc (range 2.4–227 cc), respectively. Mean GTV-P values for different primary sites, T status, and stage groups are depicted in Table 2.

While correlating GTV-P with the nodal status, mean GTV-P in node-negative patients was 24 cc as compared to 54 cc in node-positive patients showing statistically significant difference ($P = 0.00$).

Outcomes

At a median follow-up of 21.4 months for the entire cohort and 36 months in surviving patients, the OS was 60%. Median OS was 33.2 months, estimated 2-year and 5-year OS was 56% and 42%, respectively. 2-year LRC was 62.4%.

CR was seen in 99 patients (66%) where the mean GTV-P values were smaller as compared to non CR, as shown in Table 2. Those who achieved CR also had significant OS benefit (median OS-not reached vs. 9.1 months, $P = 0.00$).

On univariate analysis GTV, N0 status, N_0–N_1 nodal group, stage III disease, RT dose per fraction −2.12 Gy, use of cisplatin chemotherapy, and CR to treatment showed statistically significant OS ($P < 0.05$). On multivariate analysis, only CR and 2.12 Gy fractionation showed OS benefit.

Of the 51 patients who did not achieve CR, 4 developed metastasis all of whom had loco-regional residual disease. The mean GTV-P and GTV-P+N in them were 70.1 cc and 102 cc. Of the 99 patients who had CR, 29 patients have expired. 5 developed second primary, 6 had local only, 1 had loco-regional-distal, 2 had distal (bone only) failures, and 15 patients died of other causes. Rest are alive and disease-free. The mean GTV-P and GTV-P+N in those with distal failure was 40 cc and 62 cc, respectively.

Table 2: Tumor volume parameters

Parameter	GTV-P*	SD (+/−)	Range
Overall	44.5	36.8	2.4-169.3
Site			
Oropharynx	56.2	38.9	4.5-169.3
Hypopharynx	31.7	23.8	3.8-122
Larynx	42.6	44.1	2.4-169.3
T status			
T2	24.1	12.9	3.8-54.5
T3	37.6	32	2.4-169.3
T4a	74.7	41.1	18.9-169.3
T4b	104.2	24.9	73.1-126.7
Stage group			
III	25.2	16	2.4-63.2
IVA-B	63.1	41.6	9.6-169.3
Response			
CR	34.2	29.7	2.4-137.6
Non-CR	64.2	41.3	9.6-169.3

*Mean volume in cc. GTV: Gross tumor volume, SD: Standard deviation, CR: Complete response

Outcome difference with respect to receiver operating characteristics cutoff points

Complete response rates

GTV-P <30 cc, GTV-N <4 cc, and GTVP+N <50 cc had better CR rates – 82.6%, 74%, and 81%, respectively ($P < 0.05$), as shown in Figure 1.

Overall Survival

The median OS in patients with GTV-P <30 cc, GTV-N <4 cc, and GTVP+N <50 cc was better with 59.2 months, as shown in Figure 2.

Survival difference within different primary sites, T status, and stage group

While the defined ROC cut offs showed significant survival difference in oropharynx and hypopharynx, none showed in larynx. Hence, the cutoff points were defined separately for each of the sites and was noted that the cutoff values differed for each of the sites-for oropharynx, hypopharynx, and larynx the GTV-P, GTV-N, and GTV-P+N cutoff values were 45 cc, 20 cc and 29 cc; 7 cc, 2 cc and 2 cc; 60 cc, 31 cc and 35 cc, respectively. Even then significant ($P < 0.05$) was noted for GTV-P and GTV-P+N for oropharynx, GTV-P for hypopharynx, and none for larynx.

Within the T3 disease category, when dichotomized with cut off values, the median OS for GTV-P <30 cc was 59.2 months ($P = 0.00$). Such difference was not seen within T2 or T4 category where the patient numbers were less.

Across stage III disease, statistically significant median OS difference was seen for GTV-P+N and only for GTV-P among stage IV patients.

Details are shown in Table 3.

Discussion

The mean GTV-P, GTV-N, and GTV-P+N values in our study were different and spread over a wide range with larger

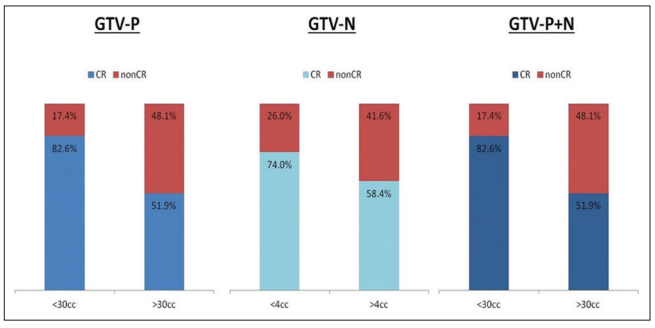

Figure 1: GTV and response rates. GTV: Gross tumour volume

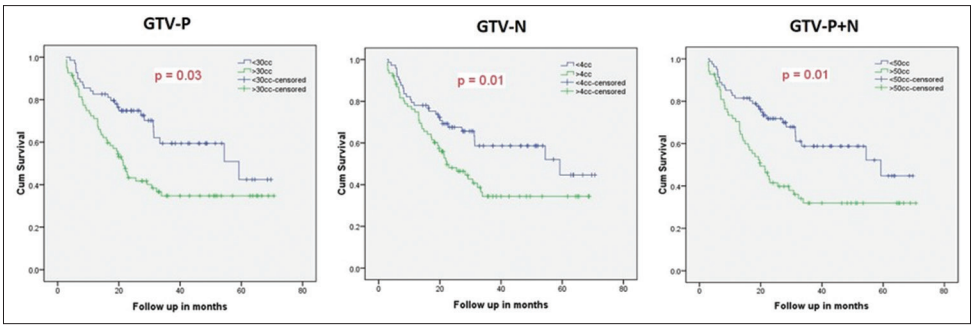

Figure 2: GTV and overall survival. GTV: Gross tumor volume

Table 3: Survival outcomes with respect to receiver operating characteristics threshold

Parameter	Median OS months	*P*
Site		
Oropharynx		
GTV-P*	54.4 versus 20.8	0.007
GTV-N*	54.4 versus 22.2	0.08
GTV-P+N*	NR versus 16.3	0.00
Hypopharynx		
GTV-P	33.3 versus 19.8	0.04
GTV-N	31.3 versus 19.8	0.07
GTV-P+N	31.3 versus 19.8	0.32
Larynx		
GTV-P	59.2 versus NR	0.99
GTV-N	59.2 versus NR	0.74
GTV-P+N	59.2 versus NR	0.77
T Status		
T2 GTV-P	NR versus NR	0.14
T3 GTV-P	54.4 versus 19.8	0.004
T4 GTV-P	NR versus 18.1	0.36
Stage group		
Stage III		
GTV-P	59.2 versus NR	0.57
GTV-N	59.2 versus 29.3	0.27
GTV-P+N	NR versus 19.8	0.02
Stage IV		
GTV-P	33.1 versus 18.1	0.03
GTV-N	22.7 versus 21.4	0.60
GTV-P+N	31.3 versus 19.6	0.50

*ROC CUT OFF cc=GTV-P<30 versus>30, GTV-N <4 versus >4, GTV-P+N <50 versus >50. ROC: Receiver operating characteristics, OS: Overall survival, GTV: Gross tumor volume, GTV-P: GTV primary, GTV-N: GTV nodal, NR: Not reached

standard deviation, as shown in Table 2. Depicting that, even within the well-accepted prognostic groups of T status, stage-group and site, heterogeneous volumes were seen and thus varied response to treatment. Furthermore, defining a cutoff based on mean value is not meaningful as done in many studies.[12,17]

As per the defined cutoffs based on the ROC for median OS, GTV-P <30 cc, GTV-N <4 cc and GTV-P+N <50 cc had better CR rates and OS (median OS-59 months) implying, GTV is not only of prognostic value but also predictor of response to treatment. The literature also suggests similar cutoff values for GTV-P – a mean of 35 cc in patients treated with CCRT, with 5-year progression-free survival of 61%.[12] One of the largest studies by Knegjens *et al*.[11] proposed a GTV-P cutoff value of 30 cc for advanced tumors, which is similar to ours.

As patients with CR had better OS, it was seen that the mean GTV-P and GTV-P+N volumes in them were smaller compared to non-CR patients, corresponding to 34.1 versus 64.2 cc and 45.9 versus 81.1 cc, respectively. These values had good concordance with the predefined ROC cutoffs as well. In line with our findings, Strongin *et al*.[12] reported that patients with loco-regional failure had a larger mean GTV-P volume (64 cc vs. 27.3 cc).

Our study included only pharynx and larynx primaries, which is a relatively homogeneous patient population among the head-and-neck cancers in terms of definitive treatment (CCRT). While the defined GTV-P and GTV-P+N cutoffs correlated well with OS in oropharyngeal primaries, only GTV-P and none of the GTV cutoffs correlated in hypopharyngeal and laryngeal primaries, respectively. The volume cutoff values also differed for each site which was more for oropharynx (GTV-P – 45 cc, GTV-P+N – 60 cc). Hence, GTV cutoff values are unique to each site, single cutoff value cannot be defined and applied across all sites. The same is reported in the studies, where the median GTV-P for laryngeal tumors was very less in the range of 3–6 cc[18] for oropharyngeal tumors 32.7 cc[13] and for hypopharynx 30 cc.[19]

Assuming the tumor increases by one cm in all the directions, an increase in the tumor size from 1 cm to 2 cm brings about an eight-fold increase in the TV and from 1 cm to 3 cm twenty-seven-fold increase! Hence, even within the two-dimensional diametric definition of each T in TNM staging, there is nonhomogeneity identified.[20] This was evident in our study where, within T3 category which constituted two-third of the cases, a statistically significant OS difference was seen for all GTV volume cutoffs with a median OS of 54.4 versus 19.8 months ($P = 0.004$). Similar findings in T2 and T4 were not seen though, as the patient numbers were less. Hence, probably there is a need to sub-categorize T also

for better prognostication. Similar findings were seen within Stage III and Stage IV too.

Although the prognostic value is somewhat obvious its predictive value is usually undermined. The defined cutoffs in our study did show that volumes above and below this could predict the treatment response – GTV-P <30 cc had better CR rates (83%) than >30 cc (52%) and achieving CR to treatment is the single most important factor for predicting survival too.

Overall, only seven patients (4.6%) had distal failures. Four in patients with non CR and 3 in CR on follow-up with mean GTV-P in them being 70 cc and 40 cc, respectively. The literature also shows that the larger TVs (>70 cc) predicted distal failures and probably might guide us to use aggressive systemic therapy at the beginning of treatment.[10] However, the same cannot be concluded from our study as the patterns of recurrence were largely loco-regional and isolated distal failures were less.

The volume estimation is not only unique to the patient, easy to obtain, and precise estimation of tumor burden but also volume of tumors act as surrogate marker for hypoxia[21] and hence can predict radio resistance and the ultimate treatment outcomes especially large volume tumors. If predicted response is favorable, strategies to decrease the toxicities and if unfavorable aggressive strategies such as dose escalation or a palliative approach can be planned.

As the prognostic and predictive value of GTV is immense and evident, this volumetric information can supplement the traditional TNM. In recent times, the TNM staging in head-and-neck cancers has been evolving and dynamic. As pathological TNM gets integrated with clinical staging TNM in tumors primarily treated with surgery, this valuable data can be integrated as volumetric TNM (vTNM) in tumors of treated with CCRT. Documentation as vTNM will help in effective communication with the patient, among institutions and to plan a personalized treatment. Studer *et al*.[10] in fact showed that volumetric staging as superior to TNM staging.

Although our study is retrospective in nature, it has reasonably demonstrated the prognostic and predictive significance of GTV and further evaluation in a larger prospective study might strengthen this evidence.

The drawback of our study is that PET-CT was not used for contouring. PET-CT-based GTV delineation poses many uncertainties as the physiological uptake in the surrounding organs makes it difficult to differentiate the tumor signal from nontumor signal. Literature shows that PET underestimates the TVs.[22] Furthermore, there is a lack of uniformity in defining the PET tumor contours as tumor delineation may change depending on the chosen segmentation method – standardized uptake value (SUV) max, SUV threshold, percentage of SUV max intensity levels, or even simple visual evaluation.[23] Hence, not incorporating PET in the treatment planning process might not be a major setback.

The GTV was contoured by single radiation oncologist in majority of cases or was reviewed by the same radiation oncologist before planning as the cases were treated under a single unit, reducing the observer bias.

While we have moved on from 2D era of the past and busy with the big data of the radiomics of the future, we have failed to exploit the present-day technology where the prized GTV information pops up on the window with the click of a button.

Conclusion

GTV should not just be limited for contouring but has to be recognized as a prognostic factor of significant value. Incorporating GTV as vTNM as a supplement to routine TNM has to be explored.

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Conflicts of interest

There are no conflicts of interest.

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