Research article

Clinical and dosimetric risk stratification for patients at high-risk of feeding tube use during definitive IMRT for head and neck cancer

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A R T I C L E   I N F O

A B S T R A C T

Introduction: To identify organs to which dose limitation using intensity modulated radiotherapy (IMRT) can potentially modify the incidence and duration of feeding tube use, during and immediately following therapy for head and neck cancer.

Materials and methods: One hundred and fourteen patients treated with definitive IMRT (± concurrent chemotherapy) head and neck mucosal cancers were included. Patients received a prophylactic feeding tube and followed up by a dietician for at least eight weeks post-radiotherapy. Salivary and swallowing organs were delineated for each patient. Tumour and dosimetric variables were recorded for all patients and analysed for incidence and duration of feeding tube use for at least 25% of dietary requirements.

Results: Multivariate analysis showed T-classification ≥3 and level II lymphadenopathy as independent significant predictors of incidence and duration of feeding tube use in oral cavity, pharyngeal and supraglottic primaries. Mean dose deposited in the cervical oesophagus over 36Gy further increased the incidence and duration of feeding tube use. Mean dose deposited in the base of tongue and superior pharyngeal constrictor muscles affected incidence and duration of feeding tube use, respectively.

Discussion: In patients treated with definitive IMRT, T-classification and Level II lymphadenopathy, combined with a mean cervical oesophagus dose over 36Gy can a stratify patients into eight distinct risk groups for using feeding tubes for at least 25% of their dietary requirements.

Introduction

Intensity modulated radiotherapy (IMRT) is a radiotherapy (RT) technique that can be used to intentionally spare normal structures essential to alimentation [1–9]. Reducing dose deposition in these organs may lessen RT-induced swallowing difficulties during head and neck RT. Enteral feeding via a feeding tube is a method of providing patient nutrition during and immediately following RT in as many as 80% of patients who are unable to maintain a sufficient oral diet [10–14]. While feeding tubes are a convenient way to optimize patient nutrition and impact positively on patients' short-term quality of life [15–18], gastrostomy tubes can be associated with severe short and long-term complications [15,19–21]. Hence, patient selection is crucial to insert gastrostomy tubes in only patients whom are likely to benefit, while sparing a larger population the risk of harm.

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We have previously described a risk assessment tool for identifying patients needing feeding tubes for more than 25% of their nutritional requirements. This tool stratifies patients into four risk groups based on two clinical variables: T-classification [22] (TC) and presence of cervical level II adenopathy (LTA) [23]. While these disease-related variables are not modifiable, the risk of feeding tube-use may be modifiable by constraining dose deposited in nominated aerodigestive and salivary structures. The purpose of this study was to identify organs to which dose limitation using IMRT can potentially modify the incidence and duration of feeding tube-use, during and immediately following therapy for HNC.

Methods and materials

Patients

Following Institutional Ethics Committee approval, the patient population was retrospectively accrued from the institution's radiation oncology database. To be eligible, patients were required to receive primary, definitive IMRT (with or without concurrent systemic treatment) for mucosal cancers of the head and neck. Patients with stage II–IVB disease were included. Patients were excluded if they underwent therapeutic surgery to the primary site or neck dissection prior to commencing RT. Patients received a prophylactic feeding tube prior to treatment, as per departmental policy. This includes patients with tumors of the oral cavity, larynx, and pharynx who are planning to receive $\geq$64 Gy with bilateral nodal irradiation, or patients with a pre-existing nutritional deficiency. All patients had nutritional assessment and follow-up.

RT planning and treatment

Target volumes were delineated by one radiation oncologist. Pre-treatment evaluation, planning, and delivery have been described previously [23]. The elective (prophylactic) nodes were defined according to consensus guidelines [24]. All patients received bilateral, elective irradiation of levels II to IV nodes. Patients with oropharynx or nasopharynx cancers had bilateral, elective irradiation of level IB nodes. In patients with oropharynx or hypopharynx cancers elective irradiation of ipsilateral level V nodes and the 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 an elective dose. All T0 (unknown primary) patients in this cohort were treated electively to bilateral nodal basins, including level IB, while bilateral tonsils and base of tongue (BOT) were treated as intermediate-risk clinical target volume (CTV). A 5 mm isotropic expansion was made from CTV to planning target volume (PTV).

Clinically and radiologically involved nodes were contoured individually. The prescribed doses were planned with a simultaneous integrated boost to high-risk PTV (66–70 Gy), intermediate-risk PTV (63 Gy) and low-risk PTV (56 Gy). Treatment was delivered five fractions per week over six to seven weeks. Target coverage and dose volume constraint goals are listed in Table 1 [25]. Medically fit patients were considered for concurrent systemic therapy based on disease stage and comorbidities.

Swallowing organs at risk (SWOARs) were retrospectively delineated on each of the included patients by four investigators, as per the University of Groningen, CT-based delineation guidelines for radiation induced swallowing dysfunction [26]. No dose-volume constraints were placed on these structures at the time of planning. Contoured SWOARs were the superior, middle and inferior pharyngeal constrictor muscles (PCM), cricopharyngeal muscle (CP), esophagus inlet muscles (EI), cervical esophagus (CE), BOT, supraglottic larynx and glottic larynx. Additionally, bilat-

Table 1
Target coverage and OAR goals.

Target	Constraint	OAR	Constraint
GTV	V98% $\geq$ 98%	Brainstem	$D_{max} \leq 54$ Gy
PTV$_{High-risk}$	V95% $\geq$ 95%	Spinal Cord	$D_{max} \leq 45$ Gy
PTV$_{Intermediate-risk}$	V95% $\geq$ 95%	Parotid Glands	$D_{mean} \leq 26$ Gy
PTV$_{Low-risk}$	V95% $\geq$ 95%	Larynx	V50Gy < 33%
		Mandible	$D_{max} \leq 70$ Gy

Abbreviations: D_{max} = Dose Maximum; D_{mean} = Dose Mean.

eral parotid glands and bilateral submandibular glands were delineated as recognition of their pertinent role in salivary production. An extended oral cavity was delineated as per Eisbruch et al [27] and the BOT was excluded from this structure for analysis. Dose received by 2% (D2%) and 50% (D50%) of these structures was recorded for analysis. D50% was chosen as the organs under investigation are predominantly believed to be parallel in structure. D2% was also analyzed in this hypothesis-generating study, given structural and functional uncertainties.

