Mayo Clinic Cancer Center

MC1273, Phase II Evaluation of Adjuvant Hyperfractionated Radiation and Docetaxel for HPV Associated Oropharynx Cancer

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Drug Availability

Commercial Agents: *Docetaxel (Taxotere)*

√Study contributor(s) not responsible for patient care.

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Protocol Resources

Questions:	Contact Name:
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Protocol document, consent form, regulatory issues	[redacted], Research Protocol Specialist Phone: [redacted] Email: [redacted]
Adverse Events (AdEERS, MedWatch, Non-AER, AML/MDS)	[redacted], SAE Coordinator Phone: [redacted] E-mail: [redacted]

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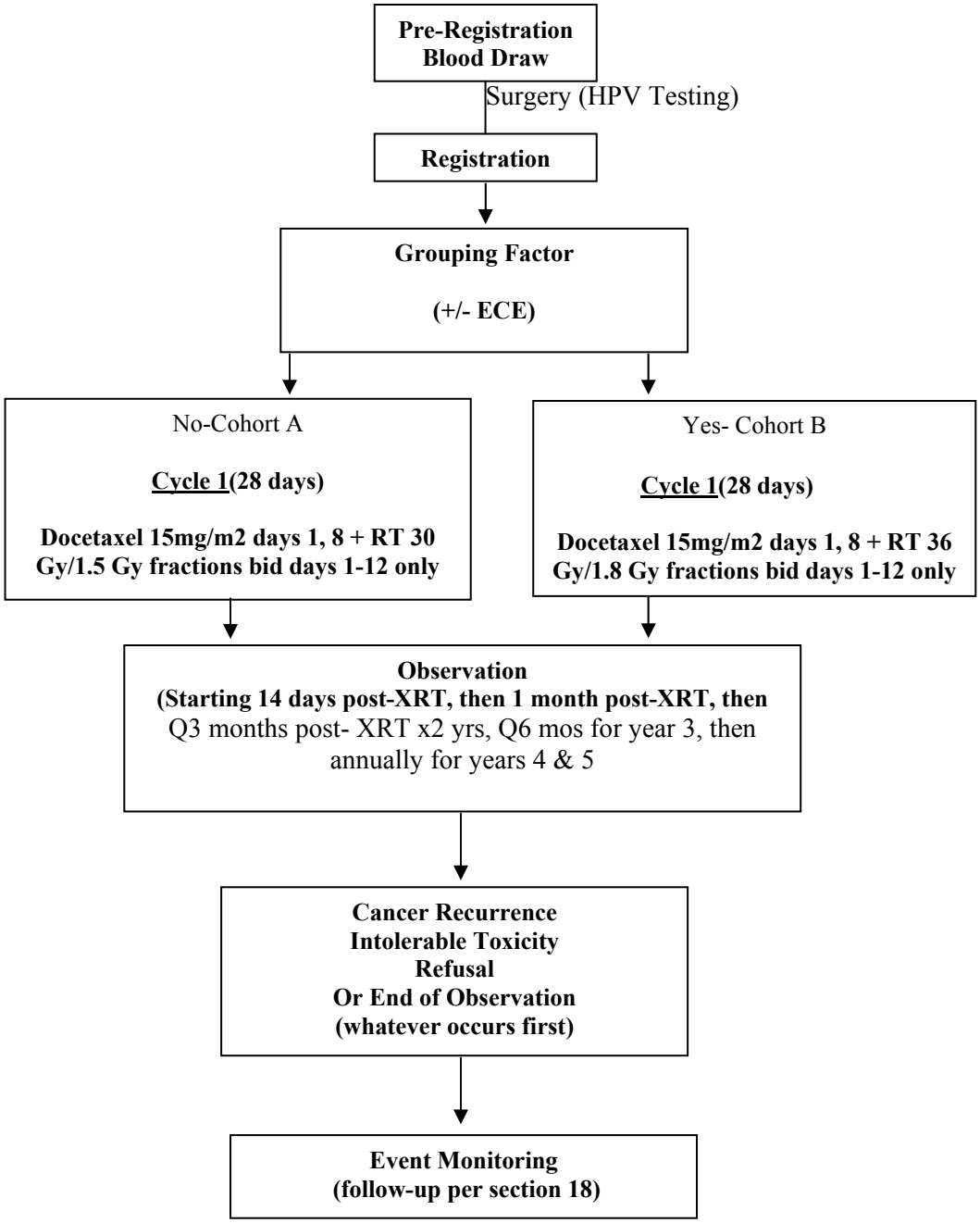
Schema



If a patient is deemed ineligible or a cancel, please refer to Section 13 for follow-up information.

