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REVIEW ARTICLE

CME

Influence of Tumour Volume on the Probability of Local Control after Radiotherapy for Squamous Cell Carcinoma of the Head and Neck

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ABSTRACT

The purpose of this literature review is to determine the influence of the primary tumour volume on the likelihood of local control after radiotherapy for head and neck cancer. Tumour volume varies within T stage. The extent of this variability depends on the primary tumour site. Tumour volume significantly influences the likelihood of local control after radiotherapy for carcinomas of the glottis and supraglottic larynx. The 'threshold', or volume at which local control decreases, varies with tumour site. The impact of volume on local control probability appears to be less pronounced for carcinomas of the nasopharynx, oropharynx, and hypopharynx. The most important variable that has an impact on local control after radiotherapy is T stage. Primary tumour volume also significantly influences the likelihood of local control in patients with laryngeal carcinomas.

Key Words: *Carcinoma, Head and neck neoplasms, Radiotherapy, Squamous cell*

INTRODUCTION

Squamous cell carcinoma of the head and neck is primarily treated with surgery or radiation therapy (RT).[1,2] Both of these modalities, in addition to chemotherapy, may also be used in the adjuvant setting.[1] The advantage of primary RT is organ preservation. Implicit is that the organ functions to an extent that it is worth preserving from the patient's perspective.[3] Various parameters that may influence the likelihood of local control after RT have been described and include primary site,[4] T stage,[5-7] histologic differentiation,[8] pretreatment haemoglobin,[9-11] p53 overexpression,[12] and primary tumour volume calculated on pretreatment computed tomography (CT), and/or magnetic resonance imaging (MRI).[1,13-25] The advantage of selecting the subset of patients unlikely to be cured with RT is that these patients may be more appropriately treated with a different approach that may be more efficacious, thereby sparing them the complications of salvage surgery. CT and/or MRI scans are obtained prior to treatment for the vast majority of patients with American Joint Committee on Cancer Staging (AJCC) II to IV disease. Calculation of the tumour volume requires minimal additional effort and no additional diagnostic studies. There are few data relating primary tumour volume to local control following RT. The purpose of this paper is to review these data.

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Determination of Tumour Volume

The primary tumour is outlined on each CT or MRI slice that contains tumour; no attempt is made to distinguish tumour from surrounding oedema (Figure 1).[13] Tumour outlines are then transferred into a RT treatment planning computer using a digitiser. The magnification factor and image slice thickness are ascertained, and a computer-generated primary tumour volume is calculated by adding the volumes for each image slice containing tumour. The primary tumour volume is expressed in cm^3.

Although most investigators have analysed primary tumour volume, the relationship of total tumour volume (TTV) and local-regional control has also been reported.

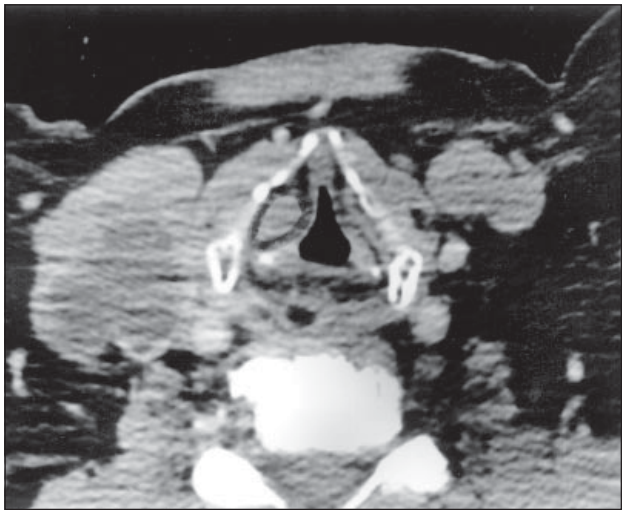

Figure 1. Low volume T2N2A squamous cell carcinoma of the right false vocal cord. The primary tumour is outlined and was 1.12 cm^3.