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.

Daily nutritional needs were calculated for individual patients. The percentage of these needs provided by enteral feeding was recorded using the Adequacy of Enteral Intake (AEI) scale. The AEI is an ordinal scale that is defined as AEI 0 = 0–24%, AEI 1 = 25–49%, AEI 2 = 50–74% and AEI 3 = 75–100% of daily nutritional needs. This score was recorded for each patient at each dietician visit. All patients who required enteral nutrition had dietician follow-up until their AEI was less than 1.

Speech pathology services were offered to all patients with oropharyngeal dysphagia to minimize aspiration and malnutrition risk. Videofluoroscopy and Fibreoptic Endoscopic Evaluation of Swallowing were available for at-risk patients. Swallowing rehabilitation was not available to this patient cohort.

Statistical analyses

Dosimetric parameters underwent univariate analysis, where values were subdivided into approximate quartiles to the nearest Gy. Potential patient and tumor related prognostic variables were subdivided according to previously reported cut-off points [23]. To explore the risk of feeding tube-use (Yes or No) we used the Fisher exact test if there were only two subgroups (e.g. combined parotid gland mean dose $\leq$ or > 25 Gy). For analysis of duration of feeding tube-use, Kaplan-Meier analysis was carried out and subgroups were compared using the Mantel-Cox log rank test for differences or the Tarone-Ware test for trend.

Outcomes measured were (1) the risk of feeding tube-use for at least 25% of nutritional requirements (AEI $\geq$ 1) and (2) the duration of such use measured in days from the first date the AEI was recorded at 1 or higher to the date when it dropped to AEI 0 or the tube was removed.

As all patients were followed up to cessation of AEI $\geq$ 1 tube-feeding, no durations were censored. All P values reported were two-sided and 95% confidence intervals (CI) were calculated. The significance criterion was P < 0.05 for previously reported prognostic factors or P < 0.005 for new prognostic factors (to adjust for multiple hypotheses).

Prognostic factors which were found to have a significant effect on the use of feeding tube (Yes or No) and duration of feeding tube-use for ≥25% of diet in the univariate analyses were tested in multivariable models to find the smallest number of independent prognostic factors. Swallowing structures that were included in the multivariate model were dose dichotomised at the approximate median values for these patients, except for the combined parotid glands, where the QUANTEC dose constraints (dose mean of combined bilateral parotid glands) were used as the point of dichotomisation instead (refer to Table 2 for values). For risk of feeding tube-use, exact logistic regression with conditional maximum likelihood inference was used for the multivariable analyses with P values obtained from the exact conditional scores test. For duration of feeding tube-use, Cox proportional hazards regression was used and the exponentials of the coefficients (e^{β}) from the final model were interpreted as "Recovery rate ratios".

Both backwards and forwards stepwise regression was performed, and variables were retained in the model if the P value was < 0.05.

Results

Between January 2007 and December 2013, 114 eligible, consecutive patients were treated with radical intent IMRT. Their median age at commencement of RT was 61 years (*Range:* 20–91) and 78% were male. The most common cancer site was oropharynx (60 patients, 53%). The other primary sites were nasopharynx (15, 13%), supraglottis (13, 11.5%), glottic larynx (14, 12.5%), hypopharynx (4, 3.5%), oral cavity, (2, 1.5%) and unknown primary (6, 5%). Twenty-nine of the 60 oropharynx patients (48%) had known HPV positive disease. Sixty-eight patients received concurrent systemic therapy (59.6%): 65 patients (57%) received cisplatin (100 mg/m^2 three weekly), and three patients (2.6%) received weekly cetuximab. The previously reported univariate analysis of patient demographic and tumor characteristics can be found in Appendix A [23].

Univariate analyses

Results of the univariate analysis on all 114 patients are shown in Table 2. Increasing size of tumor and target volumes were significantly associated for both incidence and duration of feeding tube use. The incidence and duration of feeding tube-use was associated with increasing dose to the oral cavity (D2% and D50%), superior PCM (D2% and D50%), middle PCM (D2% and D50%), combined parotid glands (Dmean), and combined submandibular glands (Dmean). Increasing dose to the CP (D2% and D50%) and glottic larynx (D2% and D50%) were significantly associated with an increased incidence of feeding tube-use. EI (D50%), CE (D50%) and BOT (D50%) were significantly associated with a longer duration of feeding tube-use. There were no significant associations between the incidence or duration of tube-feeding and dose to inferior PCM and supraglottic larynx.

Multivariable analyses

Ninety-four patients with dosimetry/tumor volume data and cancers in the pharynx, oral cavity or supraglottis were included for multivariable analyses for risk and duration of feeding tube-use for at least 25% of dietary needs.

As per our previous study [23], cancer site was a significant prognostic factor, therefore, six patients with unknown primaries were excluded from the multivariable analyses. Furthermore, only one of the fourteen patients with glottic larynx cancer needed to use a feeding tube, so these 14 patients were considered to be very low-risk and excluded from the multivariable analyses.

Our previous study found both TC (T3-4) and LTA to be strongly associated with risk and duration of feeding tube-use [23]. Additional tumor volume and dosimetric prognostic factors found to be significant for risk/and or duration of feeding tube-use at univariate analysis were tested in this multivariable analysis, alongside TC and LTA.

In the final models, TC (T3–4) (p = 0.0099), CE D50% (p = 0.0002) and BOT D50% (p = 0.022) were significant predictors of risk of feeding tube-use. LTA was of borderline significance (p = 0.051) in the multivariable model once BOT D50% was included, although it was highly significant (P = 0.0032) without BOT D50% in the model. This indicates partial confounding between LTA and median dose to the BOT. TC (T3–4) (p < 0.0001), LTA (p = 0.0040), CE D50% (p = 0.0002) and superior PCM (p = 0.0089) were significant predictors of duration of feeding tube-use (Table 3). Fig. 1 displays the observed duration of feeding tube-use when CE D50% is above or below the median of 36 Gy. A mean dose of at least 25 Gy to the combined parotid glands was of borderline significance when added to this model (p = 0.048) but it was partly confounded with LTA and the median dose to the superior PCM, increasing their p values to 0.026 and 0.018 respectively. It added to the complexity of the model while it increased the likelihood ratio by only 1.7, which was insufficient to justify its inclusion.

Several of the raw dosimetry variables were moderately correlated with each other, particularly superior PCM D50% and oral cavity D50% (r = 0.74), BOT D50% and oral cavity D50% (r = 0.64), and BOT D50% and superior PCM D50% (r = 0.62), so the inclusion of one of a pair in the model made the other factor non-significant. The CE was correlated with EI D50% (r = 0.67), but not with superior PCM D50 (r = -0.09), oral cavity D50% (r = -0.10) or BOT D50% (r = -0.11).

The recovery rate of a patient with cancer of the supraglottis, pharynx or oral cavity with T3–4 disease, LTA, CE D50 > 36 Gy and superior PCM D50 > 61 Gy is estimated to be $e^{-1.248 - 0.702 - 0.834 - 0.600} = e^{-3.384} = 0.034$ times the recovery rate of a patient with TC T1–2, no LTA and lower median doses to the CE and superior PCM (Table 3).

None of the other factors, which were significant in the univariate analyses were statistically significant in the multivariable analyses, after considering advanced TC and presence of LTA.

The outcomes observed for patients in eight prognostic groups derived from the first three prognostic factors (TC, LTA and CE D50%) are shown in Table 4 and were used to generate feeding tube prognostic groups like those generated from both TC and LTA in our previous study. While superior PCM was a significant prognostic factor for duration of feeding, incorporating this as an additional factor would result in 16 prognostic groups with very small numbers of patients, providing unreliable estimates.

Discussion

Our group has previously published a risk stratification model for feeding tube-use, based on clinical TC and presence of metastatic LTA [23]. This model stratified patients into four distinct risk groups. Through further analysis of RT dosimetry to SWOARS, the oral cavity, and parotid and submandibular salivary glands, we have developed three models to further stratify risk of feeding tube-use. The overarching model in this study produces eight main prognostic groups for both the incidence, for more than 48 hours, and duration of feeding tube-use. This model includes the two above clinical values and the mean dose to the CE. Two more sophisticated models are presented for both feeding tube-use and duration. Both include TC, LTA, and mean dose to CE. The additional

Table 2
Univariate analyses of additional prognostic factors for feeding tube use (Yes/No) and duration, following radiotherapy planning.

Prognostic factor	Subgroup	Feeding tube used*			Days of feeding tube use*		
		Yes/Total	%	P value[†]	Median	(95% CI)	P value[‡]
Cranio-caudal Length of PTV High	≤6.5 cm	18/41	44%	<0.0001	0	(0–28)	<0.0001
	>6–8 cm	23/31	74%		79	(14–130)	
	>8–11 cm	35/38	92%		112	(75–157)	
	>11 cm	25/29	86%		81	(55–149)	
GTV Primary	≤10 cc	15/40	38%	<0.0001	0	(0–16)	<0.0001
	>10–20 cc	26/34	76%		58	(35–79)	
	>20–40 cc	28/32	88%		86	(70–120)	
	>40 cc	32/33	97%		170	(118–233)	
GTV Nodes	0 cc	24/46	52%	0.0019	15	(0–59)	0.017
	>0–10 cc	19/24	79%		113	(44–161)	
	>10–30 cc	33/37	89%		77	(64–90)	
	>30 cm	25/32	78%		78	(44–149)	
GTV Total	≤20 cc	15/40	38%	<0.0001	0	(0–16)	<0.0001
	>20–40 cc	23/28	82%		69	(35–101)	
	>40–70 cc	36/40	90%		90	(75–130)	
	>70 cm	27/31	87%		149	(57–204)	
Oral Cavity (D2%)	≤54 Gy	10/26	38%	<0.0001	0	(0–68)	<0.0001
	>54–70 Gy	17/28	61%		51	(0–77)	
	>70–74 Gy	30/34	88%		79	(50–120)	
	>74 Gy	25/25	100%		136	(77–182)	
Oral Cavity (D50%)	≤27 Gy	12/28	43%	<0.0001	0	(0–42)	<0.0001
	>27–37 Gy	19/29	66%		58	(0–70)	
	>37–51 Gy	24/28	86%		92	(57–163)	
	>51 Gy	27/28	96%		129	(90–204)	
SPCM (D2%)	≤65 Gy	9/29	31%	<0.0001	0	(0–0)	<0.0001
	>65–72 Gy	20/25	80%		70	(57–101)	
	>72–75 Gy	22/24	92%		60	(35–105)	
	>75 Gy	32/35	91%		130	(90–182)	
SPCM (D50%)	≤52 Gy	10/26	38%	<0.0001	0	(0–58)	<0.0001
	>52–64 Gy	24/34	71%		47	(11–70)	
	>64–69 Gy	21/24	88%		90	(57–120)	
	>69 Gy	28/29	97%		149	(101–200)	
MPCM (D2%)	≤67 Gy	13/28	46%	<0.0001	0	(0–70)	0.0001
	>67–71 Gy	17/25	68%		66	(0–106)	
	>71–74 Gy	28/36	78%		64.5	(44–97)	
	>74 Gy	25/25	100%		161	(90–204)	
MPCM (D50%)	≤56 Gy	12/25	48%	<0.0001	0	(0–105)	0.024
	>56–62 Gy	21/33	64%		70	(0–101)	
	>62–68 Gy	26/31	84%		68	(35–125)	
	>68 Gy	24/25	96%		79	(59–233)	
IPCM (D2%)	≤58 Gy	19/26	73%	0.55	89	(18–120)	0.15
	>58–64 Gy	25/31	81%		75	(55–125)	
	>64–71 Gy	17/26	65%		33	(0–65)	
	>71 Gy	22/31	71%		77	(14–170)	
IPCM (D50%)	≤44 Gy	21/28	75%	0.11	70	(10–106)	0.86
	>44–51 Gy	26/29	90%		77	(58–113)	
	>51–66 Gy	20/32	63%		62	(0–118)	
	>66 Gy	16/25	64%		42	(0–108)	
CPM (D2%)	≤52 Gy	22/27	81%	0.012	77	(49–106)	0.56
	>52–57 Gy	25/31	81%		81	(45–122)	
	>57–66 Gy	22/28	79%		72.5	(31–149)	
	>66 Gy	13/26	50%		8	(0–108)	
CPM (D50%)	≤38 Gy	23/29	79%	0.009	66	(35–101)	0.065
	>38–43 Gy	20/24	83%		76	(45–113)	
	>43–57 Gy	27/32	84%		92	(57–157)	
	>57 Gy	12/27	44%		0	(0–68)	
EIM (D2%)	≤45 Gy	21/28	75%	0.060	68	(10–101)	0.10
	>45–51 Gy	22/26	85%		81	(58–161)	
	>51–57 Gy	25/31	81%		77	(44–157)	
	>57 Gy	15/29	52%		16	(0–70)	
EIM (D50%)	≤35 Gy	18/28	64%	>0.99	52	(0–97)	0.042
	>35–41 Gy	24/31	77%		65	(18–83)	
	>41–48 Gy	23/26	88%		123	(68–177)	
	>48 Gy	18/29	62%		57	(0–133)	
CE (D2%)	≤43 Gy	17/28	61%	0.51	17	(0–90)	0.18
	>43–49 Gy	23/30	77%		77	(44–130)	
	>49–55 Gy	25/29	86%		77	(57–113)	
	>55 Gy	18/27	67%		77	(0–133)	
CE (D50%)	≤28 Gy	17/30	57%	0.060	16	(0–70)	0.039
	>28–36 Gy	20/28	71%		62	(7–97)	
	>36–42 Gy	26/29	90%		101	(77–130)	
	>42 Gy	20/27	74%		77	(16–149)	

Table 2 (*continued*)

Prognostic factor	Subgroup	Feeding tube used*			Days of feeding tube use*		
		Yes/Total	%	P value[†]	Median	(95% CI)	P value[‡]
BOT (D2%)	≤64 Gy	9/28	32%	0.51	0	(0–42)	0.18
	>64–71 Gy	22/29	76%		68	(16–81)	
	>71–74 Gy	21/24	88%		94.5	(50–125)	
	>74 Gy	31/33	94%		105	(59–182)	
BOT (D50%)	≤46 Gy	11/28	39%	0.060	0	(0–58)	0.039
	>46–61 Gy	17/27	63%		45	(0–77)	
	>61–79 Gy	30/33	91%		101	(70–136)	
	>79 Gy	25/26	96%		101	(55–200)	
SGL (D2%)	≤66 Gy	20/27	74%	0.78	70	(35–113)	0.43
	>66–71 Gy	19/29	66%		59	(0–79)	
	>71–73 Gy	19/23	83%		90	(57–120)	
	>73 Gy	25/34	74%		66	(31–130)	
SGL (D50%)	≤45 Gy	18/27	67%	0.63	77	(0–120)	0.77
	>45–56 Gy	27/30	90%		82	(65–116)	
	>56–68 Gy	19/28	68%		53.5	(0–122)	
	>68 Gy	19/28	68%		45.5	(0–108)	
GL (D2%)	≤48 Gy	24/30	80%	0.011	77	(44–101)	0.37
	>48–54 Gy	24/26	92%		94	(58–150)	
	>54–71 Gy	19/30	63%		63.5	(0–113)	
	>71 Gy	16/28	57%		16	(0–108)	
GL (D50%)	≤34 Gy	27/32	84%	0.0016	80	(35–106)	0.42
	>34–41 Gy	22/27	81%		75	(57–118)	
	>41–66 Gy	21/27	78%		77	(59–128)	
	>66 Gy	13/28	46%		0	(0–106)	
Both Parotids (Dmean)	< 25 Gy	22/33	67%	0.0021	35	(0–70)	<0.0001
	≥25 Gy	55/59	93%		113	(79–150)	
Both SMGs (Dmean)	≤61 Gy	11/19	58%	0.0013	16	(0–106)	0.0003
	>61–64 Gy	16/21	76%		70	(11–79)	
	>64–67 Gy	18/18	100%		89	(57–149)	
	>67 Gy	15/16	94%		202	(77–451)	

* "Feeding tube use" means feeding tube was used for at least 25% of nutritional requirements.

[†] Two-sided P value from Fisher exact test for difference between 2 subgroups, Pearson chi square test for difference between 3 or more unordered subgroups, or Cochran-Armitage test for trend across 3 or more ordered subgroups.

[‡] Two-sided P value from Mantel-Cox log rank test for differences between subgroups or Tarone-Ware test for trend across 3 or more ordered subgroups.

Table 3

Final multivariable models for feeding tube use* (Yes/No) and duration (n = 94) after planning CT (i.e. including GTV, PTV and dosimetric variables).

Feeding tube use (exact logistic regression with conditional maximum likelihood inference)[†]

Factor	Reference	Level	β	s.e.$_β$	Odds ratio		Exact
					OR	95% CI	P value
T stage	T1–T2	T3–T4	2.314	0·925	10.1	1·4–124.4	0·0099
Level 2 nodes	No	Yes	1.707	0·866	5.5	0.8–51.4	0·051[#]
CE D50	≤36 Gy	> 36 Gy	3.466	1.162	32.0	3.3–1811.0	0·0002
BOT D50	≤61 Gy	> 61 Gy	1.930	0·810	6.9	1·2–55.0	0·022[#]

Duration of feeding tube use (Cox proportional hazards regression)[†]

| Factor	Reference	Level	β	s.e.$_β$	Recovery ratio		Exact
					RR	95% CI	P value
T stage	T1–T2	T3–T4	−1.248	0·258	0.287	0.17–0.48	<0·0001
Level 2 nodes	No	Yes	−0.702	0·244	0.495	0.31–0.80	0·0040
CE D50	≤36Gy	> 36Gy	−0.834	0.222	0.434	0.28–0.67	0·0002
SPCM D50	≤61Gy	> 61Gy	−0.600	0·229	0.549	0.35–0.86	0·0089

[‡] Other factors which were not significant when added individually to the models were: body mass index (<18.5 vs ≥18.5), nutrition (PG-SGA mal-nourished vs well nourished), dysphagia (Yes vs No), cancer (pharynx/oral cavity vs supraglottic larynx), human papilloma virus status (positive/unknown vs negative), N stage (N1–3 vs N0), bilateral neck nodes (Yes vs No), planned concurrent chemotherapy, PTV length (≤8cm vs >8 cm), GTV primary size (≤20 cc vs >20 cc), GTV nodal size (≤10 cc vs >10 cc), GTV total size (≤40 cc vs >40 cc), oral cavity D50 (≤37 Gy vs >37 Gy), superior PCM D50 (≤64 Gy vs >64 Gy), middle PCM D50 (≤62 Gy vs >62 Gy), esophageal inlet muscle D50 (≤41 Gy vs >41 Gy), both parotids Dmean (<25 Gy vs ≥20 Gy) and both submandibular gland Dmean (<64 Gy vs ≥64 Gy). When added individually to the above models, the P values for these factors were all >0.1 for incidence and >0.1 for duration of feeding tube use.

* "Feeding tube use" means feeding tube was used for at least 25% of nutritional requirements.

[#] Level 2 nodal involvement was of borderline significance (P = 0.051) once BOT D50 was included. However, it was highly significant (P = 0.0032) without BOT D50 in the model. This indicates partial confounding between Level 2 nodes and median dose to the base of the tongue.

[†] β = coefficient for each Level relative to the Reference category, based on 116 patients with cancers of pharynx, oral cavity or supraglottic larynx. s.e.$_β$ = estimated standard error of β. OR or RR = $e^β$. 95% CI = 95% confidence interval for the OR or RR = $e^{β \pm 1.96 (s.e.β)}$.
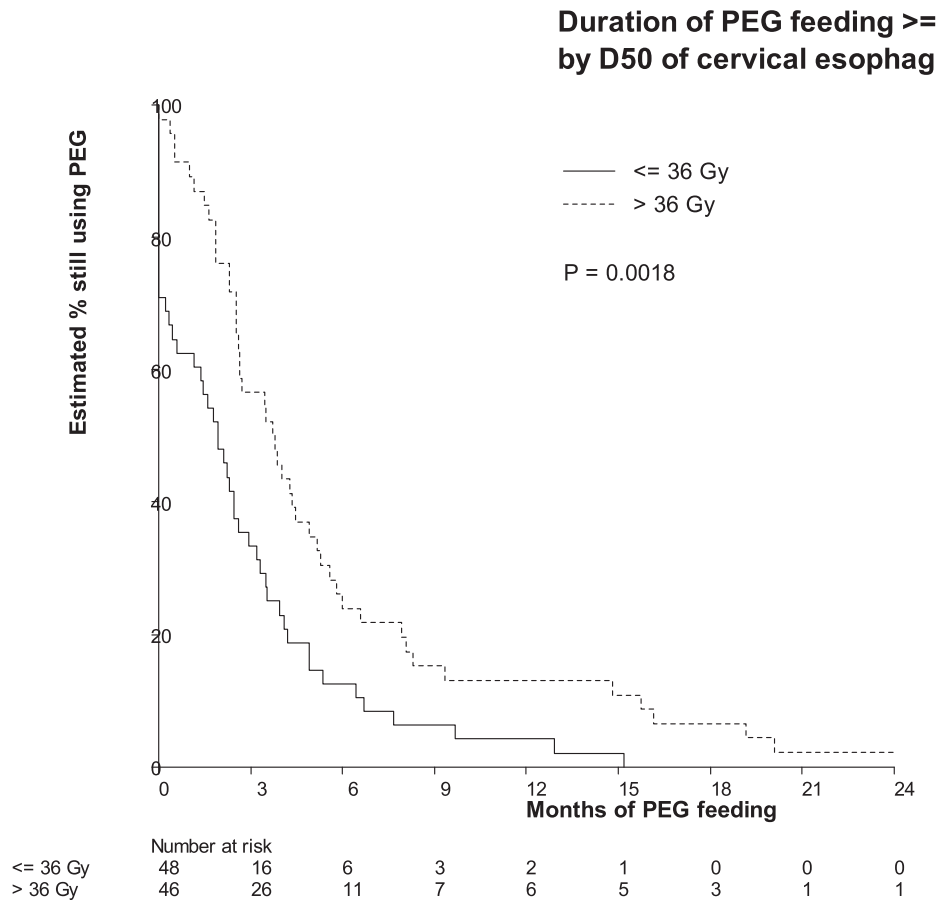
Fig. 1. Duration of feeding tube use for at least 25% of nutritional requirements by D50% of cervical oesophagus. Kaplan-Meier analysis, 94 patients.

Table 4
Prognostic groups based on T stage and Level 2 lymphadenopathy: data from 94 patients with cancers of pharynx, oral cavity or supraglottis.

T stage	Level 2 nodes	CE D50	PEG feeding $\geq$ 25% of diet		Duration of PEG feeding	
			Yes/Total	%	Median days (95% CI)	
T1–2	No	$\leq$36 Gy	3/10	30%	0	(0–42)
		>36 Gy	6/7	86%	70	(0–133)
	Yes	$\leq$36 Gy	12/16	75%	65	(0–120)
		>36 Gy	15/15	100%	83	(70–157)
T3–4	No	$\leq$36 Gy	10/13	77%	90	(0–150)
		>36 Gy	11/11	100%	116	(57–491)
	Yes	$\leq$36 Gy	9/9	100%	101	(55–393)
		>36 Gy	13/13	100%	170	(113–479)
All supraglottic/pharynx/OC patients with dosimetry			79/94	84%	79	(68–106)

variables of mean dose to BOT and superior PCM are significant for feeding tube-use and duration, respectively. This is shown diagrammatically in Fig. 2.

Mean dose, or D50%, has been selected.

The CE, like other SWOARS, is intimately associated with the physical passage of food in deglutition. An association with poorer swallowing outcomes with increasing dose to this organ has been described previously [9]. This current study shows a significant impact of a mean dose exceeding 36 Gy on both incidence and duration of feeding tube-use on patients already stratified by TC and LTA. While this impact was most pronounced in the lower risk patients for feeding tube incidence, the median (range) feeding tube duration for patients with advanced TC, LTA present, and

mean dose to CE over 36 Gy was 170 (113–479) days compared to 101 (55–393) days in similar patients with CE mean doses of 36 Gy or less. While this association, obtained from retrospective data, does not prove causality, it represents a promising variable for future, prospective studies. Limiting dose to the CE is particularly appealing, as most patients in this study (53%), and in contemporary western cohorts [28], were treated for oropharyngeal cancers. Modern volumetric modulated arc therapy techniques should easily be able to achieve doses well under 36 Gy, without compromising target coverage, in most of these patients.

The BOT is a SWOAR that a considerable amount of HNC primaries arise from, or directly invade [26]. Increasing dose to this organ has been associated with poor swallowing outcomes [9]. In
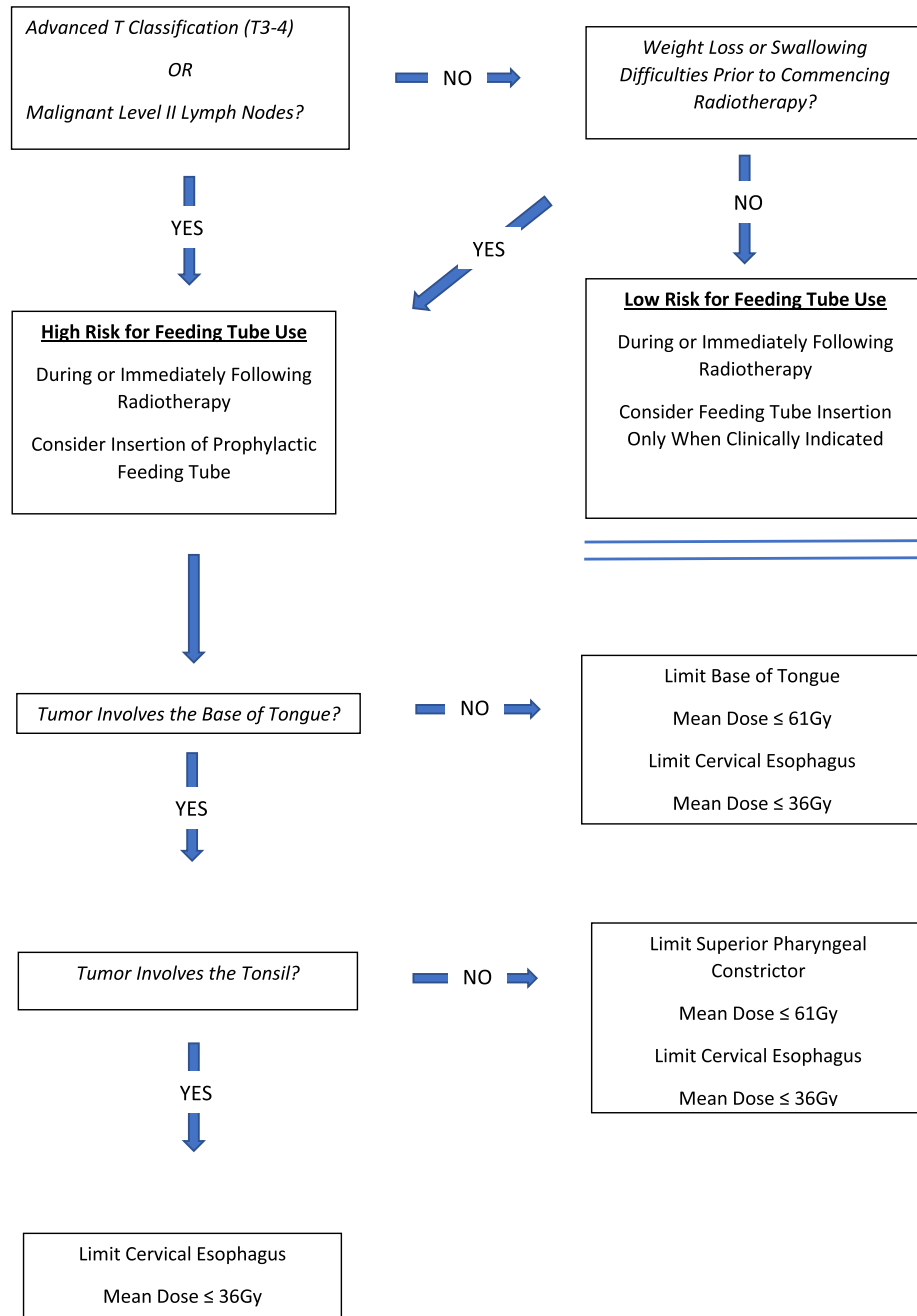
Fig. 2. Proposed treatment approach for patients for patients receiving definitive, bilateral (chemo)radiotherapy for cancers of the head and neck.

this cohort, patients who received a mean dose of over 61 Gy to their BOT were more likely to use a feeding tube than those who received lower doses, and this effect was additive to the TC, LTA and CE mean dose. Not surprisingly, a partial confounding effect was seen between BOT dose and LTA. The P-value for feeding tube-use associated with LTA rose from 0.0032 to 0.05 with the addition of BOT dose. As previously described, there are both anatomical and disease-related reasons for this confounding effect [23,26,29].

Prospective evaluation of the impact of dose limitation to the BOT would not be as straightforward as it would be for CE. Tumors arise in the BOT and invade into it from other sites and the BOT possesses rich lymphatics. Despite ongoing advances, many radiation oncologists doubt the sensitivity of three dimensional and molecular imaging for detecting the full extent of disease spread

in this region. Treatment failure in the BOT portends a poor prognosis and surgical salvage has traditionally been difficult and debilitating [30]. For these reasons, many clinicians would likely be reluctant to reduce margins around gross disease in the BOT in pursuit of a swallowing outcome.

The model for feeding tube duration in this manuscript incorporates TC, LTA, CE mean dose and mean dose to the superior PCM above 64 Gy. Like BOT, superior PCM dose is also partially confounded by LTA, albeit to a lesser degree. Similar anatomical and disease related (tonsillar and BOT primaries tend to metastasize to level II) mechanisms for this interaction likely hold. In this model, we also see partial confounding with mean parotid gland dose. This makes intuitive sense based on the above reasoning, as parotid glands sit immediately lateral to level II [24]. Prospective evaluation of dose limitation to the superior PCM would be diffi-

cult in patients with tonsillar primaries, particularly with advancing TC. This may be more appropriate for patients with BOT and other non-tonsillar primaries. Conversely, BOT is a more appealing avoidance structure in patients with tonsillar primaries.

submandibular glands produce 65–90% of mucin rich saliva and 95% of salivary flow during a 24-hour period [31]. Studies have shown that a mean dose of less than 39 Gy to submandibular glands results in both patient and observer reported xerostomia [31]. Wopken et al have observed a significant increase in 6-month feeding tube dependence with every increasing Gy of mean dose to the ipsilateral (OR 1.13; p < 0.001) and contralateral submandibular gland (OR 1.10; p < 0.001) [9]. Our univariate analysis showed increasing incidence and duration of feeding tube-use with increasing mean dose to submandibular glands over 61 Gy. In this patient cohort, bilateral level IB nodal regions were electively irradiated in all patients with naso or oropharyngeal primaries, and submandibular glands are contained in this region [24]. This has led to universally higher submandibular gland doses in this study compared to other cohorts with selective IB omission. This higher overall dose likely contributes to the non-significance of submandibular gland dose in our multivariate models. There is ample retrospective data supporting the safety of submandibular sparing techniques [31–34] and this should be pursued where appropriate.

In our univariate analysis, limiting the mean dose to bilateral parotid glands to under 25 Gy was associated with reduced incidence and duration of feeding tube-use. This is consistent with previously published data [9]. Other studies have shown that mean dose to the contralateral parotid gland alone is associated with xerostomia and use of feeding tube, six months following RT [9,35]. It is well known that avoiding the irradiation of parotid glands can reduce the incidence and severity of xerostomia [9,35–37] and as such is already a priority in IMRT plans worldwide.

This study reports on two dependent variables, the incidence and duration of feeding tube-use. Regarding incidence, 70% of patients with early TC, with no LTA and a low mean CE dose were able to avoid any tube-feeding. This represents a truly low-risk population and this risk is lower still in patients with low mean BOT dose. These findings may have implications for resource allocation, certainly with regards to avoiding gastrostomy tubes, and perhaps regarding less intensive speech therapy and dietetic support.

The duration of feeding tube-use is a particularly valuable endpoint with regards to selecting patients who may benefit from a prophylactic gastrostomy. Substantial controversy exists as to whether HNC patients are best managed via reactive or prophylactic feeding tubes [21], and a thorough discussion of same is beyond the scope of this manuscript. However, even departments that adhere to strict reactive feeding tube protocols insert prophylactic tubes in a subset of high-risk patients, and, conversely, departments with policies of liberal, prophylactic feeding tube-use will choose to spare a low-risk subset of patients from undergoing the insertion procedure. All patients in this study were recommended a prophylactic feeding tube and this potentially affected the overall duration of feeding tube-use seen. Many studies have previously shown higher feeding tube-use at six months with prophylactic use of a feeding tube [15,38,39]. However, Salas et al found no difference between reactive and prophylactic feeding tube and Silander et al reported lower rates of grade 3 dysphagia

in patients with a prophylactic gastrostomy tube (2% vs 9%) [16,18].

In this study, no patient had access to swallowing rehabilitation. A randomized controlled trial has shown that swallowing exercises led to less deterioration of swallowing muscles and functional swallowing ability during chemoradiotherapy for HNC [40]. Patients randomized to swallowing exercises were more likely to maintain an oral diet and were less likely to use a feeding tube [40]. Adherence to swallowing exercises can improve maintenance of an oral, or partial oral, diet during chemoradiotherapy. This appears to be associated with better long-term diet and shorter feeding tube-use [20]. The lack of swallowing exercises in this study may limit the applicability of our data to patients who are performing swallowing exercises. However, the complete absence of these exercises in this cohort contributes to the uniformity of our data and possibly adds to the internal validity of our findings. Swallowing exercises have definite patient benefits, but not all patients are adherent to prescribed swallowing exercises and many patients are partially adherent, making these benefits difficult to quantify [20,40]. Whether swallowing exercises may be especially valuable to patients receiving higher doses to SWOARs, could be the subjective of future, prospective study.

This study possesses all the limitations inherent to a single-institution, retrospective analysis. We are unable to provide data on patients' functional swallowing ability; however, we were able to accurately report on patients having oral, or partial oral diet at various time points due to comprehensive, prospectively recorded nutritional data. All patients were treated by a single radiation oncologist; however, it must be acknowledged that these patients were treated over seven years, a sufficient time period for individual practice to vary. All patients were treated in the FDG-PET and IMRT era. This lends to uniformity in staging, volume delineation and treatment delivery across the cohort. This study expands upon a simple and novel clinical risk stratification tool and identifies the CE, BOT and superior PCM as avoidance structures for further prospective study.

Conclusion

In patients with pharynx or supraglottic larynx cancers treated with definitive, bilateral IMRT, with or without concurrent systemic therapy, two clinical risk factors, namely T-classification (T3–4) and level II lymphadenopathy, combined with a mean cervical esophagus dose over 36 Gy, can potentially stratify patients into eight distinct risk groups for using feeding tubes for at least 25% of their dietary requirements. This stratification may be useful in the clinic prior to commencing radiotherapy, so that patients at risk may have a feeding tube inserted early prior to further nutritional status deterioration. Prospective studies on dose limitation to the cervical esophagus, base of tongue and superior pharyngeal constrictor muscles are warranted.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Univariate analyses of prognostic factors for feeding tube use (Yes/No) and duration in 139 patients

Prognostic factor	Subgroup	Feeding tube used*			Days of feeding tube use*		
		Yes/Total	%	P value[†]	Median (95% CI) P value[‡]		
Cancer site	Pharynx or oral cavity	86/101	85%	<0.0001	89	(70–120)	<0.0001
	Larynx, supraglottis	10/15	67%		16	(0–79)	
	Larynx, glottis	1/14	7%		0	(0–0)	
	Unknown primary	4/9	44%		0	(0–66)	
Human papilloma virus (HPV)	Negative	22/23	96%	0.13	163	(81–233)	0.004
(for 87 oropharynx/unknown 1°)	Positive	35/46	76%		61	(31–90)	
	Unknown	13/18	72%		59	(0–77)	
T stage	X, 0	4/10	40%	0.0007	0	(0–66)	<0.001
	1	15/23	65%		50	(0–77)	
	2	31/47	66%		44	(7–75)	
	3	34/40	85%		119	(79–173)	
	4	17/19	89%		150	(57–262)	
N stage	0	22/44	50%	0.0004	7	(0–59)	0.006
	1	16/20	80%		75	(44–120)	
	2	60/70	86%		86	(70–122)	
	3	3/5	60%		45	(0–>295)	
Bilateral neck node disease	No	70/104	67%	0.016	59	(28–75)	0.025
	Yes	31/35	89%		118	(57–170)	
Retropharyngeal node disease	No	93/131	71%	0.11	66	(50–79)	0.025
	Yes	8/8	100%		153	(14–>834)	
Level 1 node disease	No	85/120	71%	0.28	70	(57–83)	0.58
	Yes	16/19	84%		55	(18–113)	
Level 2 node disease	No	36/62	58%	0.0010	37	(0–68)	0.0054
	Yes	65/77	84%		83	(65–120)	
Level 3 node disease	No	72/107	67%	0.012	65	(31–79)	0.53
	Yes	29/32	91%		86	(57–136)	
Level 4 node disease	No	90/127	71%	0.18	68	(49–79)	0.14
	Yes	11/12	92%		124	(45–393)	
Level 5 node disease	No	92/128	72%	0.73	70	(49–81)	0.55
	Yes	9/11	82%		58	(0–393)	
Concurrent chemotherapy	No	30/55	55%	0.0002	16	(0–59)	0.0048
	Yes	71/84	85%		86	(75–118)	
Dysphagia or odynophagia	No	75/110	68%	0.020	59	(42–77)	0.009
	Yes	26/29	90%		133	(70–200)	
Nutrition (PG-SGA)	Well-nourished	72/106	68%	0.012	58	(42–75)	0.001
(1 missing)	Malnourished	29/32	91%		147	(77–211)	
Body Mass Index	Underweight (<18.5)	10/12	83%	0.51	208	(81–479)	0.002
(15 missing)	Not underweight (≥18.5)	80/112	71%		65	(45–77)	
Age on commencing RT	≤65 years	70/88	80%	0.019	75	(58–90)	0.74
	>65 years	31/51	61%		31	(0–106)	
ECOG Performance Status	0	43/58	74%	0.87	58	(35–79)	0.17
	1	53/74	72%		70	(50–116)	
	2	5/7	71%		128	(0–>303)	
Charlson Comorbidity Index	0	55/72	76%	0.23	70	(45–101)	0.85
	1	16/22	73%		59	(10–108)	
	2	19/27	70%		77	(16–170)	
	3, 4, 5	11/18	61%		17	(0–136)	
Tobacco smoking	Never or minimal	39/46	85%	0.13	70	(50–101)	0.53
(4 missing)	Past	27/42	64%		55	(0–90)	
	Current	33/47	70%		70	(42–128)	
Alcohol drinker	Never or social	69/94	73%	0.73	66	(44–90)	0.46
(5 missing)	Past	8/11	73%		120	(0–200)	
	Current	20/29	69%		57	(14–77)	

*"Feeding tube use" means feeding tube was used for at least 25% of nutritional requirements.

[†]Two-sided P value from Fisher exact test for difference between 2 subgroups, Pearson chi square test for difference between 3 or more unordered subgroups, or Cochran-Armitage test for trend across 3 or more ordered subgroups.

[‡]Two-sided P value from Mantel-Cox log rank test for differences between subgroups or Tarone-Ware test for trend across 3 or more ordered subgroups.

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