Generic name: Docetaxel Mayo abbreviation: Taxotere Availability: Commercially available

1.0 Background

1.1 Oropharynx Cancer: Current State of Practice and Purpose of this Trial

Several treatment modalities are available for patients with oropharyngeal cancer, including definitive surgery, definitive radiotherapy, and chemoradiation. After definitive surgery, certain factors place patients at increased risk for disease recurrence. These patients receive either adjuvant radiotherapy or adjuvant chemoradiotherapy. Advances in both systemic and radiation therapy in the adjuvant setting have been associated with improved survival and local control.

Adjuvant treatment comes at the cost of increased acute and late toxicity. Furthermore, it is unclear if recent improvements in outcome can be completely attributed to the aggressiveness of adjuvant care. The recent rise in the incidence of oropharyngeal cancers associated with human papilloma virus (HPV) have prompted a re-evaluation of past trial outcomes. HPV associated oropharyngeal cancers have been demonstrated to be more chemo and radiation sensitive compared to non-HPV related tumors. Large phase II/III studies which evaluate less morbid treatment approaches for definitive chemoradiation in HPV-associated patients are currently ongoing. However, clinical trials designed for patients in the post-surgical setting are lacking.

The overall goal of this trial is to identify a less toxic approach to HPV-associated cancers of the oropharynx while preserving the high survival currently associated with aggressive adjuvant radiation courses. We first aim to demonstrate the feasibility of a novel adjuvant therapy course using low-dose, hyperfractionated radiation with concurrent docetaxel. We also aim to show that low-dose, hyperfractionated chemoradiation will substantially reduce the burden of acute toxicity, result in faster recovery, carry lower rates of late effects, with similar rates of long-term survivorship compared with historical results from standard adjuvant care.

1.2 Role of HPV in Oropharyngeal Cancers

HPV-associated cancers have been shown to be distinct from HPV-negative cancers in regards to risk factor profiles, molecular characteristics, treatment response, and prognosis. In a meta-analysis of retrospective studies, HPV-associated oropharynx cancer had an estimated 50% reduction in risk of death when compared to patients with HPV-negative tumors. (Dayyani F, Etzel CJ, Liu M*, et al.*) This may be due to the fact that HPV-associated tumors are more responsive to chemotherapy and radiation. In an ECOG trial prospectively evaluating the effect of tumor HPV status, HPV-associated tumors were found to have a higher response rate to induction paclitaxel and carboplatin when compared to HPV-negative tumors. (Fakhry C, Westra WH, Li S*, et al.*) Similarly, an analysis on survival outcomes in RTOG 0129, a randomized trial where patients received accelerated versus standard fraction radiotherapy, patients who were HPV-associated had a 51% reduction in risk of progression or death compared to HPV-negative patients. Among HPV-associated patients, there is a further stratification of outcome based upon smoking status. In a further sub-group analysis of RTOG 0129, HPV-associated patients who had <10 pack-year smoking history were found to have a 3 year OS of 93% compared with a 70.8% OS among HPV-associated patients with a >10 pack-year smoking history. (Ang KK, Harris J, Wheeler R*, et al.*)

Given these excellent results, two large clinical trials are currently investigating whether HPV-associated patients can be spared the long-term complications of intensive, multimodal therapy without compromising their survival. RTOG 1016 is a Phase III trial that randomizes HPV-related oropharyngeal patients to receive definitive chemoradiation consisting of 70 Gy in 2 Gy fractions delivered over 6 weeks with cisplatin vs cetuximab. ECOG 1308 is a phase II trial that uses induction chemo followed 54 Gy in 2 Gy fractions with cetuximab if patients have a complete response to induction. Patients with partial response receive the standard dose of 70 Gy with cetuximab.

Though RTOG 1016 and ECOG 1308 both address the issue of treatment de-escalation for HPV-associated oropharynx patients, both trials are testing de-escalation in the setting of definitive chemoradiation. There currently are no large trials testing equivalent strategies for de-escalating radiation for post-operative patients. Whether HPV-associated patients could benefit from milder treatment in the post-operative setting is now a highly relevant clinical question.

1.3 Adjuvant Radiation Therapy: Risk factors and Dose

Previous retrospective trials have highlighted risk factors that place patients at increased risk for local recurrence and death after definitive surgery. (Lundahl RE, Foote RL, Bonner JA*, et al.*) These risk factors include positive margins, extracapsular extension of tumor from a lymph node (ECE), number of involved lymph nodes, lymph nodes larger than 3 cm, lymphvascular space invasion (LVSI), close margins, and perineural invasion (PNI).

