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Reduced-Intensity Therapy for Advanced Oropharyngeal Cancer in Non-Smoking Human Papilloma Virus (HPV)-16 Positive Patients

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1.0 INTRODUCTION

Improved outcomes of patients with head and neck cancer are achieved with the administration of concurrent chemoradiotherapy, compared with radiotherapy alone (1), however, this improvement is associated with increased toxicity, primarily acute mucositis and late dysphagia (2). Efforts to improve the therapeutic ratio for oropharyngeal cancer include customization of the intensity of therapy to important prognostic factors, and using advanced radiotherapy to reduce doses to the anatomical structures whose damage causes dysphagia. These issues are the subjects of the proposed study and are discussed below.

Over the past three decades, there has been an increase in the incidence of tonsil and tongue squamous cell carcinomas.[3, 4] Recent evidence in the literature as well as from our own studies has identified high-risk human papillomavirus (HPV), particularly HPV-16 (as well as other high risk HPV types), as a causative agent for a subset of HNSCCs, accounting for over 60% of squamous cell carcinomas of the oropharynx (SCCOP) in the United States.[5-9] HPV-positive SCCOP has a distinct risk factor profile[5] and oncogenic mechanism[10, 11] and portends a more favorable prognosis than HPV-negative SCCOP.[5, 12-17]

Conflicting data exist on the combined effect of HPV and smoking on prognosis. Some investigators have found that non-smoking patients with HPV-positive tonsillar squamous cell carcinoma have a better disease-specific survival rate than their smoking counterparts.[13] HPV induced and tobacco-related HPV-negative SCCOP are widely considered to represent distinct clinical entities. However, our observations of patients with HPV-induced SCCOP who use tobacco indicate that they have a worse prognosis than non-users, suggesting that this is a third category of SCCOP (9).

Despite the favorable prognosis associated with, HPV-positive tumors, this biologic marker has not yet been used to determine therapeutic management. We postulate that there are two subsets of HPV-positive SCCOP patients; those who are cured by current therapies but may be suffering unnecessary morbidity from over-treatment and those who are at higher risk for disease progression and require more aggressive therapies. In prior work, we have investigated tobacco use and the HPV-16 biomarker as variables that can differentiate patients to one of those two subgroups, thereby allowing clinicians to safely develop more selective therapies for subsets of HPV-positive SCCOP patients.

One hundred and twenty-four patients with newly diagnosed, stage III or IV SCCOP whose tumors were analyzed for HPV presence and type were included in this study. Patients were treated according to one of two consecutive treatment protocols at the University of Michigan. Of the 124 patients, one hundred two were HPV-positive (82.3%) and 22 (17.7%) were HPV negative. Thirty- two (32/102, 32.4%) had disease progression (DM, LR, or SP). Seventeen patients (17/124, 13.7%) developed DMs (12 HPV-positive; 5 HPV-negative), nine (9/124; 7.3%) developed LRs (5 HPVpositive; 4 HPV-negative), and 8 (8/124; 6.5%) developed SPs (5 HPV-positive; 3 HPV-negative). Of thirty-three HPV-positive never-tobacco users, only one patient had disease progression (DM) (1/32, 3%), and an additional patient had a second primary in the oral cavity. Approximately two- thirds (68%) of the 102 HPV-positive patients were former or current tobacco users. Of these 69 patients, 18 (26%) developed a total of 20 disease progression events. All of the 22 HPV-negative SCCOP patients were tobacco users at some time. Twelve of the 22 (55%) HPV-negative former or current tobacco users had disease progression events (five DMs, four LRs, and three SPs). Sixteen

(16/22; 72.7%) of the HPV-negative patients were current tobacco users; of these, eight (8/16; 50%) had disease progression events (four DMs, three LRs, and one SP). Of the six HPV-negative former tobacco users, (4/6; 68%) developed disease progression events. In conclusion, in this series of 124 patients with advanced SCCOP, HPV-positive never-tobacco users had 93% disease-specific survival, a 6% risk of developing a DM or SP, and no evidence of LR tumors. Thus, less aggressive treatments that reduce morbidity may be more appropriate for the subset of HPV-positive SCCOP patients who never used tobacco. The protein p 1 6ink4 also known as CDKN2A is normally undetectable, however it is strongly upregulated when the HPV E7 oncoprotein is expressed. Thus, this protein is an accepted surrogate marker for transcriptionally active HPV in HPV induced tumors. In our study, (Worden et al JCO, 2008) the association between p16 expression and HPV presence had a p value of 0.0001. Since this test can be rapidly performed in pathology on the pretreatment biopsy tissue this assay will be used to categorize a tumor as HPV positive. HPV type and copy number will be assessed after all of the specimens have been collected. The assay will be the Sequenome Attosense Technology developed at U of M by Dr. David Kurnit and licensed to Sequenom.

The Epidermal Growth Factor receptor (EGFR[1]) plays a key role in head and neck cancer, in that its over-expression is associated with more aggressive behavior. In our prior study of oropharynx cancer patients treated with induction chemotherapy followed by chemo/RT we observed that EGFR intensity was associated with marginally poorer response to CRT (p=0.055) and poorer overall survival (p=0.001) and (p=0.002). Higher HPV titer/lower EGFR intensity as combined markers were associated with better overall survival (pHPV=0.03, pEGFR=0.008) and disease specific survival (pHPV=0.016, pEGFR=0.01) (Kumar et al. JCO 2008). High EGFR expression may modify the effect of HPV on response to therapy and outcome, thus targeting EGFR together with radiation in HPV-positive non-smokers is a reasonable strategy. Bonner *et al* investigated the benefit of the addition of cetuximab, a monoclonal antibody to EGFR, concurrent with radiation for locally advanced HN cancer. Cetuximab improved locoregional control and survival compared with RT alone, while common toxic effects associated with radiotherapy, notably mucositis, did not increase compared to RT alone (18). Subset analysis showed that patients with oropharyngeal cancer were those who mainly benefited from concurrent cetuximab-RT. The advantage of cetuximab-RT compared with RT alone regarding local-regional control was 10%, which is similar or higher than the advantage reported in multiple randomized studies for chemo-RT compared with RT alone. A separate analysis showed that the addition of cetuximab has not affected adversely patient-reported QOL (18a). The combination of cetuximab-RT however has not been adopted as standard of care for advanced FIN cancer because to date there has not yet been a randomized study comparing cetuximab-RT to chemo-RT. However, in the sub-group of patients with local/regional advanced oropharyngeal cancer whose prognosis is excellent, cetuximab-RT may offer a reduced-intensity regimen, compared with chemo-RT, thereby reducing toxicity without affecting excellent survival outcomes.

One of the possible explanations for the good prognosis of HPV-related cancers in nonsmokers is a high sensitivity of EGFR in these tumors and high tendency for degradation following therapy. We propose to assess both the level and degradation of EGFR soon after the administration of the loading dose of cetuximab in order to compare these with smoking-related oropharyngeal tumors treated on

[1] Abbreviations: CR, complete response; EGFR, epidermal growth factor receptor; MAPK, mitogen-activated protein kinase; **PI3K,** phosphatidylinositol 3-kinase; PR, partial response; RT, radiation treatment/therapy; STAT, signal transducer and activator of transcription; TMA, tissue microarray.

other UMCC protocols. Initial *in vitro* studies demonstrated that prolonged exposure of cells to EGF could enhance the effects of radiation in head and neck cancer cells (19, 20). It is likely that this radiosensitivity was achieved through EGF-induced EGFR degradation. Additional studies showed that monoclonal antibodies that target EGFR could increase radiation- induced apoptosis (21). Furthermore, there was an inverse correlation between EGFR expression levels and radiation response (22-23). This relationship between EGFR expression and poor prognosis was confirmed in human head and neck carcinoma samples (24-27). Previous efforts to predict the response to EGFR inhibition using the pre-therapy EGFR expression levels have failed. Although the focus for developing a predictive assay has been on assessing pretreatment paraffin embedded specimens, it seems possible that a predictive assay may require determining the response to treatment (i.e. a pharmacodynamic endpoint). As has been noted by Mendelsohn and Balsega (28), successful application of EGFR targeted therapy may require not only the presence of activated EGFR, but also that the cancer depends on this pathway for cell survival. This dependence ("addiction") might be best determined not simply by assessing pretreatment specimens, but by comparing pre- and post-treatment specimens to determine if the inhibitor has actually inhibited both EGFR phosphorylation and downstream signaling. For example, in patients with rectal cancer receiving cetuximab-based chemo-irradiation, disease-free survival was better in patients if EGFR expression was upregulated in the tumor after the initial cetuximab dose (28a). In this protocol we plan to assess EGFR and its down-stream signaling both pre-therapy and following the loading dose of coniximah, in order to address this issue.

In order to reduce dysphagia after chemo-irradiation, in recent years, we have utilized highly conformal radiotherapy (intensity modulated radiotherapy, IMRT) sparing specific anatomical structures, pharyngeal constrictors and the glottic and supraglottic larynx, which we have previously identified as structures whose damage is the likely cause of long-term dysphagia (28). We have demonstrated that it is possible to reduce the doses to these structures without under-treating the target volumes (29). In a phase II study in patients with oropharyngeal cancer treated with chemoRT (weekly carboplatin and taxol concurrent with a 7-week course of IMRT that spared the swallowing structures and delivered a total of 70 Gy tumor dose) we have demonstrated high local- regional tumor control rates (94%) (30). There were no tumor recurrences near the spared swallowing structures in 104 patients. Prospective evaluation of swallowing, including objective studies of swallowing (videofluoroscopy, VF), patient-reported, and observer-rated dysphagia, are encouraging (Feng et al, manuscript in preparation). Notably, strong statistically significant correlations were found between each of the three measures of dysphagia and the doses delivered to the swallowing structures (29, 30). While these relationships do not prove cause-and-effect relationships, they strengthen the hypothesis that reducing the doses to these structures as much as possible can yield clinically significant improvement in dysphagia.

Taking into account the high local-regional control rates achieved in our oropharyngeal cancer patients after 7 weeks of concurrent chemo-RT, we hypothesize that additional gains in our efforts to reduce treatment sequelae may be achieved if we could safely reduce the intensity of therapy in those patients who are most likely to respond completely. A recent analysis of RTOG study comparing accelerated to standard fractionation concurrent with chemotherapy, found that in the oropharyngeal sub-set of patients, those tumors were HPV(+) fared better than those with HPV(-) tumors. Furthermore, the risk of death increased significantly with each pack-year of tobacco smoking. Using recursive-partitioning analysis, patients were classified as having low-risk of death if they had HPV(+) tumors, smoking history of $\leq$10 pack year or equivalent, tumor stage <T4 and nodal stage <N3 (Ang KK et al, NEJM 2010;363:24-35). In this protocol we will select patients with oropharynx cancer (OP) cancer who are at low risk according to these criteriafor reduced treatment intensity, using RT concurrent with cetuximab instead of chemotherapy. This therapy will be compared to our experience in the past

few years using full dose chemo-RT, and will use the same detailed measures of toxicity, specifically measures of dysphagia, for comparison.

2.0 STUDY HYPOTHESIS AND RATIONALE

Taking into account the excellent prognosis of patients with HPV-positive oropharyngeal cancer with ≤ 10 pack-year smoking , we hypothesize that reducing the intensity of therapy for these patients will reduce treatment sequelae, notably long-term dysphagia, without affecting their cure rates. The main Aim is to assess whether reducing treatment intensity, by replacing concurrent chemotherapy with cetuximab, will indeed achieve improved long-term toxicity. This Aim will be tested in a prospective study in which acute and long-term sequelae will be graded by observers (using CTCAE v4.0) and by patients (via HN-specific QOL questionnaires). Dysphagia will also be assessed objectively by videofluoroscopy. These measures will be compared to our historical control group (consisting of non-smoking patients with advanced oropharyngeal cancer who received standard-intensity chemo-RT and were evaluated by the same tools on UMCC protocol 2-21). Strict stopping rules will be enacted to ensure that reducing treatment intensity does not increase tumor failures compared with our previous results using standard therapy.

EGFR expression and down-stream signaling will be tested before and after the loading dose of cetuximab (before radiotherapy starts). We hypothesize that in this population with good prognosis, EGFR downstream inhibition after cetuximab test dose will be achieved in the large majority of patients, and that these characteristics will differ significantly from the characteristics of EGFR inhibition which will be observed in poor-prognosis oropharyngeal patients who smoke and/or have HPV- tumors. (These patients will be treated on a different, parallel protocol in which the intensity of therapy will be increased and in whom EGFR level will also be examined before and after a loading dose of cetuximab.)

3.0 OBJECTIVES

3.1 Primary Objectives

3.1.1 To confirm that reducing treatment intensity in patients with HPV related oropharyngeal cancer and ≤ 10 pack-year smoking history by replacing concurrent chemotherapy with concurrent cetuximab, does not significantly increase the proportion of patients whose tumors recur, compared to our previous experience in similar patients receiving chemo-RT.

3.1.2 To compare the toxicity in patients receiving cetuximab-RT to similar patients treated with 7 weeks of chemotherapy concurrent with RT ("standard therapy") in UMCC 2-21.

3.2 Secondary Objectives

3.2.1 Characterize the changes in tumor EGFR, pEGFR, downstream signaling, following a loading dose of cetuximab.

3.2.2 Compare normal mucosa EGFR to EGFR in the tumor sample.

3.2.3 Explore if baseline EGFR, Bc1xL, p53 and p16 tumor expression are related to treatment response.

4.0 INCLUSION CRITERIA

4.1 Patients must have pathologically-confirmed, previously untreated, stage III-IV(excluding N3 or T4) squamous cell carcinoma of the oropharynx, without evidence

of distant metastasis

4.2 Pretreatment tumor biopsy with sufficient tumor for HPV or p16 analysis is required. The tumor must be HPV(+) or p16(+)

4.3 Smoking history <10 pack-year or equivalent (including cigarettes, cigars, pipes, chewing tobacco, and/or marijuana.) One cannabis joint is equivalent to 5 cigarettes. (Aldington etal, Thorax 2007; 62:1058-1063)

Smoking status definitions (National Health Interview Survey and Behavioral Risk Factor Surveillance System (Nelson DE etal al, Am J Pub Health 2003;93:1335):

- Smokers: smoking now every day or some days in past month
- Quitters: at least 100 cigarettes/lifetime and not smoking in the past 1-12 months
- Former smoker: at least 100 cigarettes/lifetime and not smoking >12 months
- Never smokers: <100 cigarettes (or equivalent)/lifetime

4.4 KPS $\geq$ 80 (see Appendix A)

4.5 Patients must undergo pre-treatment endoscopic tumor staging and PET-CT scanning

4.6 Laboratory criteria:

- WBC > 3500/ul
- granulocyte > 1500/ul
- Platelet count > 100,000/ul
- Total Bilirubin < 1.5 X ULN
- AST and ALT < 2.5 X ULN

4.7 Creatinine clearance >30 cc/min

4.8 Patients must sign study specific informed consent

4.9 Patients must have, in the opinion of a treating physician, tumor that is accessible to biopsy in the clinic.

5.0 EXCLUSION CRITERIA

5.1 Prior head and neck malignancy or history of other prior non-head and neck malignancy (excluding skin cancer and early stage treated prostate cancer) within the past 3 years

5.2 Prior head and neck radiation or chemotherapy

5.3 Any medical or psychiatric illness, which in the opinion of the principal investigator, would compromise the patient's ability to tolerate this treatment or limit compliance with study requirements

5.4 Patients residing in prison

5.5 Patients with prior anti-epidermal growth-factor receptor antibody therapy (antibody or small molecule)

6.0 PRE-TREATMENT EVALUATION

6.1 Complete history and physical examination (including smoking status), multidisciplinary examination by Surgical, Radiation and Medical Oncology, documentation of extent of primary tumor and regional disease

6.2 Satisfactory biopsy of the primary tumor confirming pathologic diagnosis, HPV or p16 positivity, and specimen submission to the Radiation Oncology research laboratory.

6.3 Buccal swab

6.4 Complete dental evaluation, as per standard of care for patients receiving radiation therapy

6.5 CBCP with differential and Comprehensive panel, including Magnesium

6.6 Initial staging PET-CT scan

6.7 Baseline toxicity, QOL, and swallowing function assessments

7.0 STUDY DESIGN

7.1 Schema

7.1.1 Cetuximab loading dose followed by daily radiation therapy with weekly cetuximab

7.1.2 Toxicity assessment, QOL, videofluoroscopy: pre-therapy and periodically after therapy

7.1.3 Tumor biopsy and mucosal swabs for EGFR expression: pre-therapy and after the loading dose of cetuximab.

7.2 Overview

Patients who smoked $\leq$ 10 pack-year with p16(+) or HPV(+) tumors will be enrolled.

Patients will receive a single dose of cetuximab 400 mg/m^2 (Day 0). On day 7 (+/- 2 days), a repeat biopsy will be performed for EGFR expression, if it can be done without general anesthesia. Within 4 days, definitive radiation will be started (70 Gy in 35 fractions over 7 weeks to the gross tumor, 50-60 Gy to subclinical target volumes) concurrent with weekly cetuximab 250 mg/m^2, delivered on Monday or Tuesday each week.

Twelve to 14 weeks (+/- 1 month) following the completion of therapy, patients will undergo standard restaging evaluation, including PET-CT, endoscopy and repeat tumor site biopsies if deemed necessary.

Toxicity evaluation: Observer-rated toxicity according to CTCAE v4.0, patient-reported QOL (HNQOL, UWQOL, and XQ questionnaires), and videofluoroscopy (VF), will be performed before and periodically after therapy.

7.3 HPV or p16 tumor status for eligibility requirements will be determined in biopsy tissue by immunohistochemical analysis by standard biotin-avidin complex technique performed on formalin-fixed, paraffin-embedded tissue sections using mouse monoclonal antibodies to $p16^{INK4A}$ (Biocare Medical, Concord, CA, dilution 1:200) following heat-induced antigen retrieval with 0.1M citrate buffer (pH 6.0). Positive staining results consist of diffuse and strong staining of both cytoplasm and nucleus in tumor tissues.

