A Phase II Study on Treatment De-Intensification in Favorable Squamous Cell Carcinoma of the Oropharynx

Principal Investigators:

Harry Quon, M.D.
Radiation Oncology

Arlene Forastiere, M.D.
Medical Oncology

Co-Investigators:

Shanthi Marur, M.D., Medical Oncology
Christine Chung, M.D., Medical Oncology
Nishant Agrawal, M.D., Head & Neck Surgery
Ralph P. Tufano, M.D., Head & Neck Surgery
Christine Gourin, M.D., Head & Neck Surgery
Jeremy Richmon, M.D., Head & Neck Surgery
Wayne Koch, M.D., Head & Neck Surgery
Nafi Aygun, M.D., Radiology
William Westra, M.D., Pathology
Heather Starmer MA CCC-SLP, Speech therapy
Kim Webster, MA MS CCC-SLP, Speech therapy
Donna Tippett MPH, MA, CCC-SLP, Speech therapy
Todd McNutt, Ph.D., Physics
Amanda Blackford, Sc.M., Statistics

Research Nurses:

Kelly Szajna, R.N., B.S.N
410-502-9242
kszajna1@jhmi.edu

Shirl DiPasquale, R.N.
410-614-1598
sdipasq1@jhmi.edu

Beth Griffith, R.N.
410-502-9243
bgriffit@jhmi.edu

Study Coordinators:

Katharine Oteiza
410-614-3158
koteiza1@jhmi.edu

Ryan Assadi
410-955-8652
rassadi1@jhmi.edu

Helen Kim
410-614-3950
hkim91@jhmi.edu

Other study staff:

Sarah Bonerigo, P.A.

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SCHEMA

Treatment Plan:

The protocol combines *selective* RT dose de-escalation (from 70 Gy to 63 Gy and from 58.1 Gy to 50.75 Gy, same number of fractions (N=35) in 7 weeks) in patients with HPV-associated cancers of the oropharynx receiving standard of care treatment based on clinical stage. Image guided RT with daily cone-beam CT imaging will be used with CTV to PTV margins of 5 mm. Outcome will be evaluated both in terms of tumor control (and pattern of failure) and toxicity/QoL.Endpoints: Prevalence of grade 3+ toxicity at 2 yrs according to CTCAE 4.0 <15%; locoregional control at 2 yrs >85%.

SCC oropharynx, HPV positive,

Tx, T1-2 and Nx (without ECE), N0-1, N2a (<5 cm) → de-escalated IMRT alone ± S for residual disease

T3 and/or Nx (with ECE) N2a (≥5 cm), N2b-c, N3 (resectable) → de-escalated IMRT + conc CDDP ± S for residual disease

Eligibility:

- Confirmed histopathologic diagnosis of oropharyngeal *(tonsil, base of tongue, pharyngeal wall, soft palate)* squamous cell carcinoma;
- Human papillomavirus (HPV) positive;
- Stage T1-T3, N0-N3 (resectable), M0; both sides of the neck are judged to be at risk of metastatic disease
- Surgery of the primary tumor is limited to incisional or excisional biopsies; any surgery is allowed in the neck; patients with surgery at both primary and nodal sites and without macroscopic residual disease (cTxcNx) are excluded)
- ANC ≥ 1200 /mm^3
- Platelets >100,000/ mm^3
- Adequate hepatic function with bilirubin < 1.5 mg/dl
- AST < 2x the upper limit of normal
- ALT < 2x the upper limit of normal
- Serum creatinine < 1.3 mg/dl
- Normal serum calcium (or normal corrected serum calcium)

(Please note*: Formula for corrected calcium if albumin value is below normal range: Corrected calcium (*mg/dl*) = [4 – [patient albumin (g/dl)] x 0.8 + patient calcium (mg/dl)

- Cannot have Serum creatinine >1.3 or ULN
- Cannot have CCL < 60 cc/min
- ECOG performance status 0-1
- Nutritional condition must be considered compatible with the proposed radiotherapeutic treatment (cannot have unintentional and/or surgically unrelated weight loss >20% in the preceding 3 months)
- Patients cannot be a current smoker at time of treatment
- Patient cannot have a smoking history of > 10 pack years
- No prior radiotherapy to the head and neck;
- No prophylactic use of amifostine and/or pilocarpine;

- No concurrent enrollment in another therapeutic protocol for the same diagnosis;
- No active untreated infection;
- No major medical or psychiatric illness that would preclude treatment compliance;
- Signed study-specific informed consent form prior to registration;
- No other malignancy except for non-melanomatous skin cancer, early stage prostate cancer (T≤2a and PSA<10 and GLS≤7) or a carcinoma not of head and neck origin disease free for ≥ 5 years

Required Sample Size: 60 patients

1 BACKGROUND AND RATIONALE

1.1 Disease control of contemporary oropharyngeal cancer

As for many other primary subsites of the head and neck district, two main options have been traditionally employed for the treatment of squamous cell carcinoma of the oropharynx (ORO-SCC), surgery and radiotherapy (RT). The latter has been shown to be less `invasive` and morbid than radical surgery [1] and therefore has gained consensus as first line option in ORO-SCC at many Institutions across the country.

Surveillance Epidemiology and End Results (SEER) data from 1975 to 2002 show an approximate 5% to 8% improvement in 5-year overall survival for squamous head and neck cancer [2]. Most of this improvement occurred in oropharyngeal carcinoma. Table 1 summarizes results from contemporary series using non-surgical-based approach for ORO-SCC. They consistently show that long-term locoregional control rates are in the order of 80-95%.

Table 1. IMRT±chemotherapy for oropharyngeal SCC: literature data with emphasis on the pattern of failure.

Author	Period	# pts	# def (%)	% T3-4	% N2-3	% Chemo	FU (mths)		2-yr^^	
							Min^	Median	LRC	OS
Wash U	1997-2001	74	31 (42%)	71%	NA	55%	24	33	77% (4)	
MDACC	2000-2002	51	51 (100%)	0	53%	10%	15	45	93%+ 96% (T)	94%
MSKCC	1998-2004	50	48 (96%)	34%	NA	86%	8.4	18	98% (T) 86% (N)+	98%
	1998-2004	41	41 (100%)	39%	75%	100%	20	31	92%(3)+	91% (3)
RTOG 0022	2001-2005	67	67 (100%)	0	10%	0	2.4	19.2	95.5%	
Univ IOWA	2000-2004	66	62 (94%)	41%	82%	74%	11.5	27.3	98.8%(3)+	78.1% (3)
UTMB	2002-2006	50	50 (100%)	38%	60%	0	12.1	32.6	94% (3)(T) 85% (3)(N)	

^ for living patients
*6 pts without identification of the origin of primary tumor
+ including neck dissection for residual neck disease
^^ unless otherwise specified in parenthesis
Abbreviations: # def: number of patients treated with definitive intent; chemo: chemotherapy; FU: follow up duration; mths: months; Wash U: Washington University; MDACC: MD Anderson Cancer Center; MSKCC: Memorial Sloan Kettering Cancer Center; RTOG: Radiation Therapy Oncology Group; UTMB: University of Texas Medical Branch; T: tonsillar fossa; BOT: base of tongue; SP: soft palate; PW: pharyngeal wall. For references please see[3]

Ameliorations in treatment approach that could have lead to this include:

1. Introduction of a more sophisticated and precise way to plan and deliver RT or Intensity Modulated RT (IMRT). IMRT has been associated with more precise target coverage and less long-term toxicity on selected organs such as the parotid glands [4];
2. Introduction of concomitant systemic chemotherapy (CHT) to RT particularly in locoregionally advanced disease (AJCC stage III & IV) [5, 6]. Chemotherapy exploits a local cooperation with RT.
3. Better support of patients during treatment in terms of pain control and nutritional status that allows more aggressive treatment to be delivered [7];
4. Wider and wiser use of planned neck dissection after primary RT±CHT and refinement of surgical techniques of reconstruction with more salvage options after failure of primary chemoradiotherapy.

Finally, nowadays a significant percentage of ORO-SCC is associated with the Human Papilloma Virus type 16 (HPV-16) or less frequently, with other types. It has been postulated that the biology of HPV-related ORO-SCC may be more benign than the classic alcohol-tobacco-related cancers [8], and preliminary clinical data seem to confirm this hypothesis [9]. Currently the prevalence of ORO-SCC which test positive for HPV referred for definitive (chemo)radiotherapy at JH is around 80% (unpublished data).

1.2 Favorable subgroup of patients with ORO-SCC

Patients with low tumor burden or early stage disease (I-II, T1-2N0-1, primary tumor equal/less 4 cm in greatest dimension and/or nodal disease up to 3 cm) have a favorable outcome. In the MDACC series on 175 patients with stage I-II disease treated from 1970 to 1998 without IMRT and systemic treatment, 5-yr local control (LC), regional control (RC) and locoregional control rates (LRC) were 85%, 93% and 81%, respectively [10]. Recently, RTOG protocol 0022 on IMRT alone for early stage (T1-2, N0-1) oropharyngeal carcinoma has produced a 2-yr LRC of 91% (95%CI: 97.9-84.2%)[11]. T-stage is a strong predictor of local control by radiotherapy ± chemotherapy [12]. T4 tumors do significantly and consistently worse than T1-3 [13]. Interestingly, up to T3, oropharyngeal primary tumor staging is based on tumor dimensions, but in two separate studies this did not correlate with primary tumor volume as measured before treatment on CT [14, 15]. Nathu et al. demonstrated a significant variation of oropharyngeal tumor volume for a given T-stage. T2 tumors ranged from 0 to 32.5 cm^3, T3 from 0 to 48 cm^3, and T4 from 6.5 to 99.9 cm^3. The variation in tumor volume appears to be greater for tumors of the oropharynx than tumors of other head and neck subsites[14]. Therefore, it is not surprising that the predictive role of tumor volume on outcome after (chemo)radiotherapy is a controversial issue with both negative [14-16] and positive [17-19] studies. While this seems to contradict one of basic principles of RT that is the number of clonogens in the tumor is directly correlated with the risk of failure [20], other radiobiologic factors may well overcome and override the negative effect of clonogen number. One possible explanation is that intrinsic radiosensitivity of ORO-SCC is greater than that of SCC arising from other subsites of the HN district, which is often reported [15], although this has not been documented. Another (more reliable) explanation is that tumors that show an exophytic pattern of growth are more sensitive to radiation because of better oxygenation and a smaller hypoxic component due to better vascular supply [20]. It is not an uncommon observation in the clinic that bulky, exophytic tumors `melt` during a course of radiotherapy and show good long

term control. This is indirectly supported by the evidence that Hypoxia-Inducible Factor-1-α (HIF1α) is over-expressed in the vast majority of patients with squamous cell cancer of the oropharynx [21, 22]. Interestingly, the degree of expression has been found to predict the likelihood of success of curative radiation therapy [22]. Moreover, in one study HIF-1a expression was a more significant adverse prognostic factor in the tonsil (hazard ratio [HR], 23.1; 95% confidence interval [CI]. 3.04–176.7) than the tongue-base tumor (HR, 2.86; 95% CI, 1.14–7.19) group (p = 0.03, test for interaction)[21].

Based on these considerations, it is reasonable to consider as having a favorable prognosis those ORO-SCC`s that present at an early T stage, T1 and T2, and thus radiotherapy alone is a reasonable option. For T3`s, combined chemoradiotherapy is the treatment of choice as discussed below in 1.3.

Regarding N stage, despite excellent locoregional control rates with RT alone followed by neck dissection for residual/persistent nodal disease[12], combined chemoradiotherapy is the treatment of choice for patients with single nodes greater than 3 cm (N2a, N3) or multiple nodes (N2b-c) in attempt to minimize the need for post treatment neck dissection.