For patients with positive margins or extracapsular extension, adjuvant radiation therapy plus concurrent cisplatin has historically been the standard of care. These risk factors were identified as high risk on a meta-analysis of the two largest randomized trials addressing adjuvant radiotherapy (RTOG 9501 and EORTC 22931.) (Bernier J, Cooper JS, Pajak TF*, et al.)* In this analysis, patients with ECE or positive margins had a benefit to local control and overall survival from high dose chemoradiation. In this joint analysis, however, the addition of chemotherapy to adjuvant radiotherapy did not improve overall survival in patients with intermediate risk factors such as 2+ lymph nodes, PNI, LVSI, or Stage III-IV disease.

The optimal implementation of adjuvant radiotherapy in patients with only intermediate risk factors is less clear. Only one prospective randomized trial opened in 1983 has investigated the post-operative radiation dose for these patients. (Kokal WA, Neifeld JP, Eisert D, *et al.*) This study was limited by using outdated treatment techniques (^{60}Co machines) in a patient era that was pre-HPV. Despite these limitations, the control rate for the neck in patients with intermediate risk factors was 89% with doses between 52.2-54.0 Gy. The current standard of care for adjuvant radiation alone is a dose of 60-66 Gy. This is based upon the control arm of the EORTC/RTOG trials, not prospective data.

The use of ECE as a high risk factor for adjuvant therapy is also unclear in the HPV era. Both RTOG 9501 and EORTC 22931 were conducted in an era where oropharynx cancer was mostly secondary to smoking and alcohol, rather than HPV. A recent large, multi-institutional retrospective analysis on HPV-associated patients, for example, demonstrated that ECE was a poor predictor of disease recurrence after surgery in the

modern era (Lewis JS, Carpenter DH, Thorstad WL, et al.) These data have been the foundation for the ADEPT trial, an ongoing treatment de-escalation trial for post-surgical, HPV-associated patients with positive ECE. However, the treatment de-escalation in ADEPT is restricted to chemotherapy (radiotherapy plus/minus cisplatin) and does not the address the question of radiation de-escalation.

1.4 Toxicity of Standard Adjuvant Treatment

Adjuvant radiotherapy is associated with acute and late toxicities that significantly impact a patient's quality of life. When looking at acute reactions on EORTC 22931, adjuvant radiation alone was associated with a 21% rate of severe, grade 3+ mucositis, a 20% risk of severe xerostomia, and a 5% risk of grade 3+ muscular fibrosis. These acute reactions also translated into late complications. The rate of late, severe xerostomia was 22% while the rate of severe muscular fibrosis was 5%. Similar numbers were also seen in RTOG 9501. In this trial, 34% of patients receiving adjuvant radiotherapy alone had an acute adverse effect of grade 3 or higher while 17% of the radiotherapy alone group had severe late adverse effects.

The etiology of these acute and late complications is well known. Radiation complications are related both to the total dose received by normal structures, and the size of each individual radiation fraction. The radiation dose limits for a variety of normal tissues within the head and neck have been previously documented. For example, a mean radiation dose of 26 Gy to a parotid gland has a 20% risk of rendering the organ non-functional, while a mean dose of 50 Gy to the pharyngeal constrictors carries a 20% risk of long-term dysphagia and aspiration. (Eisbruch A, Ten Haken RK, Kim HM*, et al.*) (Blanco AI, Chao KS, El Naqa I*, et al.*) (Kuhnt T, Jirsak N, Muller AC*, et al.*) (Levendag PC, Teguh DN, Voet P*, et al.*) (Debelleix C, Pointreau Y, Lafond C*, et al.*) Since these normal structures directly abut against areas standardly treated to 60 Gy, it is often impossible to keep these normal structures below their radiation dose constraints. Furthermore, using twice-daily fractionation with smaller radiation doses has been previously demonstrated to decrease toxicity in head and neck patients. Thus an adjuvant therapy strategy that utilizes both decreased total radiation dose, and twice daily fractionation is expected to have a large impact on patient quality of life.

1.5 Preliminary Data: Increased treatment sensitivity of HPV+ tumors

Cell and animal studies have detailed the increased sensitivity of HPV-associated tumors to both radiation and chemotherapy. Cell lines containing E6 isoforms associated with HPV have an eightfold reduction in surviving cells fraction after receiving 10 Gy of radiation when compared to cell lines containing non-HPV related isoforms. (Pang E, Delic NC, Hong A*, et al.*) In vitro studies of HPV-associated tumors implanted within immunocompetent mice have demonstrated complete clearance of tumor with 20 Gy of treatment while the HPV-negative counterparts demonstrated persistent growth after 20 Gy. The sensitivity of HPV-associated tumors was also seen with cisplatin in this study. Cisplatin in vivo cleared HPV-associated tumors but not HPV-negative tumors. (Pradier O, Rave-Frank M, Lehmann J*, et al.*) Collectively, these data support the hypothesis that patients with HPV-associated tumors do not require as much chemotherapy nor radiotherapy for complete disease clearance.