7.4 In addition, a standardized assay of HPV type and copy number may be performed .in the cancer center DNA core. In brief, HPV analysis involves real-time competitive polymerase chain reaction and matrix-assisted laser desorption/ionization-time of flight mass spectroscopy separation of products on a matrix-loaded silicon chip array. This method uses primers designed to amplify the E6 region to detect 13 high-risk HPV types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68).

7.5 EGFR Status

7.5.1 Clinical Staging Biopsy

A diagnostic pretreatment biopsy tissue block (not just submitted slides) suitable for isolation of DNA for HPV or p16 testing is required for inclusion in the study. This pre-treatment tumor biopsy will be used for diagnostic pathology, initial p16 analysis or in situ HPV hybridization analysis. The tissue blocks will also be used for creating tissue microarrays for biomarker analysis. Tissue cores from the biopsy will be taken for DNA isolation for HPV testing, p16 testing, p53 analysis, or other mutations.

7.5.2 Research Biopsies

Two research biopsies will be obtained. These research biopsies will be delivered directly to the Radiation Oncology research laboratory. The pre-treatment research biopsy (5-10 mm3) will be taken prior to therapy to assess baseline EGFR pathway activation. This pre-treatment biopsy will be performed for research purposes if a suitable clinical biopsy specimen is not available. A clinical specimen will be suitable if the biopsy was performed at UMHS within 30 days of consent. The second biopsy will be obtained 7 days (+/-2 days) after the loading dose of cetuximab and will be examined for changes in EGFR pathway activation. Both biopsies will be performed in the clinic, under local anesthesia, by an otolaryngologist or oral surgeon who is a co-investigator of the study. The second biopsy will only be obtained if it can be done without general anesthesia.

7.6 Normal Oral Mucosa Sampling

Baseline EGFR of the normal oral mucosa may be obtained by buccal swab. At least 3 normal oral mucosa buccal swab samples will be acquired. Similarly, post-cetuximab buccal swab will be performed on day 7 (+/- 2 days) after cetuximab.

7.7 Schedule

7.7.1 Day 0: Patients will receive a single loading dose of cetuximab 400 mg/m2

7.7.2 Day 7 (+/- 2 days): Second buccal mucosa swab will be obtained. Second biopsy will be obtained if it can be done without general anesthesia.

7.7.3 Daily radiation therapy with weekly cetuximab (250 mg/m2) will be initiated within 4 days

7.8 Cetuximab Dose Levels

	Starting Dose	**Dose Level —1**	**Dose Level —2**
Cetuximab	400 mg/m^2 (day 0) 250 mg/m^2 (day 7 and weekly during RT)	200 mg/m^2 (weekly)	150 mg/m^2 (weekly)

NOTE: Once the dosage of Cetuximab has been decreased, it will remain at that level unless further dose reductions are required, at which time all dosages will remain at that level. Dosages CANNOT be increased once a dose reduction has taken place.

7.9 Cetuximab Dose Modification for Hematologic Toxicity

NCI CTCAE Toxicity Grade (CTCAE v. 4.0)	**Cetuximab Dose [a,b] at Start of Subsequent Cycles of Therapy**
Neutropenia	
1 (1500-1999/mm^3)	Maintain dose level
2 (1000-1499/mm^3)	Maintain dose level
3 (500-999/mm^3)	Decrease by 1 dose level with occurrence
4 (<500/mm^3)	Decrease by 1 dose level with occurrence
Neutropenic Fever[c]	Decrease by 1 dose level
Thrombocytopenia	
1 (≥75,000/mm^3)	Maintain dose level
2 (50,000- 74,999/mm^3)	Maintain dose level
3 (25,000 – 49,999/mm^3)	Decrease by 1 dose level with occurrence
4 (<25,000/mm^3)	Decrease by 1 dose level with occurrence

[a]Dose levels are relative to the starting dose in the previous cycle. Dose reductions of Cetuximab below the –2 dose level will not be allowed.
[b]Provided that all the retreatment criteria are met (see section 7.1.3)
[c]One reading of oral temperature ≥38.5ºC and ANC ≤ 500

7.10 Cetuximab Dose Modifications for Non-Hematologic Toxicity

NCI CTCAE Toxicity Grade (CTCAE v. 4.0)	**Cetuximab Dose [a, b, c]**
Fatigue (Asthenia) ≥ Grade 3	Decrease by 1 dose level
Nail changes (Paronychia) Grade 2	Decrease by 1 dose level
Diarrhea Grade 3 despite maximal medical management	No dosage adjustment
Grade 3 recurrent, despite maximal medical management	Decrease by 1 dose level
Grade 4 despite maximal medical management	Decrease by 1 dose level
Headache ≥ Grade 3	Decrease infusion rate by 50%
≥ Grade 3 despite decreased infusion rate and use of analgesic	Decrease dose by 1 dose level
Stomatitis/Mucositis	All patients are evaluated weekly. The dosage adjustments will be determined by the practicing clinicians at each visit. If a reduction is required, the dose will be decreased by 1 dose level. If > 2 dosage reductions are required, Cetuximab will be discontinued.

[a]For CTCAE Grade ≤ 2 non-hematologic toxicity not described above, maintain dose level of drug, provided that all the retreatment criteria are met as detailed in section 7.1.3.

[b]Dose levels are relative to the previous dose. Dose reductions of cetuximab below the —2 dose level will not be allowed.

[c]In any case of cetuximab treatment delay, there will be no reloading infusion, and all subsequent treatments will be at the assigned dose level.

7.11 Management of Cetuximab Hypersensitivity Reactions

CTCAE Grade	Hypersensitivity Reaction
Grade 1	Transient flushing or rash, drug fever <38°C (<100.4°F); intervention not indicated
Grade 2	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for <=24 hrs
Grade 3	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)
Grade 4	Life-threatening consequences; urgent intervention indicated

[a] Symptoms of hypersensitivity reactions should be managed per institutional chemotherapy infusion policy guidelines.

[b] Study Therapy Retreatment Following Hypersensitivity Reactions: Once a cetuximab infusion rate has been decreased due to an allergic/hypersensitivity reaction, it will remain decreased for all subsequent infusions. If the subject has a second allergic/hypersensitivity reaction with the slower infusion rate, the infusion should be stopped, and the subject should receive no further cetuximab treatment. If a subject experiences a Grade 3 or 4 allergic/hypersensitivity reaction at any time, the subject should receive no further cetuximab treatment. If there is any question as to whether an observed reaction is an allergic/hypersensitivity reaction of Grades 1-4, the Principal Investigator should be contacted immediately to discuss and grade the reaction.

7.12 Cetuximab Special Instructions

If cetuximab is omitted for more than four consecutive infusions for toxicity due to cetuximab, or for an intercurrent illness (e.g., infection) requiring interruption of therapy, the subject should be discontinued from further cetuximab therapy. If toxicities prevent the administration of cetuximab, the subject may continue to receive radiation therapy.

7.13 Retreatment Criteria for cetuximab

7.13.1 Cetuximab may only be administered if all of the following criteria are met regardless of cycle, providing no criteria for discontinuation are met (see Section 13.0).

7.13.2 Acne-like rash is ≤ Grade 2 (see Section 7.14)

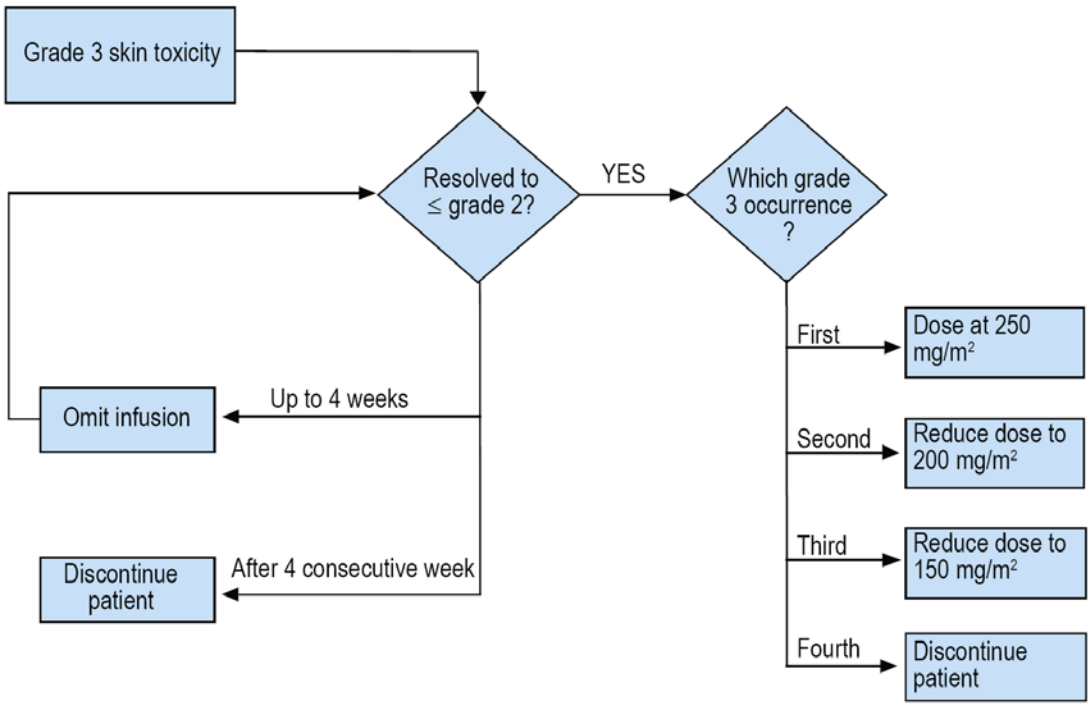
7.13.3 Grade 3 - 4 hematologic toxicities have resolved to ≤ CTC Grade 2