Finally, preliminary clinical data from two separate controlled studies support the concept that viral-related as opposed to tobacco/alcohol-related ORO-SCC`s have a better prognosis after definitive chemoradiotherapy [9, 23]. While the positive effect of HPV-associated disease on outcome may be somewhat mitigated by a previous history of smoking, evaluation of HPV-status appears to identify a group of patients with a better prognosis to IMRT.

1.3 On systemic treatment for ORO-SCC

Systemic treatment is part of the initial management of patients with locally advanced ORO-SCC`s based on results obtained from randomized controlled trials in all subsites [summarized by [24]] and specifically for the oropharynx [6]. At JH, cisplatin-based chemotherapy concomitant with RT is usually recommended for stage III-IV disease that includes patients with T3 disease and/or advanced nodal disease (N2-3). Patients with a single node equal/less than 3 cm, even if technically assigned to stage III according to AJCC, have a good prognosis with RT alone[10]. However, Cisplatin and other systemic therapies enhance radiation cytotoxicity by a number of mechanisms leading to better control of local and regional disease that has translated into significantly improved survival in the majority of randomized controlled trials and in 4 meta-analyses. Other potential benefits include a lessening of the need for salvage surgery, better functional, cosmetic and quality of life outcomes. Principles of treatment that correlate with outcome and apply to radiotherapy, such as the overall duration of treatment time and the total dose of radiotherapy, may not apply when RT is delivered with concomitant chemotherapy.

Other situations in which cisplatin concurrent with RT is recommended are positive resection margins at the primary tumor site and extracapsular nodal extension[25]. However, whether previous excisional biopsy in the form of wide local excision, radical or simple tonsillectomy, or just `shaving off` the tumor has any role in the management of patients with ORO-SCC is unclear with advocates on both sides: `debulking` certainly reduces the number of clonogens, but whether it translates into a better outcome is not proven; on the other hand, surgery usually

leaves a scarred, potentially hypoxic bed that is less likely to respond to RT or to be reached by drugs. While this is an unresolved issue, it has been reported that patients who undergo an excisional biopsy (thus staged as cTx before definitive local treatment if no residual macroscopic disease is present) have a good outcome after postoperative radiotherapy regardless of their margin status[10]. Moreover, we doubt that a positive microscopic margin at the primary tumor after a simple excisional biopsy carries the same predictive value as after a radical, oncologic procedure (such a `commando` procedure). Therefore, we advocate the use of concomitant CDDP only for those cases were ECE is present, and the use of radiotherapy alone for a microscopic mucosal margin after excisional biopsy. In the latter case, a `full dose` of RT at the surgical site (70 Gy) is currently delivered.

A new class of drugs targeting the Epidermal Growth Factor Receptor (EGFR) has been developed based on evidence that the receptor is over expressed in most head and neck SCC (although constitutive EGFR activation can occur in the absence of increased expression). Many studies have reported antitumor effects when EGFR targeting strategies were used in preclinical head and neck SCC models [26]. Several therapeutic approaches have been developed including monoclonal antibodies, tyrosine kinase–specific inhibitors, ligand-linked immunotoxins, and antisense approaches. Cetuximab is a monoclonal antibody that targets the extracellular domain of the EGFR. A phase III study has shown that cetuximab added to RT reduced the relative risk of death with locoregional failure and all-cause mortality by 32% and 26%, respectively [5]. Most (≈60%) of the patients enrolled in this trial had oropharyngeal cancer and in subset analyses, this patient group showed the most benefit. At present, there is no data on how cetuximab plus IMRT compares with IMRT and concomitant chemotherapy. Therefore, for tumors at high risk of locoregional failure (T3-4`s, N2, N3 disease and/or presence of extracapsular extension after surgery) chemoradiotherapy is still the treatment of reference. For patients without these unfavorable risk features treatment with IMRT alone is supported by the data previously shown (1.1, table 1).

1.4 Treatment morbidity

While contemporary results for ORO-SCC are improved compared to historical controls[7], treatment morbidity on selected organs/tissues may have increased as well, bringing into question the real advantage in terms of therapeutic index.

Attention has been focused on organs and structures involved in swallowing that are in close proximity to ORO-SCC[27]. Several papers have reported deterioration of swallowing function after RT±CHT (summarized by[28]). In one study, the incidence of severe aspiration was 11% (7/63 pts) before radiotherapy and 38% (24/63 pts) afterwards, with 6 pts dying from complications of aspiration[29]. In another report on 96 pts after radiotherapy, 31 (32%) had clinically significant aspiration and 36 (37%) developed a stricture[30]. Altogether the results show that a more aggressive approach may yield better oncologic outcome but at a greater expense in terms of both sub-acute and late toxicity. Currently up to 15% of patients are long-term PEG tube dependent after combined chemotherapy and IMRT for advanced oropharyngeal cancer[31]. In another study of sequential therapy (induction chemotherapy followed by chemoradiation), Goguen et al periodically assessed the swallowing status of 54 head and neck cancer patients[30].

At one year follow up, 80% were able to eat either a regular or a soft diet and 19% still had their gastrostomy feeding tube.

In addition to the salivary glands and those structures involved in swallowing function (including the larynx), several other structures can potentially be affected: mandible-osteonecrosis, brachial plexus-palsy, thyroid gland-hypothyroidism, masticator muscles and temporomandibular joints – trismus, oral mucosa-mucositis, ears-deafness, sternocleidomastoid muscles-fibrosis, carotid arteries-stroke.

Late toxicity after (chemo)radiotherapy for head and neck SCC is, in general, poorly documented, but unfortunately quite prevalent. A retrospective analysis of patients treated with concomitant radiotherapy (3D conformal) and chemotherapy for advanced head and neck cancer within 3 RTOG studies (RTOG 91-11, 97-03, and 99-14) showed that 43% of assessable patients had a severe late toxicity defined as chronic grade 3 to 4 pharyngeal/laryngeal toxicity and/or requirement for a feeding tube >or= 2 years after registration and/or potential treatment-related death (eg, pneumonia) within 3 years[32].

In one other recent prospective study, the actuarial prevalence of grade 3+ CTC AE v3.0 toxicity after altered fractionated IMRT for oropharyngeal SCC was 30.9% and 26.1% at 2 and 3 years, respectively [33].

At UTMB, 58 patients with ORO-SCC were treated with IMRT alone (conventional fractionation to 70 Gy, 24 pts; hypofractionation to 66 Gy, 9 pts; hyperfractionation to 78 Gy, 25 pts) from 09/02 to 09/06. At a median follow up of 22 months (range: 3-53.4 months), the actuarial prevalence of selected grade 3+ CTCAE 3.0 toxicity is 35.1% (Figure 1)(unpublished data).

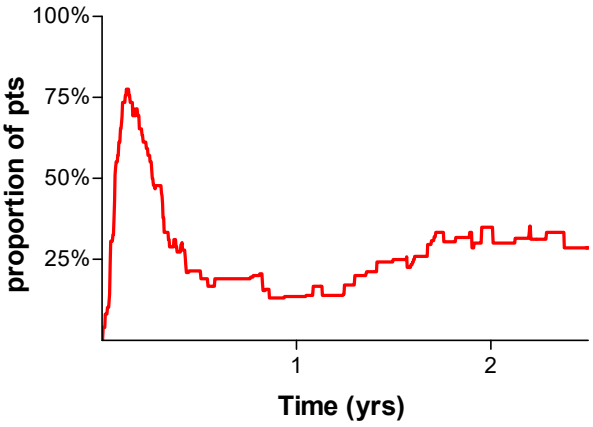


Figure 1.

The actuarial prevalence curve shows two `waves` of toxicity: the first one, corresponding to acute toxicity during and after treatment, which subsides by 6 months and a late wave due to late toxicity.

This increase in toxicity seems contradictory because it is well recognized that IMRT allows for sparing of selected structures (i.e. parotid glands) and thus fewer complications (i.e.

xerostomia)[34]. However, the dose to other organs at risk (OAR- such as the swallowing structures and the larynx) remains high due to their proximity or even `embedding` to the target. Another intrinsic limitation of IMRT is that about 25-30% of the prescribed dose is distributed across all structures surrounding the target. The resulting `dose bath` may be high enough to have clinical implications [35].

Therefore, besides the few organs at risk (cord, brain, brainstem, parotids, mandible, larynx) whose sparing is usually prioritized, this sparing is usually not possible for the remaining structures in the context of standard IMRT planning. This is due to both physical (unless the dose comes from inside the pt, as in the case of brachytherapy, it has to go through the patient) and clinical reasons (proximity of the tumor to the organ at risk).

The addition of chemotherapy to IMRT has been shown to increase acute mucosal damage compared to RT alone, and thus increases the risk of acute toxicity (intensity and duration of mucositis, pain, need and duration of PEG tube…). More importantly, acute toxicity can lead to subacute and late toxicity (so called `consequential late toxicity`)[36]. It has been reported that bone exposure and osteo- necrosis may result as consequence of overlying mucosal denudation [36]; more recently it has been postulated that pharyngeal constrictor muscle damage may result from a breakdown of the overlying mucosa, leading to edema, inflammation and ultimately fibrosis of the muscles [37].

1.5 Strategies to decrease toxicity

There are several steps that can potentially reduce or mitigate the risk of toxicity. Regarding IMRT, there are several levels of intervention as illustrated in table 2.

Table 2. Examples of radiation treatment de-intensification strategies

Strategy	Feature	Example
Dose reduction	To high dose volume	Lower Px dose (S1)
	To low dose volume	Lower Px dose (S3)
	To organs at risk	To PTV-OAR overlap (S2)
		SF-IMRT
		Surgical transfer of submandib gland
Volume reduction	Contoured CTV3	Avoid medial RP nodes
	CTV3	Avoid anterior part of ipsi lv IB
	CTV3	Avoid controlat lvs IB & V
	CTV3	Allow unilateral tmt only
	CTV2	Reduce volume
	CTV1	Limit to metabolically active

Irradiated	Reduce CTV to PTV exp – IGRT Brachytherapy boost

Dashed: strategies exploited in the current protocol

We have identified a solution that involves several individual strategies, as extensively discussed elsewhere[38]. Briefly, in the context of dose painting IMRT (where CTV1 covers the gross tumor volume, CTV3 the volume at low (<10%) risk of microscopic disease, and PTV1-3 represent an expansion of CTV1-3 to account for set-up errors and tissue deformation), we plan a reduction of the prescription dose from 70 Gy equivalent dose at 2 Gy per fraction (ED2) for PTV1 and from 50 Gy ED2 for PTV3 to 60 Gy ED2 and 44 Gy ED2, respectively. The rationale of the entity in dose reduction is reported in table 3. How these `experimental` doses compare to standard ones is reported in table 4.