1.6 Selection of Chemoradiation Dose

The doses and schedule for chemoradiation were chosen based upon the results of prior and current multi-institutional studies. Docetaxel at 15 mg/m2 was used as part of a radiosensitizing regimen in RTOG 0234 with a milder toxicity profile compared to cisplatin. Preliminary results also suggest that docetaxel may have a greater radiosensitizing effect when compared with cisplatin. (Le QT, Raben D. *et al.*)

The radiation dose of 30-36 Gy in 1.5-1.8 Gy fractions b.i.d. was selected to be proportionally equivalent to the degree of dose reduction seen for HPV-status and treatment acceleration seen on past and current multi-institutional clinical trials. Using the linear quadratic model for determining a biologically equivalent dose (where n = # fractions, d = fractional dose, and $\alpha/\beta = 10$):

$$BED = nd\left(1+\frac{d}{\alpha/\beta}\right)$$

yields that 30 Gy in 1.5 Gy fractions is equivalent to **34.5 Gy_{10}**. (Hall EJ, Giaccia AJ., *et al.*)

Concerning HPV-status, ECOG 1308 is an ongoing multi-institutional trial for definitive treatment of HPV-associated oropharyngeal cancers. The standard of care for treating definitive oropharyngeal cancers is 70 Gy in 2 Gy fractions (84 Gy_{10}) with concurrent cisplatin. On ECOG 1308, patients receive induction chemotherapy followed by 54 Gy in 2 Gy fractions (64.8 Gy_{10}) with concurrent cetuximab. (Peres J.) This translates into a 23% dose reduction in chemoradiation compared with standard of care due to HPV-positivity.

Concerning accelerated radiation, a multi-institutional trial run by the University of Chicago (9502b) used 39 Gy in 1.5 Gy b.i.d. fractions (44.85 Gy_{10}) for microscopic disease while the standard dose for microscopic disease is 54 Gy in 1.8 Gy fractions (63.72 Gy_{10}.) (Haraf DJ, Rosen FR, Stenson K, *et al.*) This translates into a 29% dose reduction compared with standard of care due to treatment acceleration.

Combining the dose reduction due to HPV-positivity and treatment acceleration yields a dose reduction of 52% compared to standard of care. A dose reduction of 52% on the standard of care dose of 60 Gy in 2 Gy fractions (72 Gy_{10}) is equal to **34.56 Gy_{10}**, a figure essentially equivalent to 30 Gy in 1.5 Gy fractions bid.

In terms of normal tissue toxicity (using an $\alpha/\beta = 3$), 30 Gy in 1.5 Gy fractions is equal to 45 Gy_3. This compares favorably to the equivalent normal tissue dose of the standard post-operative dose (60 Gy in 2 Gy fractions), which is 100 Gy_3.

1.7 QOL Evaluation

Quality of life will be measured using previously validated metrics and compared to a prospective cohort of similar patients under standard treatment. Acute effects will be assessed weekly during treatment using the CTCAE version 4. After the completion of radiation and chemotherapy, the patient will receive clinical follow-up including physical

examination, flexible nasopharyngoscopy, and late effect assessment (xerostomia with the University of Michigan Inventory, dysphagia with the MD Anderson Dysphagia Inventory, quality of life with the Performance Status Scale for Head and Neck) every 3 months for the first two years.

A baseline swallowing assessment consisting of a videofluroscopic examination, including a modified barium swallow study, and an esophagogram will be performed by Speech Therapy after surgery, before the initiation of radiation. Swallowing will be scored (yes, no) for aspiration, penetration, velopharyngeal incompetence, epiglottic everson, tongue base retraction, and pharyngeal swallow response using metric outlined by Eisbruch et al. (Eisbruch A, Teresa L, Bradford CR, *et al.*) A swallowing assessment will be performed by Speech Therapy after surgery, before the initiation of radiation, and will be repeated at one month and 12 months after the completion of protocol treatment

2.0 Goals (same for each cohort)

2.1 Primary

2.11 To assess the cumulative incidence of local/regional failure at 2 years after study registration.

2.2 Secondary

2.21 To characterize the rate of acute grade 3 or higher functional mucosal adverse events (up to 1 month post-XRT) associated with adjuvant docetaxel + hyperfractionated radiotherapy (key secondary endpoint).

2.22 To assess changes in overall survival, disease-free survival, distant failure rates, and quality of life (QOL) associated with adjuvant docetaxel and hyperfractionated radiation. The QOL measures will include an evaluation of swallowing, xerostomia, and mucositis.

