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ORIGINAL ARTICLE

^{18}F-FDG Metabolic Tumor Volume: Association with Short- and Long-Term Feeding Tube Use in Head and Neck IMRT

James E. Jackson[1,2,3,4] · Nigel J. Anderson[1,5] · Maureen Rolfo[1] · Morikatsu Wada[1] · Michal Schneider[6] · Michael Poulsen[2,7] · Maziar Fahandej[1] · Anna Huynh[2] · Sze Ting Lee[8] · Daryl Lim Joon[1] · Vincent Khoo[1,6,9,10]

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Abstract

The purpose of this study was to investigate whether the metabolic tumor volume (MTV) of head and neck primary tumors may be a significant prognostic factor for feeding tube (FT) use and FT dependence. Seventy-nine patients with evaluable primary tumors, pre-therapy FDG-PET scans, treated with definitive intensity-modulated radiotherapy (IMRT) (± concurrent chemotherapy) for head and neck mucosal cancers were included. MTV was quantified and recorded for the primary lesion using a minimum standardized uptake value (SUV) threshold of 2.0. Patients were recommended prophylactic FT and followed up by a dietician for at least eight weeks of post-radiotherapy. Associations between MTV, dose to swallowing organs at risk, FT use, and FT dependence were analyzed. MTV was positively correlated with gross tumor volume (GTV) ($r = 0.7357$; $p < 0.0001$). MTVs larger than 17 cc were associated with higher rates of FT use (87.8% vs. 69.5%, $p = 0.0067$) and FT dependence at six weeks (76.7% vs. 41.7%, $p = 0.0024$) and six months (25.0% vs. 8.7%, $p = 0.0088$). Increasing MTV was associated with increasing mean dose to the oral cavity ($p = < 0.0001$), tongue base ($p = 0.0009$), and superior (SPCM) ($p = 0.0001$) and middle pharyngeal constrictor muscles (MPCM) ($p = 0.0005$). Increasing MTV was associated with increasing maximum dose to oral cavity ($p = 0.0028$), tongue base ($p = 0.0056$), SPCM ($p = 0.0037$), and MPCM ($p = 0.0085$). Pre-treatment MTV is a reproducible parameter that can be generated at or prior to a pre-treatment Multidisciplinary Tumor Board and may expedite decisions regarding placement of prophylactic FTs. Prospective evaluation in larger series is required to determine whether MTV is a more useful prognostic variable for FT use than clinical T-classification.

Keywords Head & neck neoplasms · Positron-emission tomography · Radiotherapy · Toxicity · Enteral nutrition

✉ James E. Jackson
jimejackson@gmail.com

[1] Department of Radiation Oncology, Olivia Newton John Cancer Wellness & Research Centre, Austin Health, Heidelberg, VIC, Australia

[2] Radiation Oncology Centres, Gold Coast University Hospital, 1 Hospital Boulevard, Southport, QLD 4215, Australia

[3] School of Medicine, Griffith University, Gold Coast, Australia

[4] Faculty of Health Sciences and Medicine, Bond University, Gold Coast, Australia

[5] Department of Radiation Oncology and Cancer Imaging, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

[6] Department of Medical Imaging and Radiation Sciences, Monash University, Clayton, VIC, Australia

[7] Faculty of Medicine, The University of Queensland, Herston, QLD, Australia

[8] Centre for PET, Austin Health, Heidelberg, VIC, Australia

[9] Department of Clinical Oncology, Royal Marsden NHS Foundation Trust and Institute of Cancer Research, Chelsea, London, UK

[10] Department of Medicine, University of Melbourne, Parkville, VIC, Australia

Introduction

Head and neck cancer (HNC) and its treatment with radiation therapy (RT), with or without concurrent chemotherapy, are associated with dysphagia and associated malnutrition and weight loss [1–5]. Enteral feeding via a feeding tube (FT) is a common method of providing patient nutrition during and immediately following RT in as many as 80% of patients [6–10]. Patients at high risk of prolonged, severe dysphagia may benefit from a prophylactic gastrostomy tube to minimize hospitalizations [11, 12], while maximizing convenience and short-term quality of life [13].