Table 3. Radiobiologic considerations on dose de-escalation

	Subclinical disease	Gross disease
General assumptions and definitions	1. 10 fold reduction of cell population means 1 Log or elimination of 90% of cells; 2. D_{10} is defined as the dose necessary to depopulate by 1 Log; 3. $D_{10}=D_0$ x 2.3; 4. Typical value of D_0 is 1.5-2.5 Gy (3 Gy if only hypoxic cells were present); here we consider 2.5 Gy; 5. According to Poisson statistics, 90% of local control means that the average number of cells surviving is about 0.1 or 10^{-1}; 99% means 0.01 or 10^{-2}; 6. If a tumor is composed by 10^{10} cells to begin with, in order to achieve a LC of 90%, 10^{-11} cells need to be killed (from 10 to -1 Logs, thus 11)	
Specific assumptions	1. In `high` risk areas at containing microscopic disease, tumor population is 10^7 cells; 2. To achieve 90% of local control, 8 Logs of cells need to be killed;	1. Subtotal resection, leaving 1% or 0.01 of cells, depopulates by 2 Logs;
Estimates	**If each Log is depopulated with 5.75 Gy (2.5 Gy x 2.3), then:** **→ 8 Logs would need 46 Gy (5.75 Gy x 8);** **→ 9 Logs, 51.75 Gy**	**→ 12 Logs would require 69 Gy** **→ 11 Logs, 63.25 Gy** **→ 10 Logs, 57.5 Gy**
Comments	These estimates would be consistent with the standard dose of 50 Gy for regions treated electively or at `low ` risk;	Consistently, after tonsillectomy with 10^{8-9} Logs left, the Px dose is between 60 Gy and 66 Gy;
Role of concomitant chemotherapy	Concomitant chemotherapy equals to a biological equivalent dose (BED) of ≈10 Gy[39]; → in presence of chemotherapy, a BED_{10} ≈10 Gy lower than needed would be expected from RT;	

	a BED_{10} of 8-12 Gy corresponds to 8-10 Gy or 1-2 Logs;	
Estimates	**In presence of concomitant chemotherapy, the dose of RT for microscopic disease would drop to ≈40 Gy for areas at low risk and to ≈50 Gy for areas at high risk**	**The dose of radiation would drop to ≈60 Gy**
Comments on disease control	44 Gy at 2 Gy per fraction is allowed by NCCN guidelines to treat electively the neck in presence of chemotherapy [40]	Clinical data obtained combining `reduced dose RT` and concomitant chemotherapy seems to be consistent to these estimates [41].
Comments on toxicity	Structures that are expected to benefit from less than 70 Gy (due to their proximity to the target), include the mandible, the constrictor mm, the larynx, the brachial plexus; Structures that benefit from an intermediate dose level reduction include the parotids, the submandibular glands, great vessels in the neck, masticatory mm, thyroid gland, esophagus	

Table 4. Equivalency of schedules in terms of radiobiological parameters

	Treatment parameters				ACUTE TOXICITY TUMOR RESPONSE		LATE TOXICITY	
	D (Gy)	d (Gy)	# fxs	OTT (dd)	BED_{10}† (Gy)	$LDED2_{10}$† (Gy)	BED_3* (Gy)	$LDED2_3$* (Gy)
Micro low risk (CTV3)								
Standard 3FT	50	2	25	33	55.2	50	83.3	50
IMRT	58.1	1.66	35	47	57.4	≈52	90.2	≈54
Experimental	50.75	1.45	35	47	47.8	≈42 (-16%)^	75.3	≈45 (-10%)^
Micro high risk (CTV2)								
Standard 3FT	60	2	30	40	64.5	60	100	60
IMRT	63	1.8	35	47	64	≈60	100.8	≈60
Macro-GTV (CTV1)								
Standard 3FT IMRT	70	2	35	47	73.7	70	116.7	70
Experimental	63	1.8	35	47	64	≈60 (-14%)^	100.8	≈60 (-14%)^

Abbreviations: D, total dose of RT (Gy); d, dose per fraction (Gy); OTT: overall treatment time BED_3 = biologically effective dose considering α/β of 3 Gy; $LQED2_3$ = linear quadratic equivalent dose in 2 Gy fractions considering α/β of 3 Gy; Standard 3FT = conventional fractionation at 2 Gy per fraction using sequential phases and standard 3 field technique; BED_{10} = biologically effective dose considering α/β of 10 Gy; $LQED2_{10}$ = linear quadratic equivalent dose in 2 Gy fractions considering α/β of 10 Gy and time factor.

* no time factor applied; assuming complete repair of sublethal damage between fractions for late responding tissues; $\alpha/\beta = 3$ Gy for late effects.
† time correction applied; $\alpha/\beta = 10$ Gy for tumor; $\alpha = 0.35$ Gy^{-1}; Tk = 21 days; Tp = 5 days;
^ % reduction compared to standard 3FT RT

It should be noted that the reduction in the prescription dose does not apply to the whole volume but only selected parts as follow:

1. to part(s) of PTV1 and PTV3 that are close (within 8 mm) or overlapping with selected organs at risk, such as the constrictor muscles, the parotids…. (for a complete list please refer to section 5.4);
2. to part(s) of PTV3 that cover the ipsilateral (to primary tumor) level IV if ipsilateral level III is clinically and radiologically uninvolved [42] (for criteria of nodal involvement please refer to section 5.3.2);
3. to part(s) of PTV3 that cover the contralateral levels III and IV if contralateral level II is negative (as defined at 2 above);
4. to part(s) of PTV3 that cover the contralateral level IV if contralateral level III is negative regardless level II status.

Moreover, most (>85%) of each PTV is still adequately `covered` by a standard dose, while there is a significant dosimetric benefit on almost each OAR considered [38] as shown in table 5 in terms of absolute difference in mean dose compared to a reference plan.

Table 5. Dose at selected dose point for various OARs: the solution proposed here vs a reference plan (modified from[38])

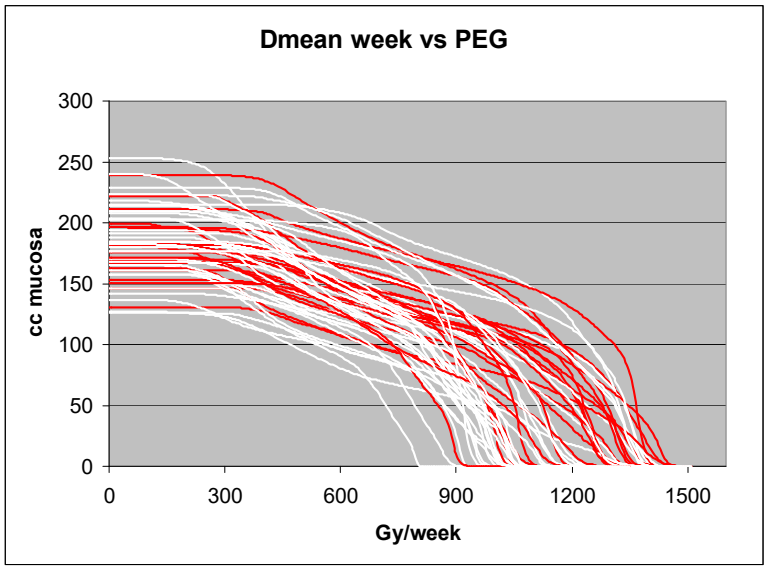
		Avr	SD	Avr abs gain	P sign
Dom parotid	Mean D (Gy)	48.4	6.3	2.3	↔
Contr parotid	Mean D (Gy)	35.6	3.5	1.2	↓
Mandible	Mean D (Gy)	49.4	3.2	2.3	↓
Larynx	Mean D (Gy)	45.5	7.5	1.4	↓
Esophagus	Mean D (Gy)	38.2	5.1	2.8	↓
Contr Inner Ear	Mean D (Gy)	35.7	8.7	1.1	↓
Dom Inner Ear	Mean D (Gy)	41.6	7.5	1.8	↓
Dom Brach Pl*	Mean D (Gy)	59.4	2.2	4.4	↓
Contr Brach Pl*	Mean D (Gy)	58.3	1.0	6.5	↓
Mucosa*	Mean D (Gy)	52.7	2.8	1.4	↓

Sup constrict m	Mean D (Gy)	67.3	2.1	3.7	↓
Mid constrict m	Mean D (Gy)	60.8	2.2	3.7	↓
Inf constrict m	Mean D (Gy)	51.5	5.9	2.9	↓
Cricophar m	Mean D (Gy)	51.0	6.7	3.6	↓
Thyroid gland*	Mean D (Gy)	60.4	1.1	5.5	↓
Dom masticat	Mean D (Gy)	55.3	3.7	2.7	↓
Contr masticat	Mean D (Gy)	41.6	2.7	2.3	↓
Contr TMJ*	Mean D (Gy)	26.5	10.9	1.1	↓
Dom TMJ*	Mean D (Gy)	38.2	5.9	3.2	↓
Dom Subm Gl *	Mean D (Gy)	68.9	1.7	4.6	↓
Contr Subm Gl*	Mean D (Gy)	59.3	2.1	1.9	↓

*: OAR`s not taken into consideration for overlap at planning
Dashed: OAR not contrained at planning
↔ no sign ($p<0.05$) difference compared to ref
↓ sign decrease compared to ref
Abbreviations: dom: dominant; contr: contralateral; Brach Pl: brachial plexus; sup: superior; mid: middle; inf: inferior; m: muscle; cricophar: cricopharyngeous; masticat: masticatory muscles; TMJ: temporomandibular joints; Subm Gl: submandibular glands

Finally, the overall duration of treatment will be kept to 7 weeks, in order to avoid an increase in acute mucosal toxicity and to reduce the risk of increasing subacute/consequential late toxicity. In addition we will enforce a novel set of dose volume objectives for the mucosa (unpublished data). According to the retrospective analysis of toxicity data obtained in 59 consecutive patients treated with IMRT alone for ORO-SCC at UTMB where a PEG tube was placed only if needed, there was a significant correlation between the absolute amount of oral mucosa that received a given *dose per week* and the need for PEG tube. In particular with cut-offs of V9.5<64.5 cc and (sensitivity: 95.5, specificity: 59.5) and V10 < 54 cc (sens: 82, spec: 62), only 1 patient needed a PEG tube (figure 2).

Figure 2. Absolute DVH for the oral mucosa of 59 patients. Red: pts necessitating PEG –tube during treatment; white: patients not needing a PEG tube during treatment. Only 1 patient with absolute volume of mucosa <50 cc receiving 9 Gy needed the PEG tube.



Acute toxicity may also translate into subacute and late toxicity as described for the mandible [36] and hypothesized for the constrictor muscles and the larynx [44,45].

1.6 Standard Supportive treatment

Regarding supportive treatment and prophylactic measures to prevent/mitigate toxicity, the following ones are generally pursued as standard of care:

- Dental evaluation and fluoride prescription/administration;
- Speech pathology evaluation including
- Baseline swallowing screening with flexible endoscopic evaluation of swallowing (FEES) followed by a formal modified barium swallowing study (MBSS) if needed. The Penetration/Aspiration Scale (Appendix 4) will be used during modified barium swallow studies.
    + baseline evaluation of jaw opening, premorbid speech disturbance and dysphonia.
    + baseline cognitive/language function screening using the Montreal Cognitive Assessment (Appendix 5).
    + implementation of prophylactic swallowing and trismus prevention exercises prior to initiation of treatment[46];
    + education regarding the role of oral hygiene and aspiration pneumonia, products to compensate for xerostomia (e.g., frequent sips of water, oral lubricants, saliva substitutes) and dentrifices.
    + documentation of the presence of a gastrostomy feeding tube, estimated percent of oral alimentation/hydration via the feeding tube; estimated percentage of PO intake at baseline.
- Nutritional evaluation with pre-treatment correction of weight loss (nutritional impairment is defined as weight loss > 20% in the preceding 3 months or food

intake below 50% of normal requirements in the week preceding enrollment) as needed. A PEG-tube will be placed routinely before or shortly after initiation of IMRT only in those patients who receive chemotherapy in addition to radiotherapy.

2 OBJECTIVES

2.1 To achieve a prevalence of grade 3+ late toxicity at 2 yrs <15% while maintaining a locoregional tumor control >85±7% at the same time interval (toxicity is scored at 5.11 and 9.5 and locoregional control at 9.4);

2.2 To determine the nature and prevalence of side effects at different time intervals and describe their relationship to pretreatment function and local dose and treated volume.

2.3 To determine the quality of life of surviving patients (5.11 and 9.5)

3 SELECTION CRITERIA

3.1 Eligibility Criteria

3.1.1 Biopsy-proven SCC of the oropharynx *(tonsil, base of tongue, pharyngeal wall or palate)*,
3.1.2 Tumor positive for infection with human papillomavirus (HPV) virus (any subtype) as per JH Pathology assessment (section 8.0);
3.1.3 Negative pregnancy test for women of childbearing potential
3.1.4 T stage: 1, 2, 3. Surgery of the primary tumor is limited to incisional or excisional biopsies (i.e. tonsillectomy) even without macroscopic disease left. Positive resection margins and/or gross residual disease at the *primary* site are allowed; evaluation of primary tumor extent may require the use of a flexible fibroscope if deemed clinically necessary by the treating physician; any N stage but resectable; lymph nodes in both sides of the neck are at risk of metastatic disease, according to clinical judgment, and require irradiation; pre-treatment surgery in the neck in the forms of incisional/excisional biopsy or a multilevel neck dissection is allowed only if there is gross tumor left at the primary site;
3.1.5 No other malignancy except for non-melanomatous skin cancer, early stage prostate cancer (T<2a and PSA<10 and GLS<7) or a carcinoma not of head and neck origin disease free for > 5 yrs.
3.1.6 - ANC > or = to 1000 /mm^3
- Platelets >100,000/ mm^3
- Adequate hepatic function with bilirubin < 1.5 mg/dl
- AST < 2x the upper limit of normal
- ALT < 2x the upper limit of normal
- estimated CCL ≥ 60 cc/min
- Normal serum calcium (or normal corrected serum calcium) (Please note*:

Formula for corrected calcium if albumin value is below normal range: Corrected calcium (*mg/dl*) = [4 – [patient albumin (g/dl)] x 0.8 + patient calcium (mg/dl)

3.1.7 Cannot have distant metastasis (M0);
3.1.8 ECOG performance status 0-1
3.1.9 Patient's nutritional and general physical condition must be considered compatible with the proposed radiotherapeutic treatment (cannot have unintentional and/or surgically unrelated weight loss > 20% in the preceding 3 months). *This assessment is a standard of care assessment for this patient population. This requirement can be waived by the investigator if the subject has an identifiable procedure which is the immediate and sole cause for the weight loss without an underlying pathological cause. An example of a situation like this would be if a participant is found to need a tonsillectomy during the pretreatment evaluations. It's obvious that this scenario would be a non-pathological reason for such a weight loss. The PI will only have this ability to waive this criterion if and only if he can substantiate and document that the weight loss does not have a pathological etiology and will correct itself within a reasonable and acceptable period of time
3.1.10 Patient is judged to be mentally reliable to follow instructions and to keep appointments. (Please note that mental reliability is not determined through any specific test rather it is ascertained by the treating physician through conversation at the time of consult)
3.1.11 No concurrent enrollment in another therapeutic protocol for the same diagnosis;
3.1.12 Signed study-specific informed consent prior to registration.
3.1.13 Subject must understand that while they are on study they cannot have any concurrent curative therapy for their cancer other than what is outlined in the protocol.

3.2 Ineligibility Criteria

3.2.1 Evidence of distant metastases.
3.2.2 Absence of macroscopic disease after upfront surgery, i.e. TxNx and TxN0. TxN+ and T1-3Nx are eligible if the T/N stage categories meet the criteria of 3.1.1
3.2.3 Previous irradiation for head and neck tumor; concurrent chemotherapy other than the treatment per protocol; previous chemotherapy ≤ 3 months from start of RT.
3.2.4 Active untreated infection.
3.2.5 Major medical or psychiatric illness, which in the investigators' opinion would interfere with either completion of therapy and follow-up or with full and complete understanding of the risks and potential complications of the therapy.
3.2.6 Use of amifostine or pilocarpine before and during radiotherapy is not allowed.
3.2.7 Serum creatinine >1.3 or ULN, CCL < 60 cc/min, Peripheral neuropathy > grade 1, and/or frequency hearing loss that interferes with activities of daily living are contraindications to cisplatin but not to carboplatin (6.2.4).
3.2.8 Patients with > 10 pack years of smoking history and/or currently a smoker at the time of treatment.

4 PRETREATMENT EVALUATIONS

4.1 Each patient must have completed the following studies prior to irradiation:
4.1.1 Complete history and physical exam including weight and performance status.

4.1.2 Complete dental evaluation. Any required dental extractions must be made and fluoride prophylaxis instituted prior to radiotherapy.
4.1.3 Speech pathology evaluation including instrumental swallowing assessment or clinical assessment of swallowing and administration of pretreatment swallowing and trismus exercises (*This assessment is a standard of care assessment for this patient population). Completion of pretreatment MD Anderson Dysphagia Inventory (MDADI) and Montreal Cognitive Assessment (MCA). Speech therapy evaluation has to take place before commencement of treatment.
4.1.4 Nutritional evaluation to be conducted within the first week of starting (chemo)radiation therapy.
4.1.5 Completion of the following laboratory studies: CBC with diff. and platelets, Metabolic Panel to include- sodium, potassium, glucose, calcium, magnesium, BUN, serum creatinine, total protein, albumin, alkaline phosphatase, total bilirubin, AST, ALT, and a creatinine clearance)
4.1.6 Completion of the following radiologic studies: CT of head and neck with < 3 mm contiguous slices in immobilization system *(with contrast, unless contraindicated*); whole body PET/CT (integration of both high resolution CT with contrast and dedicated PET acquisition through the head and neck are strongly suggested); MRI of head and neck with gadolinium including T1 and T2 weighted sequences in at least 2 different planes strongly suggested for primary tumors of the base of tongue *(optional-see 5.1.2)*.
4.1.7 Audiogram to be conducted before or within the first week of starting therapy *(if inner ear is to be irradiated at mean dose ≥ 40 Gy).*

5 RADIATION THERAPY

5.1 Treatment Planning, Imaging and Localization Requirements

5.1.1 The immobilization device is a thermoplastic mask that covers both face and shoulders. A mouth piece is also indicated for all patients but those edentulous.
5.1.2 Treatment planning CT scans will be performed with the patient in the treatment position. I.V. contrast at the time of simulation is also recommended. A planning MRI scan is optional.
5.1.3 All tissues to be irradiated must be included in the CT scan. CT scan thickness should be 0.3 cm or less through the region that contains the primary target volumes. The regions above and below the target volume may be scanned with slice thickness up to 0.5 cm. MRI and PET/CT scans may be included to assist in definition of target volumes.
5.1.4 The GTV, CTV and PTV and normal tissues will be outlined on all CT slices in which the structures exist.
5.1.5 Image Guidance for IGRT: Daily image guidance of IMRT will be achieved using Linear-accelerator mounted MV cone beam CT images.
The procedure to register treatment day imaging dataset with the reference dataset will comply with the following recommendations:

- Region-of-Interest (ROI) or “clip box” for fusion is set to encompass the high dose PTV and adjacent spinal cord; if the supraclavicular region is a part of the target volume the ROI should extend to the C6 level;

- Automatic (based on bony anatomy) registration will be used; the result of the fusion will be visually checked for the alignment of the bony anatomy, such as vertebral bodies and applicable soft tissue structures (e.g., optic nerves and/or optic chiasm).

Following the registration, the translational corrections will be applied to the treatment couch. If all the variances are less than 2.0 mm, the treatment will proceed without correction (however, the physician/team may elect to perform adjustments even for a variance < 2.0 mm). If one or more corrections are 2.0-5 mm, adjustment is necessary prior to treatment; however, re-imaging is not mandatory. If one or more of the corrections are larger than 5 mm, the imaging must be repeated in addition to performing table/positioning adjustments.

5.1.6 Management of Radiation Dose to the Patient from IGRT

The estimates of patient doses per imaging study for various imaging systems vary considerably. The doses from helical MV CT scan on a tomotherapy unit were estimated to be in range from 1 to 3 cGy for head and neck studies, similar to doses reported for kV cone beam CT on Elekta Synergy machine. Thus, the doses for 3D imaging systems are in the range from 1 to 3 cGy for head and neck imaging and can contribute from 0.5 to 1.5% to the daily dose of 2.0 Gy. These are small enough dose contributions that if there is only one or two imaging study done per treatment session, the dose does not need to be incorporated into treatment planning and is not expected to have any clinical relevance to the patient.

5.2 Volume and ICRU Reference Point Definitions

The definition of volumes will be in accordance with the 1993 ICRU Report #50: Prescribing, Recording and Reporting Photon Beam Therapy.

5.2.1 *The Gross Tumor Volume (GTV)* is defined as all known gross disease determined from CT, clinical information, endoscopic findings and MRI in the case of tumors treated after biopsy alone.

5.2.2 *The Clinical Target Volumes (CTV)* is defined as the GTV plus areas considered to contain potential microscopic disease, delineated by the treating physician. The margin between the each GTV and its CTV will be typically 1-2 cm, with a minimum of 5 mm except in those areas where the GTV is immediately adjacent to structures known to be uninvolved. In postoperative cases, The CTV includes the operative bed and margins according to an assessment of the risk of subclinical disease.

The Planning Target Volume (PTV) will provide a margin around each CTV *(i.e. both the primary tumor and the lymph nodes containing clinical or radiographic evidence of metastases)* to compensate for the uncertainties of treatment set up and tissue deformation. A minimum of 5 mm around the CTV will be required in all directions to define each respective PTV in the setting of IGRT.

5.3 Target Definition

5.3.1 *Targets* are defined as follows: CTV1 or high dose volume that encompasses the GTV with a margin; in case there is no GTV available (i.e. after tonsillectomy) CTV1 encompasses the tumor bed or where the tumor was before surgery; CTV2, that typically includes the tissue around the gross tumor volume and/or the neck nodal stations that have high (>15%) risk of cancer involvement and/or lymph nodes that look suspicious on imaging; CTV3 includes contralateral lymph nodal stations and lower neck lymph nodal stations which have relatively lower risk (5-15%) of cancer involvement and do not look suspicious at imaging.

5.3.2 Positive lymph nodes are defined as those that meet any of the following criteria on CT: maximum axial diameter > 1cm (>5 mm if retropharyngeal); focal hypoattenuation within the node suggesting necrosis; irregular enhancement pattern; presence of extracapsular penetration as judged by 21peculated margins. Suspicious are those that measure between 7-9 mm in greatest axial dimension in neck levels III through IV; have a rounded appearance defined as a width to length ratio greater than 0.5; lack fatty hilum.

5.3.3 Lymph node stations or levels in the neck follow the surgical nomenclature. A station is considered positive if contains positive lymph nodes. However, in this case, only the positive lymph node(s) and not the whole station is (are) contoured as GTV. Moreover, expansion from GTV to CTV1 does not imply that the whole level will be part of CTV1.

5.3.4 The following (entire) lymph nodal stations are considered at high (>15%) risk of containing microscopic disease when negative/normal on clinical exam and imaging: levels II and III ipsilateral to the site of a positive lymph node in the neck. The entire level is drawn as CTV2 [42].

5.3.5 For lymph node stations different from ipsilateral levels II and III (5.3.5) only the suspicious finding and not the whole level has to be contoured as CTV2;

5.3.6 The following levels are routinely included in CTV3: level IB ipsilateral to neck disease; bilateral levels II, III, IV and V. Controlateral level IB is routinely excluded from any target volume. In the rare case that level IB has a positive or suspicious node, level IB becomes part of the appropriate target volume even in absence of positive level II nodes.

5.3.7 The anterior extent of the contour of level IB when included in CTV3 will stop at the anterior extent of the submandibular gland and therefore exclude the triangular fat space lateral to the deep extrinsic muscles of the tongue as shown elsewhere [42].

5.3.8 Retropharyngeal nodes on both sides are routinely included in CTV3 from C1 to the bottom of C2

5.4 Organ At Risk (OAR) Definitions

Several organs at risk will be contoured on each patient planning CT as follows. In order to facilitate the spelling, a script will be run from Pinnacle to generate the regions of interest. OAR`s are: mandible, brain, brainstem, cord, submandibular glands, thyroid gland, parotid glands, upper gastrointestinal mucosa [47], larynx [45], masticatory spaces, upper, middle and inferior constrictor muscles, cricopharyngeous muscle, esophagus, brachial plexuses, temporomandibular joints (TMJ), inner ears, internal, external and common carotid arteries. Paired organs will be divided into those on the dominant side of disease (dominant) and those on the opposite side (contralateral). An atlas on how to contour each structure is available at the web site of the University of Texas Medical Branch, http://www.utmb.edu/radoncology/oar.htm
For planning purposes, the cord is expanded by 4 mm.

5.5 PTV and subPTV generation

Each CTV is expanded 5 mm isotropically to generate corresponding PTV`s, PTV1, 2 and 3. Each PTV is further adjusted to come off the skin, by excluding the part that is within 3 mm to skin surface (PTV= CTV + 5mm – (skin -3mm)).
In order to achieve dose de-escalation on parts of the PTV (subPTV), each PTV is further divided into subPTV`s whose prescription dose is as follows in table 6.

Table 6

Main PTV	SubPTV	Note	Px D (Gy)	Nomenclature
PTV1	overPTV1	Part of PTV1 that overlaps with larynx for edema+8 mm, superior constrictor m+8 mm, mandible + 8 mm, parotids, masticatory mm, esophagus, mid/low constrictor mm	63	PTV63
	truePTV1	Rest of PTV1	70	PTV70
PTV2	None		63	PTV63
PTV3	overPTV3	Part of PTV3 that overlaps with larynx for edema+8 mm, sup/mid/low constrictor mm+8 mm, parotids+8 mm, masticatory mm+8 mm, esophagus+8 mm	50.75	PTV50.75
	lowPTV3	Part of PTV3 that covers ipsilateral (to neck disease if present) level IV (and level III is negative) and/or contralateral (to neck disease or both heminecks if no neck disease is present) levels III and IV; if disease is present on both sides, each side is treated as ipsilateral one	50.75	PTV50.75
	truePTV3	Rest of PTV3 (or without lowPTV3 and overPTV3)	58.1	PTV58.1

5.6 Dose prescription

The common practice of this institution for H&N cancer is to prescribe three dose levels, 70 Gy, 63 Gy and 58.1 Gy to primary tumor and whole neck (PTV1-3) in 35 fractions. The Px to each PTV is reported in table 6. Now we have 4 dose levels, 70, 63, 58.1 and 50.75 Gy. In cases after primary tumor surgery where there is no residual macroscopic disease left, the total dose to PTV1 can be reduced from 70 Gy to 68.25 Gy. In this case PTV68.25 is treated as PTV70 regarding overlap with the various OAR`s.

5.7 Planning

5.6.1 A co-planar 9 beam whole field IMRT plan will be generated. The treatment plan used for each patient will be based on an analysis of the volumetric dose, including DVH analyses of the PTV and critical normal structures. An "inverse" planning using computerized optimization is used. The treatment aim will be the delivery of radiation to the PTVs and the exclusion of noninvolved tissue as feasible.

5.6.2 Dose Specification

5.6.2.1 The prescription dose is the isodose which encompasses at least 95% of the planning target volume *(PTV)*. No more than 10% of any planning target volume *(PTV*) will receive >110% of its prescribed dose (V10%≤110%). No more than 1% of any planning target volume *(PTV*) will receive <95% of its prescribed dose (V95%>99%). No more than 1% or 1 cc of the tissue outside the PTVs and any OAR (`unspecified tissue) will receive >110% of the dose prescribed to PTV1.

5.6.2.1 The prescription dose to the PTV`s and subPTV`s is reported in table 5. Breaks in treatment should be minimized. Break in treatment time of more than 5 days will be considered a major variation.

5.6.2.2 The reported doses for each PTV shall include the prescription dose as well as the maximum point dose, % target volume receiving > 110% and >115% of its prescribed dose and the % target volume receiving < 95% of the prescribed dose, and the mean dose to the PTV.

5.6.2.3 The dose prescription is to be based on a dose distribution corrected for heterogeneities

5.6.3 Critical Normal Structures

DVHs must be generated for all critical normal structures and the unspecified tissues. Dose constraints to normal tissues (and PTV`s) should be as per table 7.

Table 7.

Group	Region of interest		
1	Cord+4 mm	0.1 cc	Max dose 45 Gy
	Brainstem	0.1 cc	Max dose 54 Gy
	Brain	1 cc	Max dose 60 Gy
	Larynx for edema+8 mm-over2	Portion overlapping with PTV2	Max dose 63 Gy
	Larynx for edema+8 mm	Portion not overlapping with PTV2	Max dose 50.75 Gy
	Mandible+8 mm		Max dose 63 Gy
	Sup constrictor m+8 mm-over2	Portion overlapping with PTV2	Max dose 63 Gy
	Sup constrictor m+8 mm	Portion not overlapping with PTV2	Max dose 50.75 Gy
	Mid constrictor m – over2	Portion overlapping with PTV2	Max dose 63 Gy
	Mid constrict m+8 mm	Portion not overlapping with PTV2	Max dose 50.75 Gy
	Low constrictor m – over2	Portion overlapping with PTV2	Max dose 63 Gy
	Low constrict m+8 mm	Portion not overlapping with PTV2	Max dose 50.75 Gy
	Parotids – over2	Portion overlapping with PTV2	Max dose 63 Gy
	Parotids+8 mm – over3	Portion overlapping with PTV3	Max dose 50.75 Gy
	Masticatory mm – over2	Portion overlapping with PTV2	Max dose 63 Gy
	Masticatory mm+8 mm	Portion not overlapping with PTV2	Max dose 50.75 Gy
	Esophagus – over2	Portion overlapping with PTV2	Max dose 63 Gy
	Esophagus+8 mm – over3	Portion overlapping with PTV3	Max dose 50.75 Gy
	Mucosa -1		V66.5 Gy<64.5 cc
	Unspec. Tissue	1 cc	Max dose 77 Gy
2	overPTV1	Portion overlapping with OAR`s (table 5)	V60 Gy >99%
	truePTV1	PTV1-overPTV1	V66.5 Gy >99%
	PTV2		V60 Gy >99%
	overPTV3	Portion overlapping with OAR`s (table 5)	V48.2 >99%
	lowPTV3	Low/mid neck PTV3 (table 5)	V48.2 >99%
	truePTV3	PTV3-lowPTV3-overPTV3	V55.2 >99%
3	Mucosa -2	Portion not overlapping with any PTV	Max dose 30 Gy
	Parotids	At least one	V30<50% (whole DVH)

Brachial plexus		Max dose 60 Gy
Inner ears		Mean D <40 Gy
Esophagus-out	Portion outside PTV3+8 mm	Dmax 45 Gy

5.6.4 Planning Priorities

The priorities in addressing the protocol aims and constraints will be in the following order:

1) Group 1 (table 6),
2) Group 2 (table 6),
3) Group 3 (table 6).

5.8 External Beam Equipment and Beam Delivery Methods

Megavoltage equipment capable of delivering static or dynamic intensity modulation with a multileaf collimator is used. Whole field IMRT (without an anterior AP field) is used.

5.9 Treatment Verification and daily imaging

- Pre-treatment radiation therapy planning CT scan;
- Daily imaging with cone beam CT (5.1.5.1)

5.10 Quality Assurance of Target Volumes and Critical Structure Volumes

The DVH`s of each target and Oar will be exported and converted to excel file format.

5.10.1 Each treatment shall be scored with regard to the coverage of each PTV *(i.e. PTV70, PTV63, PTV58.1, and PTV50.75)* and with regard to the level of sparing of several OAR`s; the scores to be assigned are defined in table 8 below.

Table 8.

	Per protocol	Minor variation	Major variation
Overall treatment time	47 days	48-51 days	>51 days
PTV coverage	V95%>99%	95%<V95%<99%	V95%<95%
Cord + 4 mm	Max Dose 45Gy	Max Dose 47.5Gy	Max Dose 49.5Gy
Brainstem	Max Dose 54Gy	Max Dose 56.7Gy	Max Dose ≤ 59.4Gy
Brain	Max Dose 60Gy	Max Dose 63Gy	Max Dose 66Gy
Larynx for edema	V50 < 30%	30% < V50 < 31.5%	31.5% < V50 < 33%
Mandible	Max Dose 70Gy	Max Dose 73.5Gy	Max Dose 75Gy
Superior constrictor	V40 < 95%	95% < V40 < 100%	
Superior constrictor	V50 < 90%	90% < V50 < 94.5%	94.5% V50 < 99%
Superior constrictor	V60 < 80%	80% < V60 < 84%	84% < V60 < 88%
Superior constrictor	V65 < 70%	70% < V65 < 73.5%	73.5% < V65 < 77%
Parotids	V30 < 50%	50% < V30 < 52.5%	52.5% < V30 < 55%
Esophagus	Max Dose 45Gy	Max Dose 47.3Gy	Max Dose 49.5Gy
Brachial plexus	Max Dose 60Gy	Max Dose 63Gy	Max Dose 66Gy
Inner Ears	Mean Dose 40Gy	Mean Dose 42.5Gy	Mean Dose 45Gy

5.11 Radiation Therapy Toxicity Adjustments

5.11.1 Treatment Interruptions

Interruptions in radiotherapy are strongly discouraged based on the well known correlation between overall treatment time and outcome especially in the context of IMRT alone.

5.12 Toxicity Reporting Guidelines

5.12.1 For both acute and late effect, the NCI CTCAE Version 4.0 will be used (Appendix 1). All events will be recorded and loaded into software that is routinely used for clinical purposes in our Department called Mosaiq (v1.6 IMPAC, Sunnyvale, California).

5.12.2 The Head and Neck Cancer specific module of the MD Anderson Symptom Index (MDASI-HN)(Appendix 2) and the Xerostomia questionnaire (Appendix 3) will be used as patient-reported outcome instruments[48,49]

5.12.3 The swallowing related instruments (see 1.6) are: Penetration/Aspiration scale (Appendix 4); Montreal Cognitive Assessment (Appendix 5); MD Anderson Dysphagia Inventory (MDADI)(Appendix 6).

5.12.4 All life-threatening (*grade 4*) toxicities from protocol treatment will be reported to the PI within 24 hours of discovery. **Institutional guidelines will be followed in reporting serious adverse events to the IRB.**

6 DRUG THERAPY

Chemotherapy will be reserved for patients with T3 lesions (3.1.1) and/or clinically staged nodal disease greater than N1 and/or evidence of microscopic extracapsular extension after neck surgery (T3 and/or N2a $\geq$ 5cm, N2b, N2c, N3 stage cancer or Nx with ECE). Chemotherapy consists of single agent cisplatin or carboplatin.

6.1 Cisplatin

6.1.1 The first dose of cisplatin, 40mg/m^2 IV, will be administered within the first 3 days of the start of RT and repeated weekly for the first 3 weeks and last 3 weeks of RT. Patients will not receive chemotherapy during week 4 of treatment. The last dose of chemotherapy may be given up to one week following completion of RT. If RT is held, cisplatin will also be held.

6.1.2 Hydration: Patients should be adequately hydrated with 1-2 liters of fluid PO in the 24 hours prior to and post cisplatin administration.

6.1.3 Immediately prior to the cisplatin administration, patients should receive 1 Liter of Normal Saline over 1-2 hours.

6.1.4 Cisplatin 40 mg/m^2 should be mixed in 1 liter normal saline and infused over 2-3 hours. Cisplatin is a commercially available agent.

6.1.5 Antiemetics*:* Antiemetics must be given in conjunction with cisplatin. Antiemetic selection will be at the discretion of the treating physician and is recommended with each chemotherapy infusion. These include dolasetron, ondansetron, dexamethasone, lorazepam, or procholperazine. Therapy for prevention of delayed emesis may be considered.

6.2 Cisplatin Dose Modification for toxicity

6.2.1 Hematologic*:* Patients must have an ANC ≥ 1000 /mm^3 and platelets >100,000/ mm^3 prior to receiving cisplatin. If the patient's counts are below these levels, cisplatin will not be given and weekly dosing reinstituted the following week as long as counts are within acceptable treatment parameters. Held doses will not be made up. Grade 4 neutropenia (ANC <500/mm^3) or febrile neutropenia requiring hospitalization for antibiotics or grade 4 thrombocytopenia (platelets <25,000/ mm^3) require a dose reduction of cisplatin of 25%.

6.2.2 Neurotoxicity*:* Patients developing grade 2 sensory or motor neuropathy or > grade 2 hearing loss will have cisplatin discontinued and carboplatin substituted (see 6.3.4).

6.2.3 Nephrotoxicity*:* Measurement of serum creatinine is required before each treatment with cisplatin and must be within normal limits. Serum creatinine above the upper limit of normal necessitates creatinine clearance assessment using the modified Cockgroft-Gault formula. If the patient's calculated creatinine clearance is less than 60 ml/min, cisplatin will be held and additional hydration will be given. Serum creatinine and creatinine clearance should be repeated weekly and/or as needed after additional hydration is given. Cisplatin may be reinstituted, under the discretion of the treating physician, if the CCl improves to greater than or equal to 60 ml/min. If the creatinine clearance does not improve despite additional hydration, cisplatin will be substituted with carboplatin (see section 6.3.4). Held doses will not be made up.

6.2.4 Switch to Carboplatin: In case of any of the followings, cisplatin will be substituted to carboplatin: creatinine clearance < 60 ml/min; ototoxicity; peripheral sensory or motor neuropathy grade 2. Weekly carboplatin dosing would be at AUC=2. Dose modifications of cisplatin and carboplatin will be under the discretion of the treating medical oncologist. If the patient has peripheral neuropathy > grade 1, and/or frequency hearing loss that interferes with activities of daily living, cisplatin can be dose reduced or substituted with carboplatin.

6.3 Carboplatin

6.3.1 Carboplatin may be administered as a substitution for cisplatin when cisplatin-related toxicities occur as described in 6.3 Cisplatin Dose Modification for Toxicity or when patients present with >grade 2 sensory or motor neuropathy, >grade 2 hearing loss, or <60 ml/min calculated creatinine clearance at baseline.

6.3.2 The first dose of carboplatin, AUC=2 IV, will be administered within the first 3 days of the start of RT and repeated weekly during the 7 weeks of RT. The last dose of chemotherapy may be given up to one week following completion of RT. If RT is held, carboplatin will also be held.

6.4 Carboplatin Dose Modification for Toxicity

***6.4.1 Hematologic**:* Patients must have an ANC ≥ 1000 /mm^3 and platelets >100,000/ mm^3 prior to receiving carboplatin. If the patient's counts are below these levels, carboplatin will not be given and weekly dosing reinstituted the following week as long as counts are within acceptable treatment parameters. Held doses will not be made up. Grade 4 neutropenia (ANC <500/mm^3) or febrile neutropenia requiring hospitalization for antibiotics or grade 4 thrombocytopenia (platelets <25,000/ mm^3) require a dose reduction of carboplatin of 25%.

***6.4.2 Nephrotoxicity**:* Serum creatinine and creatinine clearance should be checked weekly before each treatment with carboplatin and/or as needed to calculate appropriate carboplatin dose and assess hydration status.

7 SURGERY

7.1 Upfront neck surgery *(excisional biopsy or neck dissection)* is at the discretion of the surgeon.

7.2 Surgery at the primary tumor is expected to consist of an incisional biopsy for diagnostic purposes only. An excisional surgery (i.e. tonsillectomy) is allowed if other gross disease is present e.g. neck lymph nodes. Patient will be also staged according to the clinical stage before any surgical procedure.

7.3 Surgery should be performed for persistent tumor following RT as documented by PET/CT (CT with thin slices and i.v. contrast for the HN part) at 8-12 weeks after the end of the treatment, or at the discretion of the surgeon. Suspected residual disease is defined as persistent FDG uptake at the site of the primary tumor qualitatively assessed by comparing to background and corresponding abnormal tissue on CT. Surgery is recommended for PET/CT positive residual disease, as described. A selective neck dissection is appropriate for patients with positive residual disease in levels II-IV and levels IB and V were initially negative. A comprehensive neck dissection is recommended in the other cases.

8 PATHOLOGY

Tumors will be evaluated for the presence of HPV16 DNA by use of the in situ hybridization – catalyzed signal amplification method for biotinylated probes (GenPoint; Dako, Carpinteria, CA)[50]. The expression status of p16 is strongly correlated with tumor HPV status and therefore it will be evaluated by immunohistochemistry, as previously described[51]. For tumors positive at P16 but negative for HPV16, a wide spectrum in-situ hybridization test will be run to exclude infection by less frequent subtypes of HPV (30, 31…). In the latter case, specimens will still be considered HPV positive and therefore eligible for the study.

9 PATIENT ASSESSMENTS

9.1 Patient Assessments

Table 9.

	Pretreatment	During treatment[1]	Follow up[2]
Weight & PS	X	X	X
History & Physical	X		
Dental Evaluation	X		
Nutritional evaluation	X[3]	X[3]	
CBC with diff. and platelet count	X	X[15]	
CMP[18]	X	X[15]	
Creatinine Clearance	X	X[17]	
Pregnancy Test	X[16]		
Thyroid Function Test (*TSH)*	X		X
PET/CT (CT w contrast)	X		X[5]
MRI of head and neck	X[6]		X[5]
Toxicity Evaluation[7]	X	X	X
Flexible fibroscope[10]	X		X
Audiogram[14]	X	X	X
Speech therapy evaluation[12]	X	X[8]	X[9]
MBSS			X[11]
Biopsy	X[13]		X[13]
Appendix 2 & 3	X	X	X

1. Weekly during radiotherapy
2. Follow-up will be performed 6-8 weeks after the end of RT (+ or – 7 days), at 3 months (+ or - 14 days) after the end of radiotherapy and every 3 months thereafter for the first two years; then every 6 months (+ or – 30 days) during years 3 to 5
3. Initial evaluation must be done within a week of starting therapy and then as clinically indicated. On treatment nutrition evaluations will be performed as clinically indicated.
4. Every 6 months for 5 years
5. PET/CT is required at 10-12 weeks after the end of treatment to evaluate response. Afterwards a PET/CT should be obtained at the discretion of treating physician. Alternatively a CT or MRI can be obtained if a PET/CT is not approved.
6. A pre-study MRI is at the discretion of the treating physician
7. See 5.12
8. At approximately the 4th week of treatment
9. To be performed 6-8 weeks, 6 months, and 12 months after the end of RT
10. Primary tumor assessment may require the use of a flexible fibroscope as deemed by the treating physician.
11. To be performed at 6-8 weeks and 12 months even in absence of specific symptoms
12. The MD Anderson Dysphagia Inventory (MDADI) will be given at each visit; the Montreal Cognitive Assessment (MCA) will only be given at baseline and 6-8 weeks after completion
13. Pretreatment Biopsy can be done outside JH provided that pathology blocks are submitted at JH for review and HPV testing; During follow up, any suspicious mucosal lesion in the upper aerodigestive tract should trigger a search for recurrent disease that may or may not include a biopsy; in the latter case, the biopsy can be done at JH or outside, but, again, the pathology specimen must be reviewed at JH. No further HPV testing is necessary on the repeat biopsy.
14. Pre-study audiogram is required if the inner ear is to be irradiated at a dose $\geq$ 40 GY (the audiogram should be done before or within 1 week after starting treatment); subsequent audiograms are under the discretion of the treating physician as indicated by symptoms.

15. Only if concomitant chemotherapy is part of the treatment
16. Only for women of child bearing potential
17. Creatinine clearance (CCL) required weekly for patient receiving chemotherapy.
18. CMP to include: sodium, potassium, glucose, calcium, magnesium, BUN, serum creatinine, total protein, albumin, alkaline phosphatase, total bilirubin, AST and ALT

9.2 Evaluations

9.2.1 Every Follow-up Visit

- All patients will enter a common follow-up program following completion of radiotherapy. Routine follow-up care: complete head and neck examination, including mirror and/or endoscopic examination (flexible fibroscope if deemed clinically necessary by the treating physician),
- Performance Status, Weight, and Toxicity Notation
- Follow up speech-language pathology evaluation will include clinical swallow assessment and inter incisors distance measurement. Prophylactic exercises will be reviewed as well as the importance of oral hygiene and strategies to ameliorate xerostomia. Patients' ability to follow through with recommended exercises and strategies will be recorded. Documentation of the presence of a gastrostomy feeding tube, estimated percent of oral alimentation/hydration via the feeding tube; estimated percentage of PO intake at baseline. In addition, at the first post-treatment follow up examination (6-8 wks), a MBSS will be obtained, even in absence of specific symptoms as well as a Montreal Cognitive Assessment (MCA).

9.2.2 Studies

- Biopsy: Any suspicious mucosal lesion in the upper aerodigestive tract; pharyngeal pain referred to the ear should trigger a search for recurrent disease; any firm node that persists longer than four weeks; epistaxis; chronic nasal congestion though not to be due to radiation mucosal changes.
- PET/CT as per 9.1
- Modified barium swallow test will be obtained 6-8 weeks after completion of treatment. Subsequently, a MBSS will be obtained only if clinically indicated.
- Audiogram: Pre-RT if the inner ear receives a mean dose ≥40 Gy, or if any hearing loss, vertigo or tinnitus occur. Subsequent audiograms will be conducted at the discretion of treating physician as indicated by patient reported symptoms

9.3 Response Criteria

9.3.1 Tumor Response Measurements (RECIST Criteria)

The use of the flexible fibroscope may be used for tumor measurement. This will be determined by the treating physician.

All tumor measurements must be recorded in centimeters and should consist of the longest perpendicular diameters. In no case will complete response be reported unless all clinically demonstrable disease has disappeared.

9.3.1.1 Complete Response (CR)
No measurable tumor is present on clinical and radiological examination.

9.3.1.2 Partial Response (PR)
A greater than 50% decrease in the product of the longest diameter multiplied by its perpendicular diameter when compared to the initial 'on-study product, providing there is no increase greater than 25% of any area of known disease or the appearance of any new lesions.

9.3.1.3 Minor Response (MR)
The difference between products is less than 50 percent of the initial product. No new lesions have appeared.

9.3.1.4 Stable Disease (SD)
Tumor size has not changed; no progression, no new lesions.

9.3.1.5 Progression (PD)
The second product shows a greater than 25 percent increase over the initial product, or appearance of new lesions.

9.4 Definition of locoregional control

9.4.1 A patient is defined as locoregionally controlled if he achieves a CR at both the primary site and the neck within 10-12 weeks from treatment end as previously defined (7.2, 9.3.1.1).

9.4.2 Patients who shows a CR at the primary site and a <CR (residual disease) in the neck at re-evaluation imaging 8-10 weeks, are evaluated for neck surgery (7.2). Patients who are cleared for residual disease in the neck by surgery are still considered having achieved a CR after treatment provided there is no residual disease left after surgery

9.4.3 Patients who fail to achieve a CR with or without neck surgery are scored as failures at day 1 of radiotherapy.

9.4.4 In order to remain controlled, patients who achieve a CR with or without neck surgery must remain cancer free at both T and N during each subsequent follow up examination (9.2.1).Treatment failure is defined as the documented (biopsy-proven) reappearance of disease at the primary site and/or the neck.

9.4.5 Distant disease is defined as the clinical or radiological appearance of metastases below the clavicles.

9.5 Scoring of toxicity (see also 5.11)

9.5.1 `Severe` toxicity is considered the one grade 3 or more in the CTCAE 4.0 (Appendix 1). Therefore, event is considered the presence of grade 3+ toxicity.

9.5.2 Similarly, in a 0-10 scale, 7 or more is considered `severe` (Appendix 2 and 3) [48].

9.6 Criteria for Removal from Treatment

9.6.1 Progression of disease while on treatment.

9.6.2 Sustained severe radiation mucositis resulting in dehydration and poor nutrition unresponsive to tube feeding and break from radiation for up to 2 weeks. Every effort should be made to sustain the patient so as to avoid such complications. Should the patient be removed from study, surgical removal followed by radiation post-operatively may be attempted.

9.6.3 Patients' wishes to stop participation on the trial.

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size

The accrual rate for this study is expected to be approximately 10 patients per year, over a 6-year accrual period. This would yield an expected sample size of 60 patients. The primary objective of this study is to estimate the prevalence of toxicity and efficacy two years following treatment administration. We expect approximately 15% of patients to die before reaching two years post-treatment, so our sample size for evaluation of our primary objective has been adjusted to 50 patients. The goal of this study is to demonstrate a maximum grade 3+ toxicity rate of 15% between six months and two years after treatment administration and a minimum locoregional tumor control rate (efficacy) of 85%. The table below shows the precision we have to estimate these endpoints with a sample size of 50 patients.

Endpoint	Prevalence	Exact 95% Confidence Interval	Precision (Half the width of the confidence interval)
Toxicity	2% 6% 10% 14%	0.05 – 11% 1 – 17% 3 – 22% 6 – 27%	5.5% 8% 9.5% 10.5%
Efficacy	84% 90% 94%	71 – 93% 78 – 97% 83 – 99%	11% 9.5% 8%

The locoregional tumor control rate in this patient population is expected to be at least 85%. We will ensure that this treatment does not reduce toxicity at the expense of efficacy. At the same time, we will monitor for excess toxicity. If convincing evidence develops that:

- Locoregional control failure rate exceeds 25%; or
- Prevalence of new grade 3+ toxicities six months post-treatment exceeds 25%, the study will stop pending a data safety monitoring committee review. The complete stopping

guideline scenarios are shown in the table below, with the proportion of toxicities and failures being considered for the first 10, 20, 30 and 40 patients enrolled. For example, if 9 of the first 20 patients have a grade 3+ toxicity six months after treatment, the study will stop. If 9 patients have either a grade 3+ toxicity or fail, e.g., 4 have toxicity and 5 fail, the trial will not stop. Once the 40th patient reaches six months of follow-up, we expect to have enrolled 48 out of the total 60 patients on the study. At this point, monitoring for excess toxicity or failures will stop, as the trial's accrual phase will nearly be completed. The upper bound for the confidence intervals is 100%.

Toxicity [Locoregional Control Failure Rate]	Number of patients who develop a toxicity [fail]	Number of patients enrolled	Lower bound of exact one-sided 90% confidence interval
25%	5 9 12 15	10 20 30 40	26.7% 29.3% 27.7% 27.1%

10.2 Monitoring for Efficacy and Toxicity

(Data Safety Monitoring Committee [DSMC])

The principal investigators (Drs. Quon and Forastiere), the Lead research nurse (Kelly Szajna), and the statistician (Amanda Blackford) will make up the Data Safety and Monitoring Committee for this trial. This is a Level 1 trial and will be monitored by The Johns Hopkins Clinical Research Office. The function and role of the Data Safety Monitoring Committee will review the protocol per their institutional standards to help ensure that the trial is running safely.

10.3 Analysis of Endpoints

10.3.1. To achieve a prevalence of grade 3+ toxicities between six months and two years post-treatment <15% while maintaining a locoregional tumor control of at least 85% during the same time interval.

The primary endpoints, prevalence of toxicity and locoregional control rate, will be reported for all patients with an exact 95% confidence interval.

10.3.2. To determine the nature and prevalence of side effects at different time intervals and describe their relationship to pre-treatment function (toxicity) and local dose and treated volume.

Patients will be grouped by whether they had none or a grade 0-2 toxicity versus a grade 3+ toxicity. We will tabulate the frequency of patients in each group by a dichotomous measure of dose and tests for differences with a Chi-square or Fisher's exact test. Patients will also be grouped dichotomously by the number of side effects experienced

and frequencies will be compared to dose category and toxicity category using Chi-square or Fisher's exact tests.

10.3.3. To determine the quality of life of surviving patients.

The results of the Head and Neck MD Anderson Symptom Inventory (MDASI-HN) will be calculated for each patient. The mean score will be reported with a 95% confidence interval. The range and quartiles of the distribution of scores will also be reported.

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APPENDIX 1 CTCAE V4.0 TOXICITY

Grade	1	2	3	4	5
Gastrointestinal disorders: **Mucositis oral** Definition: A disorder characterized by inflammation of the oral mucosal.	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death
Injury, poisoning, & procedural complications: **Skin** Radiation recall reaction (dermatologic) Definition: A finding of acute skin inflammatory reaction caused by drugs, especially chemotherapeutic agents, for weeks or months following radiotherapy. The inflammatory reaction is confined to the previously irradiated skin and the symptoms disappear after the removal of the pharmaceutical agent. OR Injury, poisoning, & procedural complications: Dermatitis radiation (Definition: A finding of cutaneous inflammatory reaction occurring as a result of exposure to biologically effective levels of ionizing radiation).	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated	Death

Grade	1	2	3	4	5
Musculoskeletal & connective tissue disorders: Superficial soft tissue fibrosis Definition: A disorder characterized by fibrotic degeneration of the superficial soft tissues.	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration; unable to slide or pinch skin; limiting joint or orifice movement (e.g. mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death
Gastrointestinal disorders: Dry mouth Definition: A disorder characterized by reduced salivary flow in the oral cavity.	Symptomatic (e.g., dry or thick (saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Moderate symptoms; oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva <0.1 ml/min		
Nervous system disorders: Dysgeusia Definition: A disorder characterized by abnormal sensual experience with the taste of foodstuffs; it can be related to a decrease in the sense of smell.	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste			
Gastrointestinal disorders: Nausea Definition: A disorder characterized by a queasy sensation and/or the urge to vomit.	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated		Death
Gastrointestinal disorders: Vomiting Definition: A disorder characterized by the	1 – 2 episodes (separated by 5 minutes) in 24 hrs	3 – 5 episodes (separated by 5 minutes) in 24 hrs	>=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or	Life-threatening consequences; urgent intervention indicated	Death

reflexive act of ejecting the contents of the stomach through the mouth.			hospitalization indicated		
Metabolism & nutrition disorders: Dehydration Definition: A disorder characterized by excessive loss of water from the body. It is usually caused by severe diarrhea, vomiting or diaphoresis.	Increased oral fluids indicated; dry mucous membranes; diminished skin turgor	IV fluids indicated <24 hrs	IV fluids or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Gastrointestinal disorders: Dysphagia Definition: A disorder characterized by difficulty in swallowing.	symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing	Severely altered eating/swallowing; tube feeding or TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Respiratory, thoracic, & mediastinal disorders: Aspiration Definition: A disorder characterized by inhalation of solids or liquids into the lungs.	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Altered eating habits; coughing or choking episodes after eating or swallowing; medical intervention indicated (e.g., suction or oxygen))	Dyspnea and pneumonia symptoms (e.g., aspiration pneumonia); hospitalization indicated; unable to aliment orally	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Respiratory, thoracic, & mediastinal disorders: Cough Definition: A disorder characterized by sudden, often repetitive, spasmodic contraction of the thoracic cavity, resulting in violent release of air from the lungs and usually accompanied by a distinctive sound.	Mild symptoms; nonprescription intervention indicated	Moderate symptoms, medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL		

Gastrointestinal disorders: Esophageal stenosis Definition: A disorder characterized by a narrowing of the lumen of the esophagus.	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Investigations: Weight loss Definition: A finding characterized by a decrease in overall body weight; for pediatrics, less than the baseline growth curve.	5 to <10% from baseline; intervention not indicated	10 - <20% from baseline; nutritional support indicated	>=20% from baseline; tube feeding or TPN indicated		
Infections & infestations: Wound infection Definition: A disorder characterized by an infectious process involving the wound.		Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Blood & lymphatic system disorders: Febrile neutropenia Definition: A disorder characterized by a decrease in neutrophils associated with fever.			present	Life-threatening consequences; urgent intervention indicated	Death
Blood & lymphatic system disorders: Anemia Definition: A disorder characterized by an reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic	Hemoglobin (Hgb) <LLN – 10.0 g/dL; <LLN – 6.2 mmol/L; <LLN –100 g/L	Hgb <10.0 – 8.0 g/dL; <6.2 – 4.9 mmol/L; <100 – 80g/L	Hgb <8.0 – 6.5 g/dL; <4.9 – 4.0 mmol/L; <80 – 65 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death

murmurs, lethargy, and fatigability.					

Investigations: White blood cell decreased Definition: A finding based on laboratory test results that indicate an decrease in number of white blood cells in a blood specimen.	<LLN – 3000/mm3; <LLN – 3.0 x 10e9 /L	<3000 – 2000/mm3; <3.0 – 2.0 x 10e9 /L	<2000 – 1000/mm3; <2.0 – 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	Death
Investigations: Neutrophil count decreased Definition: A finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen.	<LLN – 1500/mm3; <LLN – 1.5 x 10e9 /L	<1500 – 1000/mm3; <1.5 – 1.0 x 10e9 /L	<1000 – 500/mm3; <1.0 – 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	Death
Investigations: Platelet count decreased Definition: A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen.	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	Death
Respiratory, thoracic, & mediastinal disorders: Voice alteration Definition: A disorder characterized by a change in the sound and/or speed of the voice.	Mild or intermittent change from normal voice	Moderate or persistent change from normal voice; still understandable	Severe voice changes including redominantly whispered speech; may require frequent repetition or face-to-face contact for understandability; may require assistive technology		Death
Respiratory, thoracic, & mediastinal disorders: Laryngeal edema	Asymptomatic; clinical or diagnostic observations only;	Symptomatic; medical intervention indicated (e.g., dexamethasone,	Stridor; respiratory distress; hospitalization indicated	Life-threatening airway compromise; urgent intervention	Death

Definition: A disorder characterized by swelling due to an excessive accumulation of fluid in the larynx.	intervention not indicated	epinephrine, antihistamines)		indicated (e.g., tracheotomy or intubation)	
Musculoskeletal & connective tissue disorders: Osteonecrosis of jaw Definition: A disorder characterized by a necrotic process occurring in the bone of the mandible.	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (e.g., topical agents); limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Gastrointestinal disorders: Dental caries	One or more dental caries, not involving the root	Dental caries involving the root	Dental caries resulting in pulpitis or periapical abscess or resulting in tooth loss		
Musculoskeletal & connective tissue disorders: Trismus Definition: A disorder characterized by lack of ability to open the mouth fully due to a decrease in the range of motion of the muscles of mastication.	Decreased ROM (range of motion) without impaired eating	Decreased ROM requiring small bites, soft foods or purees	Decreased ROM with inability to adequately aliment or hydrate orally		
Nervous system disorders: Myelitis Definition: A disorder characterized by inflammation involving the spinal cord. Symptoms include weakness, paresthesia, sensory loss, marked discomfort and incontinence.	Asymptomatic; mild signs (e.g., Babinski's reflex or Lhermitte's sign)	Moderate weakness or sensory loss; limiting instrumental ADL	Severe weakness or sensory loss; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Nervous system disorders: Neuralgia	Mild pain	Moderate pain; limiting instrumental	Severe pain; limiting self care ADL		

Definition: A disorder characterized by intense painful sensation along a nerve or group of nerves.		ADL			
General disorders & administration site conditions: **Fatigue** Definition: A disorder characterized by a state of generalized weakness with a pronounced inability to summon sufficient energy to accomplish daily activities.	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self care ADL		
Ear & labyrinth disorders: **Hearing impaired** Definition: A disorder characterized by partial or complete loss of the ability to detect or understand sounds resulting from damage to ear structures.	Adults enrolled on a monitoring program (a 1, 2, 3, 4, 6 and 8 kHz audiogram): threshold shift of 15 – 25 dB averaged at 2 contiguous test frequencies in at least one ear or subjective change in the absence of a Grade 1 threshold shift	Adults enrolled in monitoring program (a 1, 2, 3, 4, 6 and 8 kHz audiogram): threshold shift of >25 dB averaged at 2 contiguous test frequencies in at least one ear. Adult not enrolled in monitoring program: hearing loss but hearing aid or intervention not indicated; limiting instrumental ADL	Adults enrolled in monitoring program (a 1, 2, 3, 4, 6 and 8 kHz audiogram): threshold shift of >25 dB averaged at 3 contiguous test frequencies in at least one ear; therapeutic intervention indicated. Adults not enrolled in monitoring program: hearing loss with hearing aid or intervention indicated;	Adults: profound bilateral hearing loss (>80 dB at 2 kHz and above); non-serviceable hearing	
Ear & labyrinth disorders: **Tinnitus** Definition: A disorder characterized by noise in the ears, such as ringing, buzzing, roaring or clicking.	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL		

Neoplasms benign,malignant, & unspecified: Treatment related secondary Malignancy Definition: A disorder characterized by development of a malignancy most probably as a result of treatment for a previously existing malignancy.			Non life-threatening secondary malignancy	Acute life-threatening secondary malignancy; blast crisis in leukemia	Death
Ear & labyrinth disorders: Vertigo Definition: A disorder characterized by a sensation as if the external world were revolving around the patient (objective vertigo) or as if he himself were revolving in space (subjective vertigo).	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL		
Performance status (ECOG)	1	2	3	4	5
PEG tube	No	Yes			
PO	No	Yes			
Admission(s)	No	Yes	# days_____		
Weight (kg)					

Items in grey denote modifications and additions to the original scale

APPENDIX 2 – HEAD AND NECK MD ANDERSON SYMPTOM INVENTORY (MDASI-HN)

35625

Date: ___ / ___ / ___ (month) (day) (year)

Subject's Initials: _____

Study Subject # _____

PLEASE USE BLACK INK PEN

Study Name: _____

Protocol #: _____

PI: _____

Revision: 07/01/05

M. D. Anderson Symptom Inventory - Head & Neck (MDASI-HN)

Part I. How **severe** are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been ***in the last 24 hours.*** Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	NOT PRESENT 0	1	2	3	4	5	6	7	8	9	AS BAD AS YOU CAN IMAGINE 10
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feeling of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering things** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
14. Your problem with **mucus** in your mouth and throat at its WORST?	○	○	○	○	○	○	○	○	○	○	○
15. Your difficulty **swallowing/chewing** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

35625

Date: ___ / ___ / ___ (month) (day) (year)

Subject's Initials: _____

Study Subject # _____

Study Name: _____

Protocol #: _____

PI: _____

Revision: 07/01/05

PLEASE USE BLACK INK PEN

	NOT PRESENT 0	1	2	3	4	5	6	7	8	9	AS BAD AS YOU CAN IMAGINE 10
16. Your **choking/coughing** (food/ liquids going down the wrong pipe) at its WORST?	○	○	○	○	○	○	○	○	○	○	○
17. Your difficulty with **voice/speech** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
18. Your **skin pain/burning/rash** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
19. Your **constipation** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
20. Your problem with **tasting food** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
21. Your **mouth/throat sores** at their WORST?	○	○	○	○	○	○	○	○	○	○	○
22. Your problem with your **teeth or gums** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Part II. How have your symptoms interfered with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

	Did not Interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
23. **General activity?**	○	○	○	○	○	○	○	○	○	○	○
24. **Mood?**	○	○	○	○	○	○	○	○	○	○	○
25. **Work (including work around the house)?**	○	○	○	○	○	○	○	○	○	○	○
26. **Relations with other people?**	○	○	○	○	○	○	○	○	○	○	○
27. **Walking?**	○	○	○	○	○	○	○	○	○	○	○
28. **Enjoyment of life?**	○	○	○	○	○	○	○	○	○	○	○

APPENDIX 3 – XEROSTOMIA QUESTIONNAIRE
Please circle the one that best applies to you:

1. Rate your difficulty in talking due to dryness

0 1 2 3 4 5 6 7 8 9 10

BETTER WORSE

2. Rate your difficulty in chewing due to dryness

0 1 2 3 4 5 6 7 8 9 10

BETTER WORSE

3. Rate your difficulty in swallowing solid food due to dryness

0 1 2 3 4 5 6 7 8 9 10

BETTER WORSE

4. Rate the frequency of your sleeping problems due to dryness

0 1 2 3 4 5 6 7 8 9 10

BETTER WORSE

5. Rate your mouth or throat dryness when eating food

0 1 2 3 4 5 6 7 8 9 10

BETTER WORSE

6. Rate your mouth or throat dryness while not eating

0 1 2 3 4 5 6 7 8 9 10

BETTER WORSE

7. Rate the frequency of sipping liquids to aid swallowing food

0 1 2 3 4 5 6 7 8 9 10

BETTER WORSE

8. Rate the frequency of sipping liquids for oral comfort when not eating

0 1 2 3 4 5 6 7 8 9 10

BETTER WORSE

APPENDIX 4 – PENETRATION/ASPIRATION SCALE

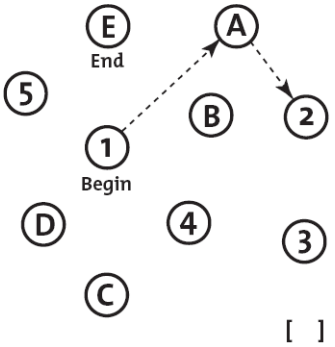
Score	Description of Events
1.	Material does not enter airway
2.	Material enters the airway, remains above the vocal folds, and is ejected from the airway.
3.	Material enters the airway, remains above the vocal folds, and is not ejected from the airway.
4	Material enters the airway, contacts the vocal folds, and is ejected from the airway.
5.	Material enters the airway, contacts the vocal folds, and is not ejected from the airway.
6.	Material enters the airway, passes below the vocal folds, and is ejected into the larynx or out of the airway.
7.	Material enters the airway, passes below the vocal folds, and is not ejected from the trachea despite effort.
8.	Material enters the airway, passes below the vocal folds, and no effort is made to eject.

APPENDIX 5 – MONTREAL COGNITIVE ASSESSMENT

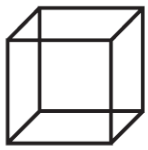
MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE



Copy cube



[ ] [ ]

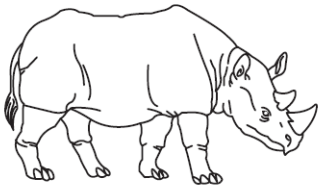
Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

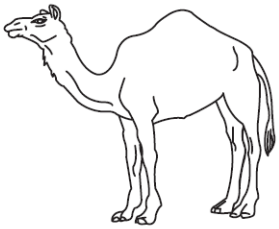
POINTS __/5

NAMING

[ ]



[ ]



[ ] __/3

MEMORY Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2 __/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B __/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** __/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ] __/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words) __/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler __/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City __/6

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Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

APPENDIX 6 – MD ANDERSON DYSPHAGIA INVENTORY (MDADI)

MDADI

This questionnaire asks for your views about your swallowing ability. This information will help us understand how you feel about swallowing.

The following statements have been made by people who have problems with their swallowing. Some of these statements may apply to you.

Please read each statement and circle the response which best reflects your experience in the past week.

E1. **My swallowing ability limits my day to day activities.**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

E2. **I am embarrassed by my eating habits.**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

F1. **People have difficulty cooking for me.**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

P2. **Swallowing is more difficult at the end of the day.**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

E7. **I do not feel self-conscious when I eat.**

Strongly]Agree	Agree	No opinion	Disagree	Strongly Disagree

E4. **I am upset by my swallowing problem.**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

P6. **Swallowing takes great effort.**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

E5. **I do not go out because of my swallowing problem.**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

F5. **My swallowing difficulty has caused me to lose income.**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

P7. **It takes me longer to eat because of my swallowing problem.**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

P3. **People ask me, "Why can't you eat that?"**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

E3. **Other people are irritated by my eating problem.**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

P8. **I cough when I try to drink liquids.**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

F3. **My swallowing problems limit my social and personal life.**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

F2. **I feel free to go out to eat with my friends, neighbors, and relatives.**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

P5. **I limit my food intake because of my swallowing difficulty.**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

P1. **I cannot maintain my weight because of my swallowing problem.**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

E6. **I have low self-esteem because of my swallowing problem.**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

P4. **I feel that I am swallowing a huge amount of food.**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

F4. **I feel excluded because of my eating habits.**

Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree

Index of Abbreviations

3D	Three Dimensional
ADLADL	Activities of Daily Living
AJCC	American Joint Committee on Cancer
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase)
AUC	Area Under the Curve
BED	Biologically Effective Dose
Brach Pl	Brachial Plexus
BUN	Blood Urea Nitrogen
CBC	Complete Blood Cell Count
CCL	Calculated Creatinine Clearance
CDDP	Cisplatin
CHT	Chemotherapy
CI	Confidence Interval
CONT	Continued
CONTR	Contralateral
CR	Complete Response
CRICOPHAR	Cricopharyngeous
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical Target Volume
DB	Decibel
Diff	Differential
DNA	Deoxyribonucleic Acid
DOM	Dominant
DSMC	Data Safety and Monitoring Committee
DVH	Dose-Volume Histogram
e.g.	Ergo
ECE	Extracapsular Extension
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
FEES	Flexible Endoscopic Evaluation of Swallowing
GI	Gastrointestinal
GLS	Mitochondrial Glutaminase
GTV	Gross Tumor Volume
Gy	Gray
HGB	Hemoglobin
HIF-1a	Hypoxia-Inducible Factor-1a
HN	Head and Neck
HPV	Human Papillomavirus
HR	Hazard Ratio
HRS	Hours

ICRU	International Commission on Radiation Units and Measurements
IGRT	Image Guided Radiotherapy
IMRT	Intensity Modulated Radiation Therapy
INF	Inferior
IV	Intravenous
JH	Johns Hopkins
KG	Kilogram
KHZ	Kilohertz
LC	Local Control
LLN	Less than the Lower Limits of Normal
LQED	Linear Quadratic Equivalent Dose
LRC	Locoregional Control
M	Muscle
M	Metastases
MASTICAT	Masticatory Muscles
MAX	Maximum
MBSS	Modified Barium Swallowing Study
MCA	Montreal Cognitive Assessment
MDACC	MD Anderson Cancer Center
MDADI	MD Anderson Dysphagia Inventory
MDASI-HN	MD Anderson Specific Head and Neck Symptom Index
MID	Middle
MOCA	Montreal Cognitive Assessment
MR	Minor Response
MRI	Magnetic Resonance Imaging
MSKCC	Memorial Sloan Kettering Cancer Center
N	Node
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
OAR	Organs at Risk
ORO-SCC	Oropharynx Squamous Cell Carcinoma
OTT	Overall Treatment Time
PD	Progression
PEG	Percutaneous Endoscopic Gastrostomy
PET	Positron Emission Tomography
PI	Principal Investigator
PO	By Mouth
POST	After
PR	Partial Response
PS	Performance Status
PSA	Prostate-Specific Antigen
PTV	Planning Target Volume
PT	Patient
Q	Every

RC	Regional Control
RECIST	Response Evaluation Criteria in Solid Tumors
ROI	Region of Interest
ROM	Range of Motion
RT	Radiation Therapy
RTOG	Radiation Therapy Oncology Group
SD	Stable Disease
SEER	Surveillance Epidemiology and End Results
SUB	Under
SUBM GI	Submandibular Glands
SUP	Superior
T	Tumor
TMJ	Temporomandibular Joints
TPN	Total Parenteral Nutrition
TSH	Thyroid Function Test
ULN	Upper Limits of Normal
Univ IOWA	University Of Iowa
UTMB	University of Texas Medical Branch
V	Volume
v.	Version
Wash U	Washington University
WK	Week
WNL	Within Normal Limits