2.23 To characterize other acute adverse events (up to 1 month post-XRT) and late grade 3 or higher non-hematologic adverse events (up to 2 years post-XRT) associated with adjuvant docetaxel + hyperfractionated radiotherapy.

2.3 Correlative Research –

2.31 To determine the genetic alterations of oropharynx tumor specimens and the detection rate of corresponding cfDNA in the pre-surgical, post-surgical, and post-radiation blood of oropharynx cancer patients.

3.0 Patient Eligibility

3.1 Pre-Registration

3.11 Provide written informed consent

3.12 Submission of research blood draw to be stored until after surgical resection of the primary tumor and confirmation of HPV positivity (Mayo Clinic Rochester patients only)

3.13 Patients with oropharynx carcinoma with a smoking history of < 10 pack-year or equivalent 10 year history of tobacco product use and no recent history (within last 5 years) of tobacco use.

3.2 Registration – Inclusion Criteria

3.21 Age ≥ 18 years.

3.22 Histological confirmation of HPV+ squamous cell carcinoma of the oropharynx. HPV positivity will be defined as positive staining for p16 on IHC.

3.23 Gross total surgical resection with curative intent of the primary tumor and at least unilateral neck dissection within 7 weeks of registration.

3.24 ECOG Performance Status (PS) 0 or 1 (Appendix I)

3.25 Smoking history < 10 pack years or equivalent 10 year history of tobacco product use.

3.26 Absence of distant metastases on standard diagnostic work-up ≤ 10 weeks prior to registration. (Chest CT, CXR, PET/CT, etc…)

3.27 Must have one of the following risk factors:
- Lymph node > 3 cm
- 2 or more positive lymph nodes
- Perineural invasion
- Lymphovascular space invasion
- T3 or microscopic T4a primary disease
- Lymph node extracapsular extension

3.28 The following laboratory values obtained ≤14 days prior to registration.
- Absolute neutrophil count (ANC) ≥1500/mm^3
- Platelet count ≥100,000/mm^3
- Hemoglobin ≥9.0 g/dL
- Direct bilirubin within upper limit of normal (ULN)
- Creatinine ≤ ULN x 1.5

3.29a Negative pregnancy test done ≤7 days prior to registration, for women of childbearing potential only.

3.29b Ability to complete questionnaire(s) by themselves or with assistance.

3.29c Provide informed written consent.

3.29d Willingness to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

3.3 Registration – Exclusion Criteria

3.31 Any significant tobacco history within the past five years.

3.32 Any of the following because this study involves an agent that has known genotoxic, mutagenic and teratogenic effects:

- Pregnant women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception

3.33 Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

3.34 Immunocompromised patients and patients known to be HIV positive.

3.35 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.36 Receiving any other investigational agent which would be considered as a treatment for the primary neoplasm.

3.37 Other active malignancy ≤ 5 years prior to registration. EXCEPTIONS: Non-melanotic skin cancer or carcinoma-in-situ of the cervix. NOTE: If there is a history or prior malignancy, they must not be receiving other specific treatment for their cancer.

3.38 History of myocardial infarction ≤ 180 days prior to registration, or congestive heart failure requiring use of ongoing maintenance therapy for life-threatening ventricular arrhythmias.

3.39 Prior history of radiation therapy to the affected site.

3.39a History of connective tissue disorders such as rheumatoid arthritis, lupus, or Sjogren's disease.

3.39b Presence of any of the following risk factors after surgery:

- Any positive surgical margin.
- Adenopathy below the clavicles

3.39c Prior systemic chemotherapy for the study cancer. NOTE: Prior chemotherapy for a different cancer is allowable.

3.39d History of allergic reaction to docetaxel.

3.39e Receiving any medications or substances that are **strong or moderate inhibitors** of CYP3A4 (for a listing of medications or substances see Appendix IV).

Use of strong or moderate inhibitors is prohibited ≤ 7 days prior to registration.

3.39f Receiving any medications or substances that are **inducers** of CYP3A4 (for a listing of medications or substances see Appendix IV).
Use of inducers is prohibited ≤ 12 days prior to registration.