TTV is obtained by adding the primary tumour volume and the volumes for all radiographically-positive cervical lymph nodes.[20,24,25]

Most tumour volume data reported to date are based on CT-calculated volumes as opposed to MRI. The bias is to use CT as the initial pretreatment imaging study for most patients with head and neck cancer, with MRI reserved for the occasional patient with questionable findings on CT.

Another source of variability in determining tumour volume is between observers (interobserver). A related question is whether significant variability occurs if the same observer calculates the volume of the same tumour on different occasions (intraobserver). Hermans et al evaluated interobserver and intraobserver variability for 5 observers who determined laryngeal tumour volume for 13 tumours during 4 different sessions.[26] Significant variability was apparent between observers ($p < 0.0001$) and between sessions ($p < 0.01$). Interobserver variability accounted for 89% of the total variability. These researchers concluded that the use of a single trained observer would significantly reduce variability in tumour volume calculations.

Impact of Primary Tumour Volume and Local Control

The data suggest that the influence of tumour volume and the volume at which local control significantly decreases after RT varies with primary site.[3,19,22,27-29] Therefore, the pertinent literature will be reviewed according to the primary site. Unless otherwise specified, the volume data cited were obtained from calculating the primary tumour volume on pretreatment CT. Additionally, unless otherwise specified, patients were staged according to the recommendations of the AJCC and have a minimum of 2 years of follow-up.[6,7]

Supraglottic Larynx

Mancuso et al reported the results for 63 patients who were treated with RT alone or RT followed by a planned neck dissection at the University of Florida.[3] Local control after RT as a function of 1983 AJCC T stage and primary tumour volume (<6 cm^3 versus ≥6 cm^3) is shown in Table 1. The relationship between primary tumour volume and local control after RT with a functioning larynx is shown in Table 2. Three patients required a total laryngectomy for chondronecrosis and thus had local control after RT, but without a functional larynx. The relationship between primary tumour volume and local control with a functional larynx is shown in Figure 2. It is apparent that in a modest subset of patients with tumours greater than 6 cm^3 the tumours are controlled with preservation of laryngeal function, but that the likelihood of this outcome decreases as volume increases. Multivariate analysis of local control after RT revealed that primary tumour volume significantly influenced this endpoint ($p = 0.0005$). In contrast, N stage ($p = 0.1706$), pre-epiglottic space invasion ($p = 0.0731$), sex ($p = 0.5897$), vocal cord mobility ($p = 0.9046$), and T stage ($p = 0.9863$) did not influence local control after RT. Similarly, multivariate analysis of local control with preservation of laryngeal function revealed that tumour volume significantly

Table 1. Supraglottic larynx: local control as a function of T stage and primary tumour volume.[3] Reprinted with permission from the American Society of Clinical Oncology.

	Local control by tumour volume	
Stage	<6 cm^3	≥6 cm^3
T1	1/1	0/0
T2	19/21	1/2
T3	13/15	12/22
T4	1/1	0/1
Total	34/38 (89%)	13/25 (52%)

Table 2. Local tumour and laryngeal function preservation versus tumour volume of the supraglottic larynx.[3] Reprinted with permission from the American Society of Clinical Oncology.

	Tumour volume				p Value
	<6 cm^3 (n = 38)		≥6 cm^3 (n = 25)		
	No. of patients	%	No. of patients	%	
Local control	34	89	13	52	0.0012
Functioning larynx	34	89	10	40	0.00004