7.13.4 Grade 3 - 4 non-hematologic toxicities have resolved to ≤ CTC Grade 2, (except fatigue (asthenia), anorexia and alopecia)

7.14 Acne-Like Rash (rash maculo-papular)

The dose of cetuximab will be adjusted for Grade 3 acne-like rash. The severity of these events will be graded according to the criteria for the CTC term "rash maculo-papular." The cetuximab dose alteration scheme is outlined in the figure below. If a subject experiences a Grade 3 acne-like rash, cetuximab therapy is to be held for up to four consecutive infusions (see table below). The Investigator could also consider concomitant treatment with topical and/or oral antibiotics and topical corticosteroids. If there are subsequent occurrences of a Grade 3 acne-like rash, cetuximab therapy may again be omitted for up to four consecutive weeks. Treatment may resume with reduced doses of cetuximab if the skin toxicity has resolved to Grade 2 or less. Cetuximab dose reductions are permanent. Cetuximab will be discontinued if there is a subsequent occurrence of a fourth episode of Grade 3 acne-like rash or there are more than four consecutive infusions held. The subject should be followed weekly until resolution of the rash. If a subject experiences a Grade 4 acne-like rash, cetuximab therapy will be discontinued.

Management of Cetuximab Acne-Like Rash



8.0 RADIOTHERAPY

8.1 Immobilization, imaging and target definitions

8.1.1 The technical details of RT planning will correspond to standard of care at the Department of Radiation Oncology as previously published (29).

8.1.2 Target doses will be similar to the doses delivered in standard practice: 70 Gy at 2.0 Gy/fraction to primary tumor and to lymph nodes with clinical/radiological evidence of metastases, and 56-63 Gy at 1.6-1.8 Gy/fraction to subclinical disease around the primary tumor or to the surgical tumor excision bed, and to the lymph nodes at risk of metastasis, all in 35 fractions, over 7 weeks.

8.2 Optimization goals regarding the salivary glands will be:

8.2.1 Mean dose to the parotid glands <26 Gy (at least one gland).

8.2.2 The dose to the volumes of the submandibular glands and oral cavity outside the targets will be minimized.

8.2.3 The doses to the swallowing structures (pharyngeal constrictors, glottic and supraglottic larynx) outside the targets will be minimized, aiming at mean dose < 50 Gy.

8.3 OPTIMIZATION CONSTRAINTS WILL BE:

8.3.1 The maximal target PTV dose will be 110% of the prescribed dose.

8.3.2 The minimum target PTV doses will be > 99% of the prescribed dose.

8.3.3 The maximal dose outside the targets will be <105% of the prescribed dose delivered to at least 0.5 cc. volume.

8.3.4 The maximal dose to the spinal cord, expanded 0.5 cm, will be < 50 Gy, to the non-expanded cord < 45 Gy, to the optic pathways < 50 Gy and to the brainstem <54 Gy.

9.0 EVALUATION OF RESPONSE TO TREATMENT

9.1 Evaluation of tumor extent will be recorded for the primary tumor and regional nodes at each f/u interval. PET-CT scans will be performed 12-14 weeks (+/- 1 month) after the completion of therapy to assess response.

9.2 Patients with any nodes who are PET-CT positive at 12-14 weeks (+/- 1 month) post cetuximab-RT may be considered for neck dissection. Patients with palpable residual nodes at 3 months whose PET-CT shows a complete response (CR) may undergo clinical observation and periodic PET scans according to the judgment of the treating clinicians.

9.3 Clinical examinations will be performed as comparable to clinical practice: at 1 month after the completion of therapy and then every 2 months during years 1 and 2, and at 3-month intervals during year 3, after which follow-up will be performed according to clinical practice. Allowable windows for these exams are +/- 1 month.

Clinical examinations will be performed by medical oncology, radiation oncology, and/or surgical oncology. To meet the examination requirements, patients need to be seen by at least one discipline (but not all three) during the aforementioned time intervals.

9.4 Once patients discontinue treatment (Section 13.0) or have tumor progression/recurrence, they will be followed as clinically indicated for 3 years following the completion of radiation and/or cetuximab.

10.0 EVALUATION OF TOXICITY AND QUALITY OF LIFE

10.1 Validated quality of life questionnaires: HNQOL, UWQOL-HN, and XQ (Appendix B) will be given to patients before and periodically after radiation (1, 3, 6, 12, 18, 24 and 36 months, with a +/- 1 month window for each). Common Toxicity Criteria Adverse Events (CTCAE, v.4.0) observer related items will be gathered weekly during treatment and at every follow- up clinic visit through 3 years. As part of data collection related to the quality of life measures, pre and post-treatment employment status will also be recorded, as well as Performance Status Scale. Patients may be asked for this information during a clinic visit or contacted via phone. The study team will attempt to obtain this information from all enrolled patients.

10.2 Objective evaluation of swallowing will be made by videofluoroscopy and esophagogram. They will be performed in patients receiving definitive RT and chemotherapy. A baseline study will be performed either before RT starts or on one of the first five days of RT. Three follow-up studies will be done: one study at 3 to 4 months following RT completion (+/- 1 month), one study at 11 to13 months following RT completion (+/- 1 month), and one study at 24 months following RT completion (with the acceptable window of 2 months prior or 6 months post). Each subject will be asked to swallow various food consistencies in varying amounts (5-15 m1). The consistencies included thin liquid barium (diluted with water) followed with non- diluted barium, followed with a puree, soft food (fruit mixed with barium) and a solid (shortbread cookie) coated with barium. The examinations will be recorded and analysis of the 3 phases of swallowing: oral, pharyngeal and esophageal will be made. Assessment will focus on bolus manipulation and control, bolus passage including cohesion, motility, and timing. The timing or duration of each swallowing phase will be determined. Also, the amount and incidence of aspiration and penetration, laryngeal sensation (response to penetrant/ aspirate) and residue/pooling after the swallow will be recorded. Laryngeal sensation will be determined to be good, reduced or poor. Reduced sensation would be consistent with a cough reflex that is delayed or intermittent. Poor sensation is defined when subjects elicit no spontaneous cough reflex or throat clear. These subjects are considered to be "silent" aspirators.

11.0 STUDY CALENDAR

Assessment	Pre-Treatment*	Day 0 Loading Dose	Day 7 (+/- 2 days)	Weekly during Treatment†	12-14 wks post RT (+/- 1 month)	Follow Up[3]
H&P/Physician Evaluation	X			X	X	X
Smoking status and tumor HPV or p16 determination	X					
Biopsy	X		X[1]			
Buccal swab	X		X[1]			
COMP, Mg	X			X	X	
CBCP with diff	X			X	X	
PET-CT	X				X[2]	
Dental Evaluation	X					
Toxicity Evaluation	X			X	X	X
QOL Questionnaire	X				X	X
Videofluoroscopy	X				X	X
Cetuximab		X		X		

* The pre-treatment period is prior to the administration of the cetuximab loading dose
† Radiation therapy will start within 4 days following Day 7 biopsy

[1]Research biopsy will be performed 7 days (+/- 2 days) after cetuximab. This second biopsy will only be obtained if it can be done without general anesthesia.

[2]Restaging PET-CT will be obtained at 12-14 weeks.

[3]Follow Up: Examinations will be performed as comparable to clinical practice: at 1 month after the completion of therapy and then every 2 months during years 1 and 2, and at 3-month intervals during year 3. Toxicity evaluation will be collected at each visit. Quality of Life Questionnaires will be given to patients at follow-up visits 1, 3, 6, 12, 18, 24 and 36 months. Videofluoroscopy will be performed at 3, 12, and 24 months after therapy. Allowable windows for all these time points are +/- 1 month.

Note: Once patients discontinue treatment (Section 13.0) or have tumor progression/recurrence, they will be followed as clinically indicated for 3 years following the completion of radiation and/or cetuximab.

12.0 MEASUREMENT OF RESPONSE

Tumor Clearance

A patient will be considered to have a complete response if there is no measurable or palpable tumor either on clinical or radiographic (CT-PET scan) examination assessed within 3 months after the completion of treatment. Complete response will be defined as complete disappearance of disease or residual radiographic abnormality that is not considered to be tumor.

13.0 CRITERIA FOR DISCONTINUATION OF TREATMENT

Unacceptable adverse event(s), intercurrent illness which prevents further administration of treatment, patient preference, progressive disease, life threatening or other unacceptable drug-related toxicity, changes in the patient's condition that render the patient unacceptable for

further treatment in the judgment of the investigators.

14.0 DRUG INFORMATION**: CETUXIMAB**

14.1 *Formulation:* Cetuximab is an anti-EGFR receptor humanized chimeric monoclonal antibody. Cetuximab is expressed in SP2/0 myeloma cell line, grown in large scale cell culture bioreactors, and purified to a high level purity using several purification steps including protein A chromatography, ion exchange chromatography, low pH treatment, and nanofiltration. Cetuximab is not known to be a vesicant.

14.2 Supply: The product is formulated to 2 mg protein/mL with phosphate buffered saline, pH 7.2 ± 0.2 and aseptically filled into sterile glass vials, 100 mg per 50 cc vial, and stored as a liquid at 2 to 8° C. Each vial contains the following active and inactive ingredients per 1.0 ml: 2 mg of cetuximab, 145 nmol/L sodium chloride, and 10 mmol/L sodium phosphate.

14.3 Safety Precautions: Appropriate mask, protective clothing, eye protection, gloves and Class II vertical-laminar-airflow safety cabinets are recommended during preparation and handling.

14.4 Preparation and Administration:

14.4.1 Cetuximab is available commercially as an injectable solution, in single-use, ready-to-use 50-mL vials containing 2 mg/mL of product. Cetuximab requires no dilution. Cetuximab should not be mixed with or diluted with other drugs or solutions for infusion such as 5%-glucose.

14.4.2 The dose and volume of the study drug to be infused are dependent upon the patient's actual BSA. The infusion rate must never exceed 10 mg/minute (5 mL/minute). The dose may subsequently be reduced for individual patients, depending on a patient's toxicity. For the duration that patients are on cetuximab therapy, adverse event monitoring should be done continuously. Patients will be evaluated for adverse events at each visit and are to be instructed to call their physician to report any adverse events between visits.

14.4.3 Cetuximab may be administered via an infusion pump or syringe pump. Cetuximab administration requires an in-line low protein-binding 0.22 micron filter. Note: one filter per dose should be sufficient, but further filters can be used if a filter becomes blocked.

<u>Administration via Infusion Pump</u>
Calculate the appropriate volume of cetuximab based on the dose and using an appropriate sterile syringe (min 50 mL) draw up the required volume from the vial(s). Add the cetuximab into a sterile evacuated container or bag (glass administration containers are not recommended). Do not shake. Attach an infusion line with a low protein binding 0.22 micron in-line filter.

Use an infusion pump for administration. Set and control the rate as noted above and infuse the whole dose.

Administration via Syringe Pump

Calculate the appropriate volume of cetuximab based on the dose and using an appropriate sterile syringe (min 50 mL) draw up the required volume from the vial(s). Do not shake. Remove the needle, and put the syringe into the syringe pump. Attach tubing with a low protein-binding 0.22 micron filter. Set and control the rate as described above. Make sure that the whole dose has been infused.

Studies have been conducted to demonstrate the compatibility of cetuximab drug product with various infusion systems. Some examples of materials, IV containers, infusion sets, and filters tested and recommended for use with cetuximab are listed below. For further examples of approved materials, please see the Investigator Brochure.

Recommended IV Containers

- IntraVia™ IV Bag with PVC Ports, Model No. 2J8002 (Baxter Healthcare Corporation)
- EVA™ IV Bag, Model No. 2B8152 (Baxter Healthcare Corporation)
- LifeCare™ IV Bag, Model No. 7951-12 (Abbott Laboratories)

Recommended Infusion Sets

- Vented Continu-Flo Solution Set™, Model No. 2C6541s (Baxter Healthcare Corporation) to be used with an in-line filter set, Model No. 2679 (Abbott Laboratories)
- Vented Paclitaxel Set™ with 0.22-µm downstream high-pressure in-line filter, Model No. 2C7553 (Baxter Healthcare Corporation)

Recommended Filters

- Vented Continu-Flo Solution Set™, Model No. 2C6541s (Baxter Healthcare Corporation) to be used with an in-line filter set, Model No. 2679 (Abbott Laboratories)
- Intrapur Plus (B. Braun AG) reference number 409 9800
- Poly-lined filtered Extension set (Alaris Medical Systems) reference number C20350

14.4.4 Normal saline should be use to clear the infusion set of residual cetuximab. The delivered drug product is > 95% for all recommended infusion sets when flushed with 50 mL of normal saline. Use a separate line for cetuximab infusion.

14.4.5 Storage Requirements/Stability: Cetuximab must be stored under refrigeration at +2°C to +8°C (+36°F to +46°F). DO NOT FREEZE CETUXIMAB. Drug supplies must be kept in a secure, limited access storage area under the recommended storage conditions. Once cetuximab is removed from the vial, the recommended maximum storage time in the infusion

container or syringe is 8 hours at room temperature or 12 hours in the refrigerator.

15.0 EGFR ANALYSIS

The primary goal of this analysis is to determine whether cetuximab given at the clinically recommended dose will affect EGFR, phospo-EGFR and down-stream signaling within the tumor as well as in the normal mucosa. The protein levels of EGFR, pY845-EGFR and various down-stream signaling molecules will be measured by immunoblotting as well as immuno-histochemical analysis in both normal and tumor samples at baseline and post-treatment as described previously (26).

15.1 Pre-Therapy Tumor Sample Collection and Initial Processing

The initial pre-treatment punch-biopsy specimen for research (about 3x3x3 mm) of the tumor and mucosa cells (or a buccal swab) will be collected in ice cold saline containing a cocktail of protease (Roche Diagnostic Co., Indianapolis, IN) and phosphatase inhibitors (Sigma, St. Louis, MO) in the presence of laboratory personnel from Dr. Mukesh Nyati's laboratory. The sample will be divided into 2 parts. The first part will be fixed in 10% phosphate buffered formalin and will be stored in paraffin blocks for immunohistochemistry, and second part will be used to extract proteins for immunoblotting.

15.2 Method of Assessment of EGFR Expression in Tumor After Cetuximab Loading Dose

At the time of the second biopsy a tumor specimen (about 5x5x5mm) along with buccal swab will be collected. The tumor specimen will be divided into 3 parts. The first two parts will be processed as described in section 15.3.1. When feasible the 3rd part will be used to isolate RNA in Dr Tom Carey's laboratory. EGFRvIII expression and p53 mutation analysis will be assessed on cDNA obtained from total RNA converted with RT-PCR.

15.3 Sample Preparation and Analysis

15.3.1 High-throughput immunoblotting and isolation of RNA and DNA for genetic studies:

Tumor samples will be processed immediately for protein extraction in Dr Nyati's laboratory. A total of 200 gg total protein will be subjected to electrophoresis on a 2D 4 to 12% bis-tris precast gel (Invitrogen, Carlsbad, CA) and transferred onto a PVDF membrane. A Miniblotter 28 dual system (Immunetics, Cambridge, MA) will be used to probe all the antibodies in duplicate. After incubating the membrane with different antibodies overnight, membranes will be washed and probed with horseradish peroxidase conjugated IgG (Cell Signaling Technology, Beverly, MA), diluted 1:5,000 in TBST for 1 hr at room temperature; the antigen—antibody complexes will be visualized by enhanced chemiluminescence (ECL-Plus; GE Biosciences, Piscataway, NJ). The films then will be scanned, and the bands analyzed using NIH ImageJ software. Proteins to be assessed include phospho and total forms of EGFR, AKT, Src, STAT3, in addition to total p27, PARP, Bel-X_L will also be assessed.

Isolation of DNA (from the FFPE pretreatment diagnostic biopsy) and RNA (from the research biopsy when possible) will be carried out using DNAeasy and RNAeasy (both from Qiagen) on the remaining sample according to the manufacturers instructions.

15.3.2 Immunohistochemistry and Scoring of TMA:

One high-density TMA will be constructed using a manual tissue arrayer (Beecher Instruments, Silver Spring, MD, USA) at the core facility at the University of Michigan using standard methods. Tissue cores from the regions of interest (tumor tissues, before and after treatment) will be targeted for transfer to the recipient array block. At least three 0.6 mm diameter replicate tissue cores will be sampled from each subregion of the selected sample. The final TMA will consist of approximately 160 cores. After construction, 4 gm sections will be cut, and hematoxylin and eosin staining will be performed on the initial slide to verify the histology. Serial 4 gm sections will be further cut and transferred to positively charged slides, these sections will be subjected to standard immunohistochemical staining procedures. Dr Nyati's lab have validated both total and phospho-antibodies that can be used successfully on formalin fixed tissue (26). The stained test slides will be reviewed by the head- and —neck pathologist co-investigator (Dr McHugh) for the expected pattern and appropriate intensity. The information about expected and appropriate staining for each antibody will be discussed with the other investigators to confirm the scoring criteria. The TMAs will be then stained by the staff at the Tissue Core. Each tissue core will be scored by a board certified oral and maxillofacial pathologist who is blinded as to the identity of the cores. Each tissue core will be scored for intensity of SCC cells staining: 1, undetectable; 2, weak; 3, moderate; 4, strong. Multiple TMA core measurements from the same subject will be averaged. This average score in its continuous scale will be used in all analyses.

16.0 OTHER THERAPY

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented as concomitant medication.

17.0 ADVERSE EVENTS (AE) AND SERIOUS ADVERSE EVENTS (SAE)

Data on all adverse events grade 2 or greater regardless of relationship to study treatment will be collected from the start of study treatment on day 1 and will continue to be collected for 30 days after the last Cetuximab and radiation dose. Adverse events believed related to treatment with Cetuximab and/or radiation will continue to be collected for 3 years following end of study treatment, as outlined on the study calendar, and captured as Late Adverse Events. Serious adverse events will continue to be followed until resolution or clearly determined to be due to a patient’s stable or chronic condition or intercurrent illness(es). The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in this protocol. During the study, when there is a safety evaluation, the investigator or site staff will be responsible for detecting AEs and SAEs, as detailed in this section of the protocol.

17.1 Definitions

The definitions of adverse events (AEs) and serious adverse events (SAEs) are given below. The following definitions of terms are guided by the International Conference on Harmonization and the US Code of Federal Regulations and are included here verbatim. It is the responsibility of the principal investigator to ensure that all staff involved in the trial is familiar with the content of this section.

17.1.1 Adverse Events (AE)

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Examples of an AE include:

• Significant or unexpected worsening or exacerbation of the condition/indication under study.

• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity (grade) of the condition.

• New conditions detected or diagnosed after investigational product administration even though may have been present prior to the start of the study.

• Signs, symptoms, or the clinical sequelae associated with a suspected interaction of the investigational product with a concomitant medication.

• Signs, symptoms, or the clinical sequelae associated with a suspected overdose of either investigational product or a concurrent medication.

Any medical condition or laboratory abnormality with an onset date before initial Cetuximab administration is considered to be pre-existing in nature.

Any known pre-existing conditions that are ongoing at time of study entry, and any events of Grade 3 or 4 severity that occur up to 30 days before study entry (even if resolved prior to study entry) should be considered medical history and recorded in the appropriate section of the case report form.

All adverse events grade 2 or greater occurring from initial investigational product administration through 30 days following the last dose of Cetuximab and/or radiation must be recorded as an adverse event in the patient's source documents and on the CRF regardless of frequency, severity (grade) or assessed relationship to Cetuximab and/or radiation.

In addition to new events, any increase in the frequency or severity (i.e., toxicity grade) of a pre-existing condition that occurs after the patient begins Cetuximab and radiation is also considered an adverse event.

17.1.2 Serious Adverse Events (SAE)

A serious adverse event is an AE which occurs after the initial dose of Cetuximab, during treatment, or within 30 days of the last dose of cetuximab and/or radiation that fulfills one or more of the following criteria regardless of cause or assessed relationship to therapy.

Any untoward medical occurrence that at any dose:

- Results in death,

- Is life-threatening
NOTE: The term 'life-threatening' in the definition of 'serious' refers to any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

- Requires inpatient hospitalization or prolongation of hospitalization
NOTE: In general, hospitalization signifies that the patient or subject has been detained (usually involving at least an overnight stay) at the hospital for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE. Planned hospitalization for surgical procedures, either related or unrelated to the patients cancer is not considered a serious adverse event.

- Results in persistent or significant disability/incapacity
NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions.

-Is a congenital abnormality/birth defect.

Or

- Important medical events
Events which may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardized the patient or subject and may require medical or surgical intervention to prevent one of the

outcomes listed in this definition.

17.2 Adverse Event Reporting Requirements

17.2.1 All Serious Adverse Events

17.2.1.1 Serious Adverse Event Reporting
Serious adverse events reports are submitted via the MedWatch form or similar form. The MedWatch report must be submitted to the University of Michigan IRB and to the Principal Investigator. AEs reported as Serious Adverse Events must also be reported in routine study data submissions including the Data and Safety Monitoring Report, in addition to the IRB.

17.2.1.2 Serious Adverse Event Reporting Timeline

17.2.1.2.1 "Serious" adverse events which occur after the initial dose of Cetuximab, during treatment, or within 30 days of the last dose of Cetuximab or last fraction of radiation (including all deaths), MUST be reported immediately, i.e., within one day (24 hours) of being identified.

17.2.1.2.2 An initial written report of the serious adverse event must be prepared using the Medwatch or similar form, and submitted within 48 hours of awareness of event.

17.2.1.2.3 All fatal or life threatening serious adverse events must be reported IMMEDIATELY and then the initial SAE report submitted within 24 hours of awareness of event.

17.2.1.2.4 This report should provide a detailed description of the adverse event. Additional information (i.e. hospitalization records) will be submitted if requested by the IRB or other governing body, and include protocol number and patient assigned study number.

17.2.1.2.5 Copies of each report will be kept in the Investigator's File. The investigator will submit, on request, copies of all these reports to the relevant ethics committee.

17.2.1.2.6 Serious Adverse Event (SAE) Reporting Follow-up
Follow-up information will be submitted to the IRB following instructions above and within 7 days of becoming available.

17.2.2 Clinical Laboratory Abnormalities and Other Abnormal Assessments as AE's and SAE's

Abnormal laboratory findings (e.g., clinical chemistry and hematology) or

other abnormal assessments (e.g., ECGs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs if they meet the definitions as defined in Section 17.1. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the patient's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs. The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

17.2.3 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

"Lack of efficacy" per se will not be reported as an AE. The signs and symptoms or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the AE or SAE definition (including clarifications). Progressive disease found by scan or on clinical evaluation should be captured but not as an AE.

17.2.4 If a subject begins another therapy for their disease (outside of a surgical intervention to remove their disease), the patient will be considered off study and adverse events will no longer be collected on this subject.

17.2.5 Grading of Adverse Events

The severity of all adverse events and laboratory abnormalities will be graded according to the US National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0 (CTCAE).

17.3 Relationship to Cetuximab and Radiation

Related Event: Any adverse event that has a temporal relationship to the administration of the investigational drug or research intervention, follows a known or suspected pattern of response, and for which an alternative cause may not be present, is definitely, probably, or possibly associated with the investigational drug/agent. Investigator needs to judge relatedness and be prepared to justify the judgment.

• Definitely Related: The adverse event is clearly related to the investigational agent(s) or research intervention: the adverse event has a temporal relationship to the administration of the investigational agent(s) or research intervention, follows a known pattern of response, and no alternative cause is present.

• Possibly Related: There is a reasonable possibility that the event may have been caused by or is linked in a significant way to the research; the adverse event has a temporal relationship to the administration of the investigational agent(s) or research

intervention, follows a suspected pattern of response, but an alternative cause is present.

• Probably Related: The adverse event is likely related to the investigational agent(s) or intervention: the adverse event has a temporal relationship to the administration of the investigational agent(s) or research intervention, follows a known or suspected pattern of response, but an alternative cause may be present.

• Unlikely to be related: The adverse event is doubtfully related to the investigational agent(s) or intervention: the adverse event has a temporal relationship to the administration of the investigational agent(s) or research intervention, but follows no known or suspected pattern of response, and an alternative cause is present.

• Unrelated (or Not Related): The adverse event is clearly NOT related to the investigational agent(s) or intervention: the adverse event has no temporal relationship to the administration of the investigational agent(s) or research intervention, follows no known or suspected pattern of response, and an alternative cause is present.

Death: Deaths occurring within 30 days of the last study treatment are reportable events regardless of whether or not the investigators deem the death to be related to the study. If death occurs later than 30 days after the last study treatment AND the subject is still onstudy (i.e. subject would have had further follow-up or intervention/interaction had death not occurred), then the death may still be a reportable event. If the subject is NOT still on-study and there is no long-term follow-up, a late death does not need to be reported the IRBMED even if the investigator learns that the subject died.

18.0 DATA AND SAFETY MONITORING

This trial will be monitored in accordance with the NCI approved University of Michigan Comprehensive Cancer Center Data and Safety Monitoring Plan.

The study specific Data and Safety Monitoring Committee (DSMC), consisting of the protocol investigators, data manager or designee and other members of the study team involved with the conduct of the trial, will meet quarterly or more frequently depending on the activity of the protocol to provide continuous review of the data and patient safety. The discussion will include matters related to the safety of study participants (SAE/UaP reporting), validity and integrity of the data, enrollment rate relative to expectations, characteristics of participants, retention of participants, adherence to the protocol (potential or real protocol deviations) and data completeness.
At the regular DSMC meetings, the protocol specific Data and Safety Monitoring Report form will be completed. The report will be signed by the Principal Investigator or by one of the co-investigators.

Data and Safety Monitoring Reports will be submitted to the University of Michigan Comprehensive Cancer Center Data and Safety Monitoring Board (DSMB) on a quarterly basis for independent review.

19.0 QUALITY ASSURANCE AND AUDITS

The Quality Assurance Review Committee (QARC) of The University of Michigan Comprehensive Cancer Center (UMCCC) performs quality assurance audits of investigator-initiated clinical trials. Audits provide assurance that trials are conducted in compliance with the protocol. Further, they ensure that study data are collected, documented and reported in compliance with Good Clinical Practices (GCP) Guidelines and regulatory requirements.

A QARC audit of each clinical trial is conducted annually. Audits occur within the month of the study's initial IRB approval (provided the trial is open, and study accrual is greater than two subjects).

All audit findings are reported by QARC to the UMCCC Data and Safety Monitoring Board. These findings are followed-up by the DSMB until they have been resolved. The DSMB can also request QARC for a 'for cause' audit of the trial if the board identifies a need for a more rigorous evaluation of study-related issues. A regulatory authority (e.g. FDA) may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the principal investigator must immediately inform the Clinical Trials Office that such a request has been made.

20.0 STATISTICAL CONSIDERATIONS

20.1 Study Design

This is a Phase II trial of seven weeks RT+cetuximab for head and neck cancer in patients with good prognoses to determine if this treatment will be at least as effective as, but less toxic than, standard therapy. A total of 43 patients will be enrolled in order to obtain 36 patients that complete radiation treatment and have both biopsies taken. Thus, both the clinical primary endpoints and scientific secondary endpoints can be analyzed, as EGFR tumor information is useful for determining potential mechanisms of resistance to cetuximab. Based on the experience of UMCC 9921 and UMCC 2-21, accrual is expected to average one patient per month. To be considered evaluable, a patient must complete the full course of radiation/cetuximab. If radiation and/or cetuximab was stopped or modified due to toxicity, the patient is still evaluable. Inevaluable patients will be replaced.

20.2 Early Stopping Rules for Toxicity or Lack of Efficacy

In UMCC 9921 and UMCC 2-21, 2/32=6% of patients similar to those who will be treated in the current trial did not achieve tumor control. An early stopping rule will only be feasible for the identification of probability of treatment failure much higher than that. Table 1 describes the stopping rule for failure to control, which was derived using the method due to Thall, Simon and Estey [31], implemented in M.D. Anderson program multc98. **Failure is defined as local-regional recurrence or metastasis, but not second primary cancer, nor microscopic disease found in elective neck dissection, nor PET findings without correlative clinical evidence of disease persistence or recurrence.** For each number of patients enrolled, if *at least* as many failures as stated occurs (e.g., 2/5), accrual will be stopped. The rule was constructed to stop the trial if the probability that the failure rate of the experimental therapy exceeded 0.1625 (0.1 more than the historical rate) is at least 0.75.

# Patients	# Failures
5	2
10	3
15	4
20	5
25	6
30	7

Table 1 Stopping rule for failure to control tumor

Because the trial will only be stopped early for failure, and the stopping rule does not constitute an interim analysis, there will be no adjustment to the p-values of the analyses in Section 20.4.

20.3 Analysis Plan

20.3.1 Primary Objectives

20.3.1.1 *To confirm that reducing treatment intensity in non-smoking patients with HPV-related oropharyngeal cancer does not significantly increase the proportion of patients whose tumors recur, compared to our previous experience in similar patients receiving standard-intensity chemo-RT.*

The primary index of recurrence will be the proportion of patients who have local recurrence, distant metastases or second primaries (secondary analyses will be performed on each of these endpoints individually) within two years of the end of treatment. In the primary analysis, *null* hypothesis that the proportion of patients who fail is *greater* than 0.20 will be tested using an exact binomial test (at significance level a=0.20). The proportion of patients who recur will be calculated, with a 95% exact binomial confidence interval.

20.3.1.2 *To compare the toxicity in patients receiving reduced intensity treatment to similar patients treated with 7 weeks of chemotherapy concurrent with RT ("standard therapy') in UMCC 2-21.*

Dysphagia and mucositis are measured on continuous scales; there are both observer and patient reports. The null hypothesis of no difference in dysphagia and mucositis at three, twelve and twenty-four months posttreatment between the reduced-intensity therapy versus UMCC 2-21 will be tested (a=0.20) in a repeated measures analysis of covariance. In addition, the statistical significance of the difference between the current trial and UMCC 2-21 in the proportions of patients experiencing clinically significant (NCI CTCAE Grade 3 or worse) toxicities will be assessed using Fisher's exact test

(a=0.20).

20.3.2 Secondary Objectives

20.3.2.1 *To characterize the changes tumor EGFR, pEGFR, downstream signaling following a loading dose of cetuximab.*

Markers to be analyzed include, but are not limited to, EGFR and pEGFR. Some are measured on a continuous scale, and some on an ordinal scale. Continuous scale variables will be expressed as percent change from baseline, and the distribution will be characterized graphically (e.g., boxplot) and by descriptive statistics. After possible transformation (e.g., logarithmic), a single sample t-test will be used to evaluate the null hypothesis that the mean change equals 0. The percent change will be related to tumor control, progression-free survival, and the various assessments of toxicity by linear regression, logistic regression, or proportion hazards (Cox) regression, as appropriate. Ordinal scale variables will be expressed as difference from baseline, followed by a similar analysis plan to relate the differences to clinical outcomes. Because this is a secondary objective, all of the analyses will be guided by descriptive displays of the data.

20.3.2.2 *Compare normal mucosa EGFR to EGFR in the tumor sample.*

Repeated measures linear models will be used to characterize the change in differences between normal mucosa and tumor EGFR across the loading dose of cetuximab and determine if there are significant demographic or clinical variables that affect that change.

20.3.2.3 *To explore if baseline EGFR, BclxL, p.53 and p16 tumor expression are related to treatment response.*

The distributions of these markers in all patients, and in patients who do and do not respond, will be characterized by descriptive statistics (e.g., mean, median) and graphics (for example, boxplots). Because the number of treatment failures is likely to be small, these analyses will be considered strictly exploratory.

20.4 Justification of Design

20.4.1 Early stopping rule for tumor control

The operating characteristics of the stopping rule were analyzed using the simulation tool in multc98. The probability the trial will be stopped early, and the distribution of the expected sample sizes, was calculated under the

assumption that the true probability of failure varied from 0.06 to 0.6. The operating characteristics are displayed in Table 2. For instance, if the true probability of failure equaled 0.2, 0.59 of the trials stopped early, 50% of the trials stopped after accruing 20 or fewer patients, and 25% of the trials stopped after accruing five or fewer patients.

		Sample Size Percentiles				
True P(Failure)	P(Stop Early)	10	25	50	75	90
0.06	0.05	35	35	35	35	35
0.2	0.59	5	5	20	35	35
0.3	0.91	5	5	10	15	30
0.4	0.99	5	5	5	10	15
0.5	0.99	5	5	5	5	19

Table 2 Operating characteristics of stopping rule for treatment failure

20.4.2 Power of primary analysis endpoints

20.4.2.1 The ultimate goal of this research program is to conduct a randomized noninferiority trial to demonstrate that reducing the intensity of therapy in low-risk patients reduces the probability of toxicity while not increasing the probability of tumor recurrence. Such a trial will require hundreds of patients and will be possible only in the cooperative group setting. The purpose of this Phase II trial is to provide preliminary evidence that reduced intensity therapy is practical, and to provide initial evidence of efficacy and toxicity that can be used to design such a trial. The use of the relatively high significance level (a=0.2) is not uncommon in early Phase II (e.g., Simon two-stage) trials with limited sample sizes. Out of 33 non-smoking HPV+ patients in the UMCC 2-21 reference set, three patients have died disease-free, and one patient has died from distant metastases. One additional patient in this group has developed a second primary tumor in the oral cavity. All other patients are alive and disease-free. Because the number of events is low, a time-to-event analysis is impractical, and analyses for sub-populations are also unlikely. Because the power will be modest even if the observed failure rates are 2-3 times the control rate, this trial will not definitively test that reduced intensity treatment is as effective as standard chemoradiation, but, if successful, will accrue sufficient data to motivate a true non-inferiority trial.

20.4.2 The power calculations for the toxicity endpoints (Primary Objective 2) will be represented by dysphagia, which is considered the most important. In UMCC 2-21, the patient-reported eating domain score of the HNQOL instrument increased from 10.5±14.9 (mean±standard deviation) pre-RT to 25.7+18.9 twelve months after treatment. Videofluoroscopy scores increased from 2.37±1.35 pre-RT to

3.7±1.18 twelve months after treatment. The power of the repeated measures analysis for Primary Objective 2 for these endpoints was assessed by Monte Carlo simulation as the mean twelve month value was reduced from the twelve-month level in UMCC 2-21 (0% decrease) to the baseline UMCC 2- 21 level (100% decrease).

20.4.3 The hypothesis test for Primary Objective 2 will have at least 80% power for the video fluoroscopy score if the reduced intensity treatment achieves a decrease in dysphagia of 58% or greater compared to UMCC 2-21. The power is somewhat lower for the HNQOL assessment.

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APPENDIX A

KARNOFSKY PERFORMANCE SCALE

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

APPENDIX B

QUALITY OF LIFE QUESTIONNAIRES

Quality of Life Questionnaire

UMCC 2009.078

Study ID # _____ **Initials _____**

Completed By: _____ **Date Completed_____**

Each of the following items lists different numbered statements. Think about what each statement says, then place a circle around the one statement that most closely describes how you have been feeling during the past week, including today. Please circle only one statement for each item.

I. PAIN (General)

A. General

10 I have no pain.
20 There is mild pain not needing medication.
30 I have moderate pain--requires regular medication (codeine or non-narcotic). 40 I have severe pain controlled only by narcotics.
50 I have severe pain not controlled by narcotics.

B. Mouth

10 I have no pain in my mouth.
20 I have mild pain but it is not affecting my eating.
30 I have moderate pain which is affecting my eating.
40 I have severe pain and need medication in order to eat.
50 I have severe pain and cannot eat even with the medication.

C. Throat

10 I have no pain in my throat.
20 I have mild pain but it is not affecting my eating.
30 I have moderate pain which is affecting my eating.
40 I have severe pain and need medication in order to eat.
50 I have severe pain and cannot eat even with the medication.

II. DISFIGUREMENT

10 There is no change in my appearance.
20 The change in my appearance is minor.
30 My appearance bothers me but I remain active.
40 I feel significantly disfigured and limit my activities due to my appearance.
50 I cannot be with people due to my appearance.

III. ACTIVITY

10 I am as active as I have ever been.
20 There are times when I can't keep up with my old pace, but not often.
30 I am often tired and I have slowed down my activities although I still get out. 40 I don't go out because I don't have the strength.
50 I am usually in a bed or chair and don't leave home.

IV. RECREATION/ENTERTAINMENT

10 There are no limitations to recreation at home and away from home.
20 There are a few things I can't do but I still get out and enjoy life.
30 There are many times when I wish I could get out more but I'm not up to it.
40 There are severe limitations to what I can do, mostly I stay home and watch T.V.
50 I can't do anything enjoyable.

V. EMPLOYMENT

10 I work full time.
20 I have a part time but permanent job.
30 I only have occasional employment.
40 I am unemployed.
50 I am retired (circle one below)
51 not related to cancer treatment
52 due to cancer treatment

VI. EATING

A. Chewing

10 I can chew as well as ever.
20 I have slight difficulty chewing solid foods.
30 I have moderate difficulty chewing solid foods.
40 I can only chew soft foods.
50 I cannot chew soft foods.

B. Swallowing

10 I swallow normally
20 I cannot swallow certain solid foods.
30 I can only swallow soft foods.
40 I can only swallow liquid foods.
50 I cannot swallow.

VII. SALIVA

A. Amount

10 I have a normal amount of saliva
20 I have a mild loss of saliva
30 I have a moderate loss of saliva.
40 I have a severe loss of saliva.
50 I have no saliva.

B. Consistency

10 My saliva has normal consistency.
20 My saliva is slightly thicker.
30 My saliva is moderately thicker.
40 My saliva is extremely thicker.
50 I have saliva that dries in my mouth and/or on my lips.

VIII. TASTE

10 I can taste food normally.
20 I can taste most food normally.
30 I can taste some foods normally.
40 I can taste few foods normally.
50 I cannot taste any foods normally.

IX. SPEECH

10 My speech is the same as always.
20 I have difficulty with saying some words, but can be understood over the phone.
30 I have moderate difficulty saying some words, and cannot use the phone.
40 Only family and/or friends can understand me.
50 I cannot be understood.

X. MUCUS OR PHLEGM

A. Amount

10 I have a normal amount of mucus.
20 I have a mild amount of mucus
30 I have a moderate amount of mucus.
40 I have a severe amount of mucus.
50 I have no mucus.

B. Consistency

10 My mucus has normal consistency
20 My mucus is slightly thicker
30 My mucus is moderately thicker
40 My mucus is extremely thicker
50 I have no mucus

Comments: _____

_____
_____
_____
_____
_____
_____
_____
_____
_____

Study ID # _____ **Initials _____**

Completed By: _____ **Date Completed_____**

Below are several questions that will help describe the dryness in your mouth and how that dryness affects your daily life. Please encircle the number that corresponds to your condition during the last week in each of the following questions:

1. Rate the discomfort of our dentures due to dryness (if you do not wear dentures please check____)

0 1 2 3 4 5 6 7 8 9 10

Comfortable Extreme discomfort

2. Rate the difficulty you experience in speaking due to dryness of your mouth and tongue:

0 1 2 3 4 5 6 7 8 9 10

Easy Extremely Difficult

3. Rate the difficulty you experience in chewing food due to dryness:

0 1 2 3 4 5 6 7 8 9 10

Easy Extremely Difficult

4. Rate the difficulty you experience in swallowing food due to dryness:

0 1 2 3 4 5 6 7 8 9 10

Easy Extremely Difficult

5. Rate the dryness your mouth feels when eating a meal:

0 1 2 3 4 5 6 7 8 9 10

No Dryness Extremely Dryness

6. Rate the dryness in your mouth while **not** eating or chewing:

0 1 2 3 4 5 6 7 8 9 10

No Dryness Extremely Dryness

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

0 1 2 3 4 5 6 7 8 9 10

None required Extremely Frequent

8. Rate the frequency of fluid intake required for oral comfort when not eating:

0 1 2 3 4 5 6 7 8 9 10

None required Extremely Frequent

9. Rate the frequency of sleeping problems due to dryness:

0 1 2 3 4 5 6 7 8 9 10

None Extremely Frequent

10. Does your mouth feel dry when eating a meal? Yes/No

11. Are you thirsty? Yes/No

12. Does the amount of saliva in your mouth seem to be:

_____Too little
_____Too much
_____Don't notice it

13. Do you have difficulties swallowing any food? Yes / No

14. Do you sip liquids to aid in swallowing dry food? Yes / No

15. Have you smoked in the last week? Yes / No

If yes, how many packs? _____

16. Do you drink alcohol more than twice a week? Yes / No

17. Do you have any medical problem/disease for which you take medication? Yes /No

Which pills/medication do you take?

UMCC 2009.078

Study ID # _____ **Initials _____**

Completed By: _____ **Date Completed_____**

INSTRUCTIONS: This survey is designed to assess how much you are bothered by your Head and Neck condition and/or treatment. Please answer every question by marking one box. If you are unsure about how to answer, please give the best answer you can.

1. As a result of your head and neck condition or treatment, over the past FOUR WEEKS how much have you been BOTHERED by your…

	Not at all	Slightly	Moderately	A lot	Extremely
A. Ability to talk to other people	☐	☐	☐	☐	☐
B. Ability to talk on the phone	☐	☐	☐	☐	☐

2. As a result of your head and neck condition or treatment, over the past FOUR WEEKS how much have you been BOTHERED by problems with…

	Not at all	Slightly	Moderately	A lot	Extremely
A. Volume of your voice	☐	☐	☐	☐	☐
B. Clarity of your voice	☐	☐	☐	☐	☐
C. Difficulty opening your mouth	☐	☐	☐	☐	☐
D. Dryness in your mouth while eating	☐	☐	☐	☐	☐
E. Chewing food (for example, pain, difficulty opening or closing your mouth, moving food in your mouth, or teeth or denture problems)	☐	☐	☐	☐	☐
F. Swallowing liquids	☐	☐	☐	☐	☐
G. Swallowing soft foods and/or solids	☐	☐	☐	☐	☐
H. Your ability to taste food (For example, loss of taste, and/or loss of appetite due to poor taste)	☐	☐	☐	☐	☐

I. Pain, burning, and/or discomfort in your mouth, jaw, or throat ☐ ☐ ☐ ☐ ☐

J. Shoulder or neck pain ☐ ☐ ☐ ☐ ☐

3. Over the past FOUR WEEKS, how often did you take pain medication?...

Never	Rarely	Sometimes	Frequently	Always
☐	☐	☐	☐	☐

4. Over the past FOUR WEEKS how much have you been bothered by…

	Not at all	Slightly	Moderately	A lot	Extremely
A. Concerns or worries about your appearance related to your head and neck condition or treatment	☐	☐	☐	☐	☐
B. Emotional problems related to your head and neck condition or treatment	☐	☐	☐	☐	☐
C. Embarrassment about your symptoms	☐	☐	☐	☐	☐
D. Frustration about your condition	☐	☐	☐	☐	☐
E. Financial worries due to medical problems	☐	☐	☐	☐	☐
F. Worries that your condition will get worse	☐	☐	☐	☐	☐
G. Physical problems related to your head and neck condition	☐	☐	☐	☐	☐

5. Were you working (employed) prior to being diagnosed with cancer? Yes ☐ No ☐ **If no, go to question 6**

5A. If yes, did your doctor declare you unable to work due to your head and neck condition or treatment? Yes ☐ No ☐

6. Have there been other problems related to your head and neck condition that were not mentioned? If so, please write them in the space below and tell us how much this problem has bothered you. (For instance, if your treatment included surgical transfer of tissue from a donor site to the head and neck, does the donor site bother you)

	Not at all	Slightly	Moderately	A lot	Extremely
A. _____	☐	☐	☐	☐	☐
B. _____	☐	☐	☐	☐	☐
C. _____	☐	☐	☐	☐	☐

7. For the past FOUR WEEKS, please rate your OVERALL amount of disturbance or BOTHER as a result of your head and neck cancer condition?	☐	☐	☐	☐	☐
8. Overall how satisfied are you with your Head and Neck cancer care at this Hospital?	☐	☐	☐	☐	☐

9. Overall how would you rate your response to treatment?

Poor	Fair	Good	Very Good	Excellent
☐	☐	☐	☐	☐

10. Approximately how long did it take you to answer this questionnaire? _____ Minutes

	Not at all	Slightly	Moderately	A lot	Extremely
11. How difficult was it to complete this questionnaire?	☐	☐	☐	☐	☐