4.0 Test Schedule

Assessments, tests and procedures	Pre-reg (prior to surgery)	**Pre-Treatment**		**Active Monitoring**		**Active Monitoring Observation**			
		≤ 10 weeks prior to registration	≤ 2 weeks prior to registration	Weekly **(+/- 3 days)**	As clinically indicated	At 14 days post-XRT	At 1 mo. post-XRT	Q3 months post- XRT x2 yrs q6 mos for year 3, then annually for years 4 & 5	As clinically indicated
Evaluation by Radiation Oncologist and/or Medical Oncologist		X[8]		X[10]		X[5]	X[5]	X[5]	
ENT/Surgeon's exam		X[9]				X[5]	X[5]	X[5]	
CT with contrast, or CT/PET, and/or MRI of H & N[2]		X	Recommended within 8 wks prior to registration		X			As clinically indicated	
Chest x-ray (or chest CT or CT/PET)[2]		X			X			X[5,6]	
Pathology Assessment (Gross total resection ≤ 7 weeks prior to registration)		X[7]							
Biopsy					X[4]				X[4]
Performance status			X	X			X	X	
CBC w/ diff & AGC			X	X	X	X	X		X

Bilirubin, AST or ALT			X	X	X		X		X
Serum creatinine			X	X					
Na, K, glucose, Ca, Mg, albumin			X						
Serum pregnancy test (if applicable)[1]			X						X
Dental evaluation		≤ 3 mos. prior to start of treatment							
Assessment of swallowing function		≤ 2 weeks prior to treatment					X		X[11]
Adverse event evaluation			X	X		X	X	X	X
Research Blood Specimens (section 14.0)[12 R]	X		X[13]					X[13]	
QOL/Functional Assessments: QLQ H&N35; FACT-H&N;; EQ-5D; XeQOLS; DLQI[3]		Prior to Treatment (Baseline)				X	X	At 3, 12, and 24 months from the end of radiation treatment	
Patient Assessment Form (completed by investigator) (see Appendix V)		Prior to Treatment (Baseline)				X	X	At 3, 12, and 24 months from the end of radiation treatment	

1. For women of childbearing potential only. Must be done ≤7 days prior to registration.
2. Specify method (e.g., CT, MRI, or PET/CT, etc.) Use same imaging throughout the study.
3. Patient questionnaire booklets **must** be used; copies are not acceptable for this submission.
4. If suspicion of tumor recurrence.
5. An initial post-treatment evaluation by Radiation and Medical Oncology will be performed 14 days after completion of RT. A general history and physical by one of the following: a Radiation Oncologist, Medical Oncologist, an ENT, or a Head and Neck Surgeon must be done at 1 and 3 months post-XRT, then q3 months for 2 years, every 6 months for year 3, then annually for year 4 & 5. A laryngopharyngoscopy (mirror and/or fiberoptic and/or direct procedure) is recommended at these time points but is not required.
6. Chest imaging (at minimum a chest x-ray or chest CT or CT/PET of chest) is required once per year for a total of 5 image sets.
7. Gross total resection/surgical pathology must be completed ≤ 7 weeks prior to registration.
8. A general history & physical by a Radiation Oncologist and/or Medical Oncologist must be done ≤ 8 weeks prior to registration
9. An examination by an ENT or Head & Neck Surgeon must be done ≤ 8 weeks prior to registration. A laryngopharyngoscopy (mirror and/or fiberoptic and/or direct procedure) is recommended but not required
10. A general history & physical by a Radiation Oncologist and/or Medical Oncologist must be done weekly.
11. One year post XRT.
12. This blood collection will only be collected for patients that are enrolled at the Mayo Clinic Rochester.
13. This blood specimen only needs to be collected post-surgery but prior to radiation therapy treatment and then only at the 3 month post radiation therapy visit

R. Research Funded

5.0 Grouping Factor:

- **Extracapsular Extension**
  - **No Cohort A**
  - **Yes Cohort B**

6.0 Pre-Registration/Registration Procedures

NOTE: Once accrual for a cohort is complete, that cohort will be closed and the other cohort will remain open.

6.1 To pre-register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the MCCC Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the MCCC web page [redacted] and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and a MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient pre-registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the MCCC Registration Office [redacted]. If the patient was fully registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

Prior to accepting the pre-registration, registration application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.2 To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the MCCC Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

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- Contact the MCCC Registration Office [redacted] If the patient was fully registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

6.3 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office (fax: [redacted]). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.4 Prior to accepting the registration, registration application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.5 Treatment cannot begin prior to registration and must begin ≤ 14 days after registration.

6.6 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.7 All required baseline symptoms (see Section 10.6) must be documented and graded.

6.8 Treatment on this protocol must commence at Mayo Clinic under the supervision of a radiation oncologist.

6.9a Patient questionnaire booklet is available on site; copies are not acceptable for this submission.

6.9b Patient has/has not given permission to give his/her blood sample for research testing.

7.0 Protocol Treatment

7.1 Treatment Schedule - Use actual weight or estimated dry weight if fluid retention.

7.11 Pretreatment medication (Same for Cohort A and B)

Agent	Dose	Route	Day
DXM	8 mg	PO BID	Day before, day of, and day after docetaxel (may substitute IV if patient did not receive PO dexamethasone).