However, the insertion of a gastrostomy tube is an invasive procedure which can be associated with major complications and occasionally death [14]. Prolonged FT use has also been associated with poor long-term swallow outcomes and even the potential for poorer survival [12, 15]. Considering these risks, the insertion of prophylactic gastrostomy tubes should be reserved for those patients likely to derive the most benefit, namely patients at highest risk of prolonged FT use.

Historically, RT has been delivered using fixed fields and simple beam-blocking techniques. Intuitively, one-dimensional measurements, such as field length, were strongly associated with the incidence of FT placement [16, 17]. Contemporary intensity-modulated radiotherapy (IMRT) produces highly conformal dose distributions around three-dimensional target volumes (Fig. 1) and may reduce unintentional radiation dose to uninvolved mucosa and other surrounding structures, whose damage may contribute to pain and difficulty swallowing [18]. T-classification, as per the American Joint Committee on Cancer (AJCC) [19], has historically been a significant prognostic factor for duration of FT use [16, 20–23] with more advanced tumors universally having higher rates of short- and long-term FT use. While this classification includes tumor size (in one dimension) and involvement of adjacent structures, it may not accurately depict the relationship between the true extent of the primary and the volume that requires high-dose irradiation, in the era of IMRT.

In addition to precise RT delivery, advances in imaging have improved RT target delineation [24, 25], reducing unintentional irradiation of normal tissues. ^{18}FDG-PET/CT (FDG-PET) is widely used for staging and response assessment of HNC [26, 27]. Semi-automated tumor delineation can be achieved by generating a metabolic tumor volume (MTV). MTV defines the volume of a tumor from the distribution of its metabolic activity [28]. MTV can be rapidly and reliably derived from FDG-PET scans, and exploratory studies have postulated that it may have more prognostic value than AJCC stage for overall and disease-free survival for cancers of the oral cavity, oropharynx, and hypopharynx [28–30].

While MTV may be a useful prognostic tool for cancer outcomes, it may also be prognostic for treatment-related toxicities. MTV is closely related to the gross tumor volume (GTV) that is contoured by Radiation Oncologists,

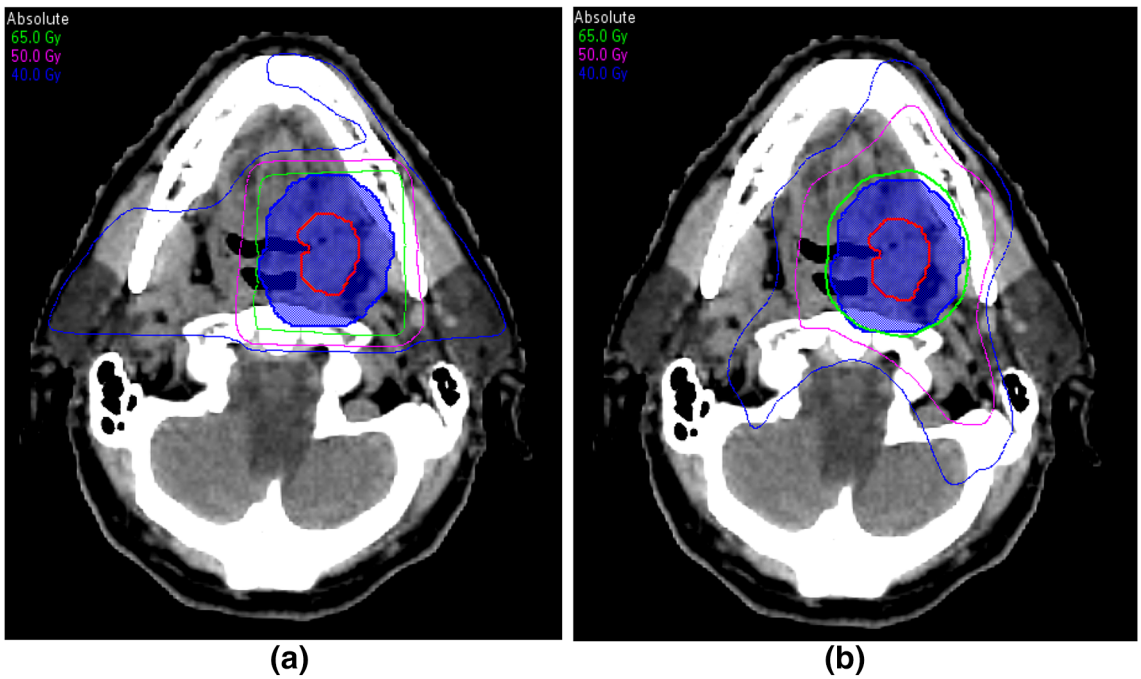

Fig. 1 Radiation doses to a left tonsillar tumor (red) within a Planning Target Volume (blue solid): **a** Conformal plan, **b** intensity-modulated radiotherapy (IMRT) plan. Volumes receiving 65 Gy, 50 Gy, and 40 gy are outlined in green, purple, and blue, respectively

which is directly related to the volume of tissue receiving high-dose irradiation. Irradiated volume has been demonstrated to affect weight loss and dysphagia [31], especially when it incorporates organs involved in the mechanical passage of food (Fig. 2) [18, 23]. These organs have been termed swallowing organs at risk (SWOARS) [32].

The purpose of this study was to investigate whether the MTV of head and neck primary tumors may be a significant prognostic factor affecting FT use and dependence, in the IMRT era.

Materials and Methods

Patients

Following Institutional Ethics Committee approval, the patient population was retrospectively accrued from the institution's radiation oncology database. To be eligible for inclusion, patients were required to receive primary and definitive intensity-modulated radiotherapy (IMRT), with or without concurrent systemic treatment for mucosal cancers of the head and neck. Patients with stage II–IVB disease were included. All patients had a staging FDG-PET scan performed and had an evaluable primary tumor on FDG-PET. Patients were excluded if they underwent therapeutic surgery to the primary site or neck dissection, prior to commencing RT. Patients were required to have been offered a prophylactic FT prior to treatment, as per departmental policy, and had to be followed up by a dietician for a minimum of eight weeks of post-radiotherapy completion.

Pre-treatment evaluation

Prior to treatment, each patient underwent diagnostic contrast-enhanced computed tomography (CECT) of the face, neck, and chest, as well as whole-body FDG-PET with low-dose CT for co-registration. Selected patients underwent magnetic resonance imaging (MRI) of the face and neck if it was thought clinically beneficial to assist in optimal target delineation.

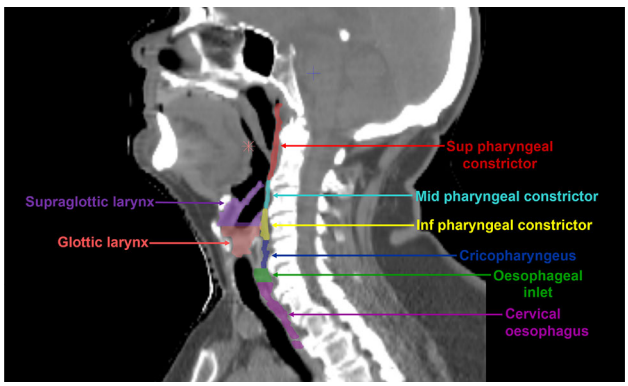

Fig. 2 Organs involved in the mechanical passage of food are termed swallowing organs at risk (SWOARS)

RT Planning and Treatment

Target volumes were outlined on the planning CECT by one radiation oncologist. The FDG-PET and MRI (if available) were co-registered with the planning CECT on the treatment planning system. The elective (prophylactic) nodes were defined according to consensus guidelines [33]. All patients received bilateral, elective irradiation of levels 2–4 nodes. Patients with oropharynx or nasopharynx cancers had bilateral, elective irradiation of level 1B nodes. In patients with oropharynx or hypopharynx cancers, elective irradiation of ipsilateral level 5 nodes and retrostyloid space was delivered to clinically node-positive hemi-necks. In patients with cancer of the nasopharynx, bilateral retrostyloid space lymph nodes were treated to at least an elective dose.

The prescribed doses were planned with a simultaneous integrated boost to a gross tumor volume (GTV), high-risk clinical target volume (CTV), and low-risk CTV. The dose to GTV (66–70 Gy), high-risk CTV (63 Gy), and elective CTV (56 Gy) was planned at five fractions per week over six to seven weeks.

Optimized IMRT plans, deliverable via seven to nine equally spaced step-and-shoot segmented beams on a 6 MV linear accelerator (Elekta Synergy, Elekta, Crawley, UK), were generated using either the Elekta CMS XiO or Monaco treatment planning systems (TPS) (Elekta, St Louis, MO, USA) on 0.25 cm CT slices.

FDG-PET Scan Acquisition and Analysis

The FDG-PET scans were performed in patients who fasted for six hours before intravenous injection of approximately 5 MBq/kg of ^{18}F-FDG according to the standard protocol. All patients were then scanned from skull vertex to upper thighs with their arms down on a Philips PET/CT system (Philips Medical Systems, Cleveland, OH, USA) following a 60-min uptake time. The scan included a low-dose 30 mA/slice CT for attenuation correction and anatomical localization. The ^{18}F-FDG-PET emission scan duration was for 3 min per bed position and processed with 3D-iterative reconstruction.

MTV Generation

Pre-radiotherapy, staging FDG-PET scans were analyzed using MedView^{TM} (MedImage Inc. Ann Arbor, MI, USA). The volume of interest (VOI) was defined for each tumor

using a semi-automated 3D seeded region growing algorithm. Maximum and average standardized uptake values (SUV_{max} and SUV_{av}) were calculated and recorded for these regions, based on standard methods involving injected dose, blood glucose level, and normalized by the patient's body weight. Using the software, volumetric analysis was also performed to measure the metabolic tumor volume (MTV), using an SUV threshold of 2.0 (Fig. 3).

Nutritional Assessment and Follow-Up

All patients had a complete pre-therapy consultation with a dietician followed by weekly nutritional reviews while on therapy. Following therapy, dietetic review, whether by phone or in-person, was conducted at least every two weeks following therapy until cessation of enteral feeding.

Adequacy of enteral intake (AEI) was recorded at each review using the scale: AEI 0 = 0–24%, AEI 1 = 25–49%, AEI 2 = 50–74%, and AEI 3 = 75–100% of daily nutritional needs. All patients were followed until their AEI was 0.

Speech pathology services were offered to all patients undergoing definitive RT to minimize aspiration and malnutrition risk. Video fluoroscopy and fibreoptic endoscopic evaluation of swallowing were available for at-risk patients. Swallowing rehabilitation was not available to this patient cohort.

Statistical Analysis

Statistical analysis was carried out using GraphPad Prism v7.02 (GraphPad Software Inc, California). Descriptive statistics were calculated for baseline demographic, disease stage, and treatment characteristics. For N-classification, nasopharynx cancers were staged as N2c if bilateral lymph node involvement was present. GTV and MTV values were dichotomized into high and low by their median value rounded down to the nearest integer, 25 and 17 cc, respectively. SWOARS were manually delineated and reviewed by at least two investigators. The mean dose and maximum dose to 2% of the individual SWOARS were calculated by Monaco TPS and reported as mean and maximum, respectively. Correlation was evaluated using parametric Pearson coefficients. For categorical variables, the frequency distributions between patients with GTV larger or smaller than 25 cc and MTV larger or smaller than 17 cc were evaluated using Fisher's Exact test. For continuous variables, frequency distributions were evaluated using the Mann Whitney *U*-test. FT use was defined as a patient deriving more than 25% of their dietician-defined nutritional needs from a FT, for 48 h or more. FT dependence was defined as patients deriving more than 75% of dietician-defined nutritional needs from a FT. The rates of FT use and FT dependence were estimated according to the Kaplan–Meier product limit method, measured from the commencement of radiotherapy. All p-values were 2-sided with a 0.05 α level of significance.

Results

Seventy-nine patients who received treatment between May 2007 and January 2012 met the inclusion criteria. Patient demographic details are displayed in Table 1. A significant correlation was seen between MTV and GTV ($r = 0.7357$, $p < 0.0001$), as displayed in Fig. 4. Median GTV was significantly larger than MTV [25.32 cc (Range: 4.1–176.9 cc) vs. 17.73 cc (Range: 1.7–130.3 cc), $p = 0.0037$]. No significant difference was seen between median MTV of oropharynx and nasopharynx primaries (21.89 cc vs. 16.00 cc, $p = 0.5243$) or oropharynx and non-oropharynx primaries (21.89 cc vs. 12.86 cc, $p = 0.0783$). Oropharynx MTVs were larger than laryngopharynx MTVs

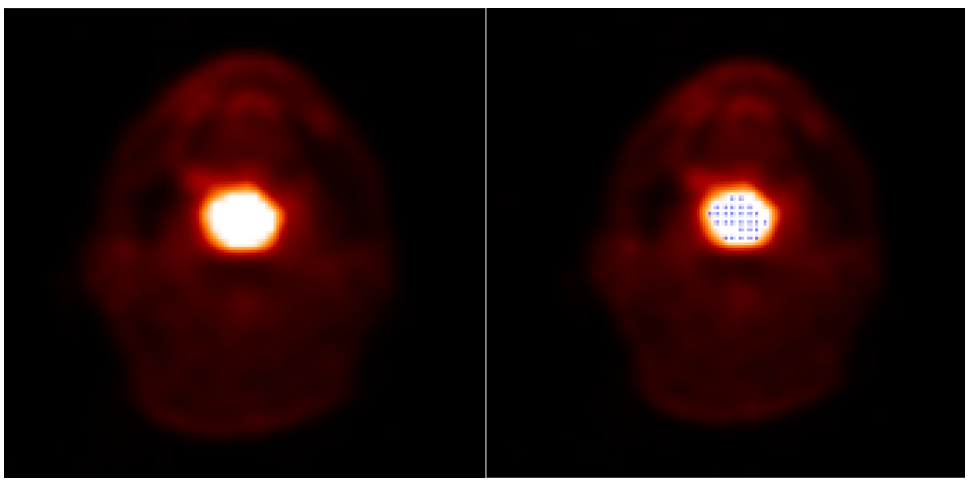

Fig. 3 Metabolic tumor volume (MTV) generation using MedView(TM) by MedImage Inc

Table 1 Patient demographics

	MTV < 17 cc (n = 36)	MTV > 17 cc (n = 43)	P value
Median age-years- (range)	61 (20–83)	60 (41–86)	
Sex- no. (%)			0.57
Male	28 (77%)	36 (84%)	
Female	8 (23%)	7 (16%)	
Smoking history (pack years)			0.49
< 20	16 (44%)	15 (35%)	
≥ 20	20 (56%)	28 (65%)	
Primary site			
Oropharynx	21 (58%)	33 (77%)	0.09
Tonsil	16 (76%)	19 (58%)	0.24
Base of tongue	5 (24%)	14 (42%)	
Nasopharynx	6 (17%)	6 (14%)	
Larynx	5 (14%)	0 (0%)	
Supraglottic larynx	4 (11%)	2 (4.5%)	
Hypopharynx	0 (0%)	2 (4.5%)	
T stage- no.			< 0.0001
T1-2	30 (83%)	12 (28%)	
T3-4	6 (17%)	31 (72%)	
T1	12 (33%)	4 (9%)	
T2	18 (50%)	8 (19%)	
T3	4 (11%)	21 (49%)	
T4	2 (6%)	10 (23%)	
N stage- no.			0.01
< N2b	26 (72%)	19 (44%)	
≥ N2b	10 (28%)	24 (56%)	
N0	13 (36%)	9 (21%)	
N1	9 (25%)	5 (11.5%)	
N2a	4 (11%)	5 (11.5%)	
N2b	7 (19%)	5 (11.5%)	
N2c	2 (6%)	17 (39.5%)	
N3	1 (3%)	2 (5%)	
Concurrent cisplatin chemotherapy	21 (59%)	35 (81%)	0.03
Altered fractionation	10 (28%)	15 (35%)	0.62

(21.89 cc vs. 10.18 cc, p = 0.0403). Oropharynx primary GTVs were larger than laryngopharynx (33.78 cc vs. 13.99 cc, p = 0.0032) and all non-oropharynx GTVs (33.78 cc vs. 16.94 cc, p = 0.0068). No significant difference was seen between median GTV of oropharynx and nasopharynx primaries (33.78 cc vs. 22.09 cc, p = 0.2227).

Increasing MTV was associated with increasing mean dose to the oral cavity (p = < 0.0001), tongue base (p = 0.0009), and superior (SPCM) (p = 0.0001) and middle pharyngeal constrictor muscles (MPCM) (p = 0.0005). Increasing MTV was associated with increasing maximum dose to oral cavity (p = 0.0028), tongue base (p = 0.0056), SPCM (p = 0.0037), and MPCM (p = 0.0085) (Table 2). Patients were less likely to have used a FT if their MTV was less than 17 cc (p = 0.0067), with 69.5% of these patients having used a FT at fifty days from RT start compared to 87.8% with larger MTVs (Fig. 5). Patients with MTVs larger than 17 cc were significantly more likely to be FT dependent for six weeks or more than those with MTVs smaller than 17 cc (76.7% vs. 41.7%, p = 0.0024). The same relationship was seen in patients with GTV larger than 25 cc, with regard to FT dependence for more than six weeks (75.0% vs. 42.9%, p = 0.0053). Long-term FT dependence was more common in patients with MTVs larger than 17 cc, with a six-month dependence rate of 25% compared to 8.7% if MTV was smaller than 17 cc (p = 0.0088), as seen in Fig. 6.

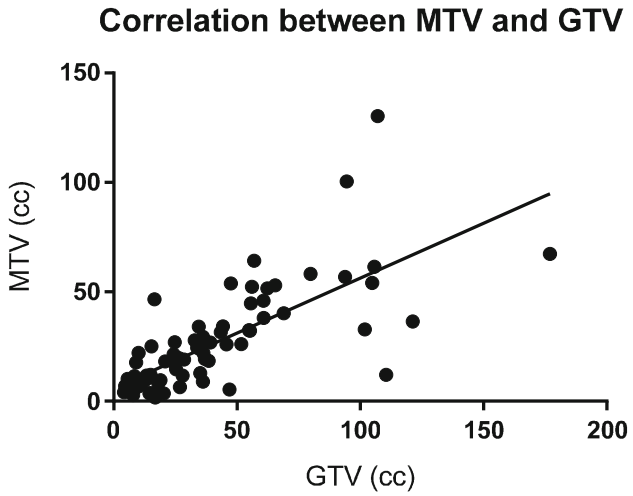

Fig. 4 Correlation between MTV and GTV

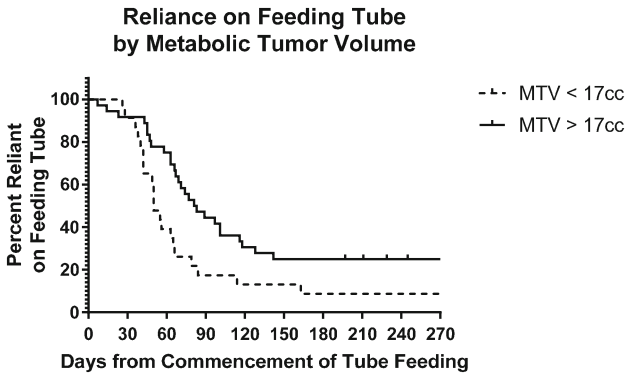

Fig. 6 Reliance on feeding tube by metabolic tumor volume

Table 2 Correlation of increasing mean and maximum radiation dose deposited in Swallowing Organs at Risk with increasing metabolic tumor volume

Organ/muscle	Maximum dose to structure		Mean dose to structure	
	r	*p*	*r*	*P*
Oral cavity	0.3455	0.0028	0.515	<0.0001
Base of tongue	0.3188	0.0056	0.3778	0.0009
Superior pharyngeal constrictor	0.3333	0.0037	0.429	0.0001
Middle pharyngeal constrictor	0.304	0.0085	0.3932	0.0005
Inferior pharyngeal constrictor	0.08188	0.4880	0.1143	0.3323
Crico-pharyngeus	− 0.06007	0.6112	− 0.05685	0.6305
Esophageal inlet	− 0.05285	0.6548	− 0.1119	0.3427
Cervical esophagus	− 0.08286	0.4828	− 0.07777	0.5102
Supraglottic larynx	0.1574	0.1805	0.1534	0.1920
Glottic larynx	0.0519	0.6605	− 0.01828	0.8772

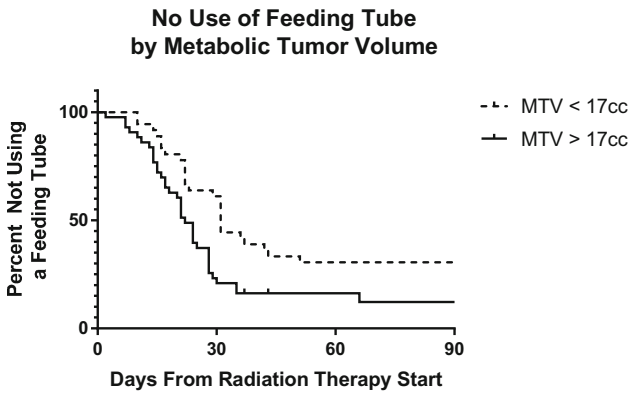

Fig. 5 No use of feeding tube by metabolic tumor volume

Discussion

The results of this study suggest the prognostic significance of pre-therapy FDG-PET parameter of MTV for FT use and dependence. The clinical importance may be best observed at a pre-therapy Tumor Board, where patient management decisions are made. MTV can be rapidly generated at, or before, this stage, to risk stratify patients and make decisions regarding the insertion of prophylactic FTs for those at high risk. While MTV is not universally calculated at all institutions, many diagnostic software packages enable rapid generation. In this study, MTV was significantly correlated with radiation oncologist-defined GTV, which was also prognostic for FT use. However, a GTV is not available at Tumor Boards and is subject to more inter-observer variability than a computer-assisted MTV [34].

While this is the first study investigating the association of MTV with RT-related FT use, several studies have associated this FDG-PET-based parameter with treatment outcomes in HNC. High MTV has been associated with worse overall survival in hypopharynx cancers [30], and worse overall and disease-free survival in oropharynx cancers [28, 29]. In the oropharynx, MTV has been shown to be more prognostic for these outcomes than TNM classification [28, 29] and these results were observed in a large series of 221 patients [29] . These findings have

prompted our hypothesis that MTV may be more prognostic for FT use, than traditional AJCC classification.

This study demonstrates a significant correlation of increasing mean and maximum (D2) dose to the following critical SWOARS: oral cavity, tongue base, supraglottic larynx, and superior and middle pharyngeal constrictor muscles. Increasing dose to these structures has been associated with worse swallowing outcomes in several studies [18, 23, 35]. It has been postulated that using IMRT to reduce dose to these structures, may improve swallowing outcomes [36]. Randomized data support the use of IMRT for improved quality of life and reduced xerostomia in patients with nasopharyngeal cancer [37]. IMRT delivers highly conformal radiation doses to three-dimensional volumes within a pharynx, where there is complex interplay between important structures involved in the passage of food. IMRT has near-completely replaced simpler techniques, where radiation prescription was made to a reference point within a volume. Intuitively, a volumetric measure of tumor volume, like MTV, would more likely reflect doses deposited in SWOARS than measurement of a single point or line, like T-classification.

The above structures are located in the pharyngeal axis, where pharyngeal primary tumors often arise. For this reason, we chose to analyze GTV and MTV of the primary tumor, not of metastatic lymph nodes, for a swallowing-related outcome. This choice was also supported by the limitations of FDG-PET in lymph nodes, which is susceptible to partial volume effects in small lymph nodes and false-positive FDG uptake in inflamed nodes. The sensitivity and specificity of FDG-PET lymph node auto-segmentation is also variable in these scenarios [38] and human papillomavirus-associated lymph nodes often display cystic necrosis [39] making FDG uptake unreliable. Undoubtedly, increasing nodal stage leads to more intensive therapy including larger volumes of high-dose irradiation and the use of concurrent chemotherapy. This has a direct effect on treatment-related toxicity, including dysphagia [23, 40, 41], but it is independent of direct dose to individual swallowing organs at risk. In this study, patients with MTVs larger than 17 cc were more likely to have a nodal stage of N2b or greater (56% vs. 28%, $p = 0.01$) and to have concurrent chemotherapy (81% vs. 59%, $p = 0.03$).

The FDG-PET parameters, SUV_{max}, and Total Glycolytic Volume (TGV) have previously been investigated for risk prediction in HNC [28–30]. SUV_{max} is a commonly used parameter that measures the highest voxel of FDG uptake within a tumor but this does not represent the activity of the entire tumor in three dimension, which MTV and TGV do [42]. While this has shown prognostic value in disease-free and overall survival [29], it is unlikely to reflect radiation toxicity or RT volumes. TGV assesses tumor volume that is weighed by the mean metabolic activity of tumor [30]. Like MTV, it has been associated with improved disease-free and overall survival in HNC, in non-randomized studies [28, 29]. As RT dose is prescribed to a volume, independent of its FDG activity, TGV is a less biologically plausible surrogate for RT-induced toxicity than MTV.

This study is inherently limited by its retrospective design. Importantly, FT use served as a surrogate measure for dysphagia, as these data were readily available to the investigators. In the HNC patient population, pain and the inability to swallow are undeniably important factors affecting FT use. In this study, every effort was made to minimize patient pain, as analgesia has been associated with a shorter duration of FT use [43]. Personal, psychological, and institutional therapeutic factors may have also impacted on FT use. The relative magnitudes of effect are unknown, particularly without directly measuring swallowing function. However, duration of FT use is undoubtedly a clinically significant measure to both patients and clinicians.

While sophisticated contouring of SWOARS and subsequent dosimetric analysis was achievable retrospectively, many pertinent outcomes related directly to swallowing were not measured. An ideal prospective study would incorporate standardized, validated patient-reported outcomes—such as the MD Anderson Symptom Inventory for head and neck cancer [44], recorded at baseline and defined intervals from therapy initiation. Likewise, trends in observer-reported outcomes, such as functional oral intake scores (FOIS) and Mann assessment of swallowing ability (MASA), could provide meaningful data. Videoendoscopic and video fluoroscopic evaluations could directly assess acute toxicities occurring in the SWOARS delineated in this study.

This study included 79 patients with primary tumors of the pharynx. While primary sites varied, a highly uniform treatment protocol was followed with no patients undergoing therapeutic, upfront surgery, or induction chemotherapy and the majority were treated with concurrent chemoradiotherapy. As expected, high MTV was associated with advanced T stage of T3 or greater (72% vs. 17%, $p < 0.0001$). Prospective evaluation, incorporating direct measures of swallowing function, would be readily achievable in a single- or multi-institutional setting.

Conclusion

Pre-treatment MTV is a semi-automated, reproducible parameter that can be generated at or prior to a pre-treatment Multidisciplinary Tumor Board and may expedite decisions regarding placement of prophylactic FTs. Prospective evaluation in large series is required to

determine whether MTV is a more useful prognostic variable for FT use and dependence than clinical T stage, in the IMRT era.

Acknowledgements Departments of Nutrition and Dietetics & Speech Pathology, Austin Health, Heidelberg, Victoria, Australia.

Compliance with Ethical Standards

Conflict of interest We state that, regarding this paper, no actual or potential conflicts of interest exist.

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