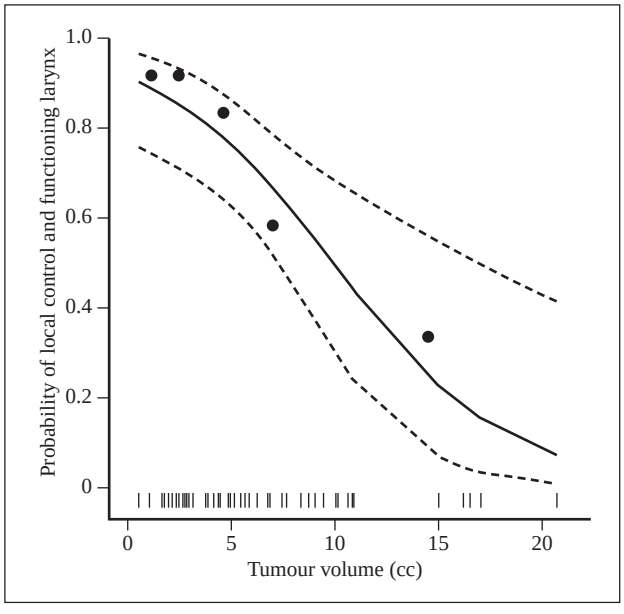

Figure 2. Supraglottic larynx. Predicted probability of achieving local control with a functioning larynx, plotted as a function of tumour volume. Predicted probabilities (—) and 95% confidence bands (- - -) were estimated via logistic regression. Individual points indicate median tumour volume and observed proportion of patients achieving local control with a functioning larynx within mutually exclusive groups of patients sorted by tumour volume (n = 12/13 per group). Vertical marks along the X axis indicate observed volumes in the study population.[3] Reprinted with permission from the American Society of Clinical Oncology.

influenced this endpoint (p = 0.0001). Parameters that did not influence this endpoint included N stage (p = 0.2073), sex (p = 0.4420), vocal cord mobility (p = 0.6888), T stage (p = 0.8888), and pre-epiglottic space invasion (p = 0.9222). A recent update of the University of Florida experience included a multivariate analysis of 114 patients with supraglottic carcinoma.[30] Primary tumour volume had a more significant influence in local control after RT than T stage (p = 0.0220 versus p = 0.2791).[30]

Kraas et al reported results for 28 patients treated with definitive RT at the Wake Forest Medical School, in Winston Salem, USA, between 1991 and 1997, with follow-up for 20 to 58 months.[14] Primary tumour volume calculated from pretreatment CT ranged from 0 cm^3 to 68.6 cm^3 (median, 3.1 cm^3). Local control after RT was 20% for patients with tumour volumes greater than 8 cm^3 and 70% for those with tumour volumes less than 8 cm^3 (p = 0.0077).

Hermans et al reported the results for 103 patients treated with RT at the University Hospital, Leuven, Belgium, in whom pretreatment tumour volume was calculated using CT.[17] Mean tumour volume correlated with T stage: T1, 1.9 cm^3; T2, 6.1 cm^3; T3, 9.1 cm^3; and T4, 19.9 cm^3. CT-determined primary tumour volume significantly correlated with the likelihood of local recurrence after RT (p < 0.0001). Multivariate analysis revealed that primary tumour volume (p = 0.0035), subglottic extension (p = 0.0012), and degree of invasion of the pre-epiglottic space (p = 0.102) influenced the probability of local control after definitive RT.

Glottic Larynx

Volume data pertaining to squamous cell carcinoma of the glottic larynx are primarily confined to T3 cancers. Pameijer et al reported a series of 42 patients treated with RT alone to the primary site at the University of Florida between 1980 and 1993.[31] Two patients had focal cartilage invasion and thus had early T4 cancers and the remaining 40 patients had T3 tumours. Local control after RT was correlated with primary tumour volume, involvement of one or more laryngeal subsites, and cartilage sclerosis. Local control after RT was significantly related to tumour volume less than 3.5 cm^3 (22 of 26 patients; 85%) compared with 3.5 cm^3 or greater (4 of 16 patients; 25%) [p = 0.0002]. The probability of local control as a function of tumour volume is shown in Figure 3. Patients were stratified into 3 risk groups based on tumour volume and the presence and number of sclerotic cartilages (Table 3). The favourable risk group, composed of patients with low-volume tumours without cartilage sclerosis, had a 90% local control rate after RT. Local control rates differed significantly between the low-risk and moderate-risk groups (p = 0.006) and between the low-risk and high-risk groups (p = 0.002). Local control rates between the moderate-risk and high-risk groups did not significantly differ (p = 0.337). A recent update of the University of Florida experience included 55 patients with glottic carcinomas.[30] Forty seven of 55 patients (85%) had T3 cancers. Multivariate analysis of local control after RT revealed that tumour volume (p = 0.0042) had a greater impact on this endpoint than T stage (p = 0.0629).

Pyriform Sinus

There are limited data pertaining to the influence of tumour volume on local control for carcinoma of the pyriform sinus. Pameijer et al reported the results for 23 patients with T1 and T2 squamous cell carcinomas of the pyriform sinus treated with RT alone to the primary site at the University of Florida between 1984 and 1993.[29] The 'optimal cutoff' was found to be 6.5 cm^3; local control rates after RT was 17 of 19 (89%)

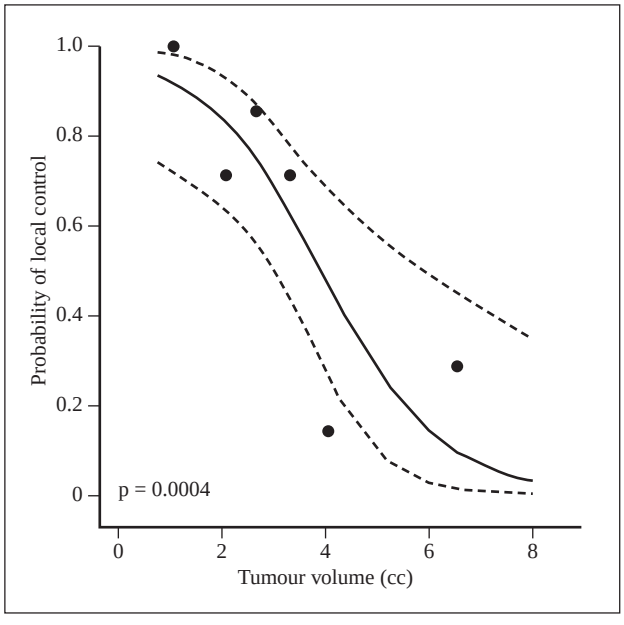

Figure 3. Predicted probabilities for local control as a function of tumour volume for 42 patients with T3 glottic larynx carcinoma. Solid line (—) shows predicted probabilities for local control as a function of pretreatment CT; dashed lines (- - -) show 95% confidence bands. Predicted probabilities were estimated by modelling the log-odds of local control as a linear function of tumour volume. Significance of the fitted model is indicated by the p value displayed in the plot. Individual points represent the proportion of patients who achieved local control in subgroups defined by ordered tumour volume intervals. Each point represents 7 patients. Reprinted with permission from Lippincott Williams and Wilkins.

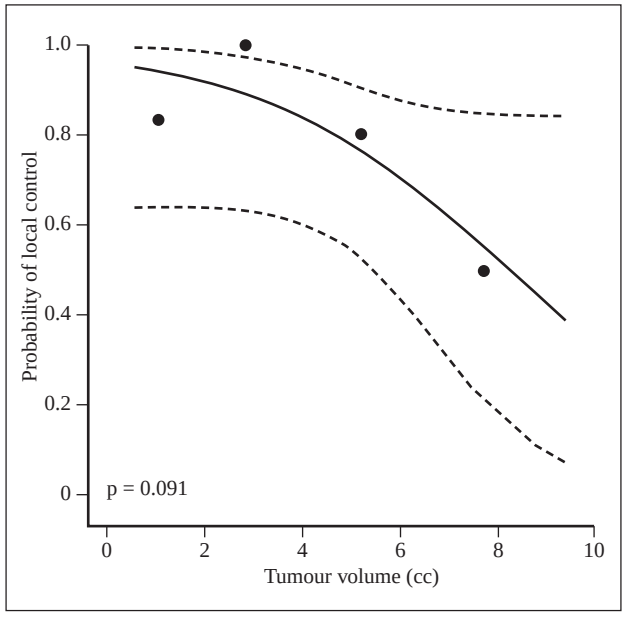

Figure 4. Predicted probabilities for local control as a function of tumour volume for 23 patients with pyriform sinus carcinoma.[3] Solid line (—) shows predicted probabilities for local control as a function of pretreatment computed tomography; dashed lines (- - -) show 95% confidence bands. Predicted probabilities were estimated by modelling the log-odds of local control as a linear function of tumour volume. Significance of the fitted models is indicated by the p value displayed in each plot. Individual points represent the portion of patients who achieved local control in subgroups defined by ordered tumour-volume intervals. Each point represents 5 or 6 patients for pyriform sinus tumours. Multiple logistic regression indicated no significant difference between the pyriform sinus and supraglottic predicted probability curves.[29] Reprinted with permission from John Wiley and Sons, Inc.

for tumours less than 6.5 cm^3 compared with 1 of 4 (25%) for those 6.5 cm^3 or larger (p = 0.021). The relationship between tumour volume and local control is shown in Figure 4. Local control after RT as a function of tumour volume and involvement of the apex of the pyriform sinus is shown in Table 4. The difference in the local control rates between the low-risk and the moderate-risk group was marginally significant (p = 0.088). Local control rates significantly differed between the low-risk and the high-risk groups (p = 0.020).

A recent update of the University of Florida experience included 45 patients with hypopharyngeal carcinomas.[30] Forty two patients had pyriform sinus malignancies and 3 patients had pharyngeal wall/post-cricoid tumours; 33 lesions (73%) were stage T2. Local control was significantly influenced by T stage (p = 0.0485) but not by primary tumour volume (p = 0.2282).

Nasopharynx

Chua et al reported the results for 290 patients treated with RT at the Queen Mary Hospital in Hong Kong between 1989 and 1991.[27] Primary tumour volume, nodal tumour volume (NTV), and TTV were calculated on

Table 3. Computed tomography risk profiles for patients with T3 glottic larynx carcinoma (n = 42).[31] Reprinted with permission from Lippincott Williams and Wilkins.

Risk groups (for local recurrence)	Criteria		No. of patients	Local control
	Volume	Cartilage sclerosis		
Low risk (n = 21)	<3.5 cm^3	0	13	
	<3.5cm^3	1	8	19/21 (90%)
Moderate risk (n = 14)	<3.5 cm^3	>1	5	
	>3.5 cm^3	0	3	6/14 (43%)
	>3.5cm^3	1	6	
High risk (n = 7)*	>3.5cm^3	>1	7	1/7 (14%)

*Two of these patients had focal cartilage erosion.

Table 4. Computed tomography risk groups for patients with pyriform sinus carcinoma (n = 22).[29] Reprinted with permission from John Wiley and Sons, Inc.

Risk groups (for local recurrence)	Criteria		No. of patients	Local control
	Volume	Bulky apex disease		
Low (n = 16)	<6.5 cm^3	No	16	15/16 (94%)
Moderate (n = 4)	<6.5 cm^3	Yes	2	—
	≥6.5 cm^3	No	2	2/4 (50%)
High (n = 2)	≥6.5 cm^3	Yes	2	0/2 (0%)

pretreatment CT scans. Patients were staged according to Ho's staging system. A large variability in primary tumour volume and TTV was observed within each stage, which was especially pronounced in advanced stage disease. The 5-year local control rates as a function of primary tumour volume were: ≤20 cm^3, 88%; >20 to 40 cm^3, 80%; >40 to 60 cm^3, 78%; and >60 cm^3, 56% ($p < 0.001$). Primary tumour volume was also significantly related to the 5-year rates of distant relapse-free survival (RFS; $p = 0.01$) and cause-specific survival ($p < 0.001$). Multivariate analysis revealed that primary tumour volume was the only variable that significantly influenced local control. Nodal tumour volume significantly influenced the 5-year rates of neck control ($p = 0.001$), distant RFS ($p = 0.002$), and cause-specific survival ($p < 0.001$). Total tumour volume was significantly related to the 5-year rates of distant RFS ($p < 0.001$) and cause-specific survival ($p < 0.001$).

Oropharynx

Hermans et al reported the results for 112 patients with squamous cell carcinoma of the tonsil treated with definitive RT at the University Hospital, Leuven, Belgium, between 1987 and 1998 and followed from 2 to 121 months (mean, 33 months; median, 24 months).[19] Primary tumour volume, NTV, and TTV were obtained by pretreatment CT. Primary tumour volume significantly correlated with local control ($p < 0.05$) but not within T stages for stages T2, T3, and T4. Although NTV significantly influenced regional control ($p < 0.01$), TTV was not significantly related to local-regional control. Multivariate analysis revealed that T stage significantly predicted local control ($p = 0.02$), whereas primary tumour volume did not significantly influence this endpoint.

Nathu et al reported 114 patients with oropharyngeal squamous cell carcinoma treated with definitive RT at the University of Florida between 1983 and 1995.[28] The distribution of tumours according to primary site was as follows: tonsillar pillar, 21(18%); tonsillar fossa, 40 (35%); base of tongue, 39 (34%); and soft palate, 14 (13%). Primary tumour volume varied quite a bit within T stage, particularly for T4 tumours (Figure 5). There

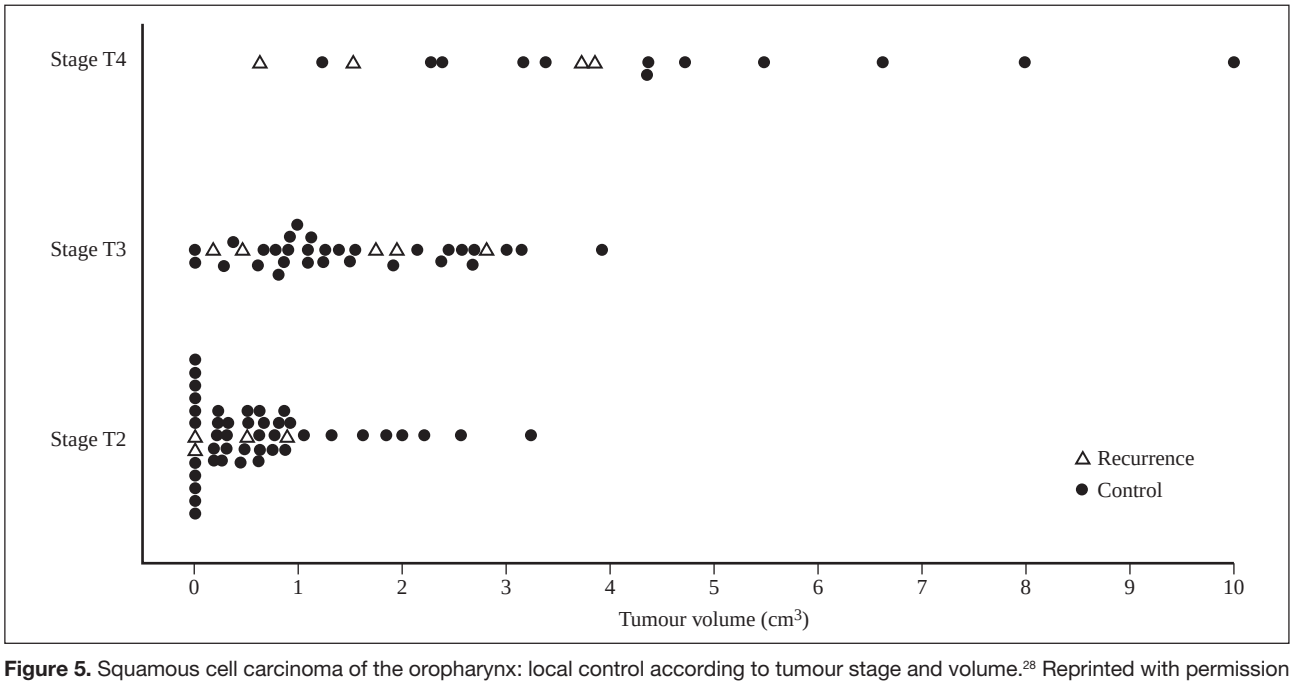

Figure 5. Squamous cell carcinoma of the oropharynx: local control according to tumour stage and volume.[28] Reprinted with permission from John Wiley and Sons, Inc.

Table 5. Multivariate analysis of local control rates in the oropharynx after radiation therapy.[28] Reprinted with permission from John Wiley and Sons, Inc.

Variable	Rank	p Value
T stage	1	0.02
Tumour volume	2	0.10
Neck stage (N0-1 versus ≥ N2)	3	0.33
Induction chemotherapy (yes versus no)	4	0.54
Primary oropharyngeal site	5	0.82
Sex	6	0.95

was no obvious volume threshold at which local control after RT appeared to decrease significantly. Multivariate analysis of local control after RT revealed that T stage was the only parameter that significantly influenced this endpoint. Primary tumour volume only marginally influenced local control in the multivariate analysis (Table 5). A recent update of the University of Florida experience included 190 patients with oropharyngeal carcinomas.[30] Multivariate analysis of local control revealed that tumour volume had no significant impact on local control after RT.

DISCUSSION

Primary tumour volume varies within T stage, particularly for squamous cell carcinoma of the nasopharynx and oropharynx. There is also considerable variation between primary sites — oropharyngeal and nasopharyngeal cancers tend to be larger at diagnosis than laryngeal cancers. The data pertaining to hypopharyngeal tumours are limited. Another confounding factor is that large oropharyngeal and nasopharyngeal tumours are likely to be treated with definitive RT, whereas high-volume laryngeal and pyriform sinus cancers are probably more likely to be treated surgically.

Primary tumour volume significantly influences the likelihood of local control after RT for patients with laryngeal cancers. The impact of primary tumour volume on local control for patients with oropharyngeal, hypopharyngeal, and nasopharyngeal cancer is less pronounced. The reasons for this are unclear but may be related to the variable radiosensitivity of pharyngeal tumours. For example, T1 and T2 squamous cell carcinomas of the anterior tonsillar pillar have consistently been shown to have a lower local control rate after RT compared with T1 to T2 tumours of the tonsillar fossa and base of tongue.[4,5]

The threshold at which local control significantly decreases may be apparent for some primary sites such as the larynx and not for others such as the oropharynx. As is apparent from Figures 2 to 4, the decreasing likelihood of local control with increasing tumour volume is variably steep, and the error bars are wide and based on relatively limited data. Therefore, the 'threshold' volume for a particular tumour site should not be utilised as the only parameter on which to base treatment decisions, but rather in conjunction with other prognostic factors. Patients with extensive tumours larger than the 'threshold' volume may be locally controlled with RT. However, patients with high volume tumours that are locally controlled are probably more likely to experience complications.

The threshold may vary between observers.[26] It is advisable to minimise the number of observers performing the volume calculations and to closely observe patients to determine whether the relationship between tumour volume and local control differs from those reported in the literature.

The threshold also probably varies with the primary treatment modality. There are few data relating primary tumour volume to local control after surgery. Mukherji et al reported 37 patients with supraglottic carcinoma treated surgically at the University of North Carolina, USA, and found that primary tumour volume was significantly related to local control ($p < 0.05$),[32] but the threshold was 16 cm^3 compared with 6 cm^3 observed in those treated with definitive RT.[3]

CONCLUSION

Primary tumour volume influences the likelihood of local control after RT. Volume data are relatively easy to obtain, and because most patients undergo pretreatment CT and/or MRI, little additional cost is incurred. Depending on the primary site, patients with high volume unfavourable tumours may be selected for treatment strategies that may be more likely to succeed.

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