Agent	**Dose Level**	**Route**	**Day**
Docetaxel	15mg/m2	IV	Day 1
Docetaxel	15mg/m2	IV	Day 8

7.3 For this protocol, the patient must return to the Mayo Clinic for evaluation every 7 days during treatment and then at 14 days post-XRT, 1 month post-XRT, followed by every 3 months post-treatment for 2 years, followed by every 6 months for year 3, then annually for years 4 & 5.

7.4 **RADIATION THERAPY**

NOTE: FOR THIS STUDY, IMRT AND IGRT ARE MANDATORY

Dose Specifications for both Arms

The prescribed radiotherapy dose will be 30-36 Gy in 1.5-1.8 Gy twice-daily fraction size (total of 20 fractions). Radiotherapy should aim to begin on a Monday. The daily dose will be prescribed such that 100% of the PTV volume receives at least 30 Gy. PTV coverage has precedence over normal tissue constraints.

Field	**Dose (Gy)**	**Number of Fractions**	**Fraction Size**	**Rx Length**	**Rx Days**
Cohort A	**30**	**20**	**1.5**	**Days 1-12**	**M-F**
Cohort B	**36**	**20**	**1.8**	**Days 1-12**	

7.41 **Technical Factors**

Treatment Planning/Delivery: Megavoltage energy photon beam irradiation is required. Any treatment planning and delivery system that has been credentialed for head and neck IMRT is acceptable.

7.42 *Image Guidance for IGRT*: Daily image guidance of IMRT may be achieved using any one or more of the following techniques:

- Orthogonal kilovoltage (KV) images, e.g. ExacTrac;
- Linear-accelerator mounted kV and MV conebeam CT images;

The institution's procedure to register treatment day imaging dataset with the reference dataset should comply with the following recommendations:

- Region-of-Interest (ROI) or "clip box" for fusion should be 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;
- If the fusion software allows the user to create an irregular ROI (e.g., ExacTrac), treatment room objects seen on in-room X-rays should be excluded from the registration;
- Both manual (e.g., based on bony anatomy) and automatic (e.g., based on mutual information) types of registration can be used; the result of the fusion must 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 and (if the appropriate technology is available) rotational corrections should be applied to the treatment couch. If all the variances are less than 2.5 mm (this typically corresponds to one half of the usual PRV margin), the treatment can proceed without correction (however, the physician/team may elect to perform adjustments even for a variance < 2.5 mm). If one or more corrections are 2.5-5 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.

7.43 **Localization, Simulation, and Immobilization**

7.431 Patients must have an immobilization device (e.g., aquaplast mask) made prior to treatment planning CT scan.

7.432 The treatment planning CT scan should be performed with *IV* contrast so that the major vessels of the neck are easily visualized. The treatment planning CT scan must be performed with the immobilization device and in the treatment position. Slice thickness should be 0.3 cm.

7.5 Target and Normal Tissue Volume Definitions

7.51 *Definition of Target Volumes*

7.510 CTV_HIGH: This volume will receive 1.8 Gy per day bid and will only apply to patients who have ECE. This volume will be restricted to the prior location of the ECE-involved lymph node, expanded by 1.5 cm, and shaving off of bone and relevant normal anatomy. In the instance where the exact ECE-involved lymph node is unclear, CTV_HIGH will be defined as the nodal station from which the ECE-involved node originated. For questions, contact the Primary Investigator, Dr. Daniel J. Ma.

7.511 CTV_LOW: This volume will receive 1.5 Gy per day bid. CTV will include the primary tumor bed (based on preoperative imaging, preoperative physical exam/endoscopy, operative findings, pathologic findings) plus region(s) of grossly involved lymphadenopathy. This volume may approach the skin but should not approach < 2mm. It is recognized that after surgery, there can be considerable distortion of

normal anatomy. If possible, map preoperative GTV(s) onto the postoperative radiation therapy planning CT scan, and add appropriate margins for microscopic spread (1.5-2 cm). CTV also will include the bilateral necks. This generally means encompassing nodal levels 2a, 3, and 4 for all cases. Nodal levels 1, 2b, 5a, and 5b are included in CTV in selected circumstances. Ipsilateral neck irradiation for the involved hemi-neck will be allowed for a well-lateralized tonsillar cancer. For questions, contact the Principal Investigator, Dr. Daniel J. Ma.

7.512 Planning Target Volumes (PTVs): In general, the PTV should not go outside of the skin surface; if it does exceed the skin surface, the application of bolus material over this portion of the PTV may be considered but is generally not recommended.

7.513 *PTV Expansion **With** Daily IGRT*
The minimum CTV-to-PTV expansion is 2.5 mm (a larger expansion may be necessary for a target volume subject to significant intra-fraction variability. In general, the CTV-to-PTV expansion (with IGRT) should not exceed 5 mm.

7.52 *Definition of Normal Tissues/Organs at Risk (OARs)*

7.521 Spinal Cord: The cord begins at the cranial-cervical junction (i.e., the top of the C1 vertebral body). Superior to this is brainstem and inferior to this is cord. The inferior border of the spinal cord is at approximately T3-4 (i.e., just below the lowest slice level that has PTV on it). The spinal cord shall be defined based on the treatment planning CT scan. In addition, however, a Planning Risk Volume (PRV) spinal cord shall be defined. The PRVcord = cord + 5 mm in each dimension. This is irrespective of whether or not IGRT is used.

7.522 Brainstem: The inferior most portion of the brainstem is at the cranial-cervical junction where it meets the spinal cord. For the purposes of this study, the superior most portion of the brainstem is approximately at the level of the top of the posterior clinoid. The brainstem shall be defined based on the treatment planning CT scan. In addition, however, a Planning Risk Volume (PRV) brainstem shall be defined. The PRVbrainstem = brainstem + 3 mm in each dimension.

7.523 Lips and Oral Cavity: These should be contoured as 2 separate structures as the goal is to keep the lip dose much lower than the oral cavity dose. The definition of lips is self-explanatory. For non-oral cavity cancers, the oral cavity will be defined as a composite structure consisting of the anterior ½ to 2/3 of the oral tongue/floor of mouth, buccal mucosa, and palate. For oral cavity cancers, the oral cavity will be defined as the subset of this composite structure that does not overlap with PTV.

7.524 Parotid Glands: Parotid glands will be defined based on the treatment planning CT scan. Parotid gland volume will not include any portion of any of the CTVs, although they can overlap the PTVs.

7.526 OARpharynx: This will be defined as the "uninvolved" posterior pharyngeal wall plus adjacent constrictor muscles. This extends from the superior constrictor region (the inferior pterygoid plates level) to the cricopharyngeal inlet (posterior cricoid cartilage level). This should not overlap the PTVs.

7.527 Cervical Esophagus: This will be defined as a tubular structure that starts at the bottom of OARpharynx and extends to the thoracic inlet.

7.528 Glottic/Supraglottic Larynx (GSL): Obviously, for patients who have had a total laryngectomy, this structure is not applicable. This will be defined as a "triangular prism shaped" volume that begins just inferior to the hyoid bone and extends to the cricoid cartilage inferiorly and extends from the anterior commissure to include the arytenoids. This includes the infrahyoid but not suprahyoid epiglottis.

7.529a Mandible: This includes the entire boney structure of the mandible from TMJ through the symphysis. It is recognized that for oral cavity cancers, this may overlap with CTVs and PTVs.

7.529b Unspecified Tissue Outside the Targets: This will be defined as tissue located between the skull base and thoracic inlet that is not included in either the target volumes or the normal tissues described above.

7.6 Treatment Planning and Delivery

7.61 Management of the Low Neck/Supraclavicular Region (No Match)
No Match: The entire clinical target volume (CTV) [upper and lower neck and primary tumor bed] is irradiated with IMRT. There is no match line between upper and lower portions of the regions at risk. In this technique, limiting radiotherapy dose to organs at risk (OARs), e.g., the cervical esophagus, is entirely achieved by inverse treatment planning via IMRT algorithms.

7.62 IMRT Dose Prescription to PTVs
See Section 6.4.1 for definitions of CTVs and PTVs. As described in Section 6.1, prescribed radiotherapy dose will be 30-36 Gy in 1.5-1.8 Gy twice-daily fraction size. For inverse planning IMRT, the goal is for 100% of the PTV_LOW to receive ≥ 1.5 Gy / fraction. It is recognized that portions of the PTV_LOW close to the skin may receive significantly less than 30 Gy. This is acceptable as long as cold spots within PTV do not exist at a depth deeper than 8 mm beneath the skin (see Section 6.7, compliance criteria). At least 98% of PTV_HIGH should receive at least 1.8 Gy / fraction. For prioritization, PTVs will be the highest priority target structure.

7.63 IMRT Dose Constraints to Normal Structures

There are two goals for the dose constraints in this protocol. First, structures such as the parotid glands and the minor salivary glands within the oral cavity have a continuous, inverse relationship between dose and function. Thus the dose constraints for these structures reflect what should be achievable using IMRT techniques. Second, the dose received by critical structures such as the spinal cord and brainstem may limit the ability for re-irradiation if such treatment is required. Thus the dose constraints on these structures have been set conservatively to facilitate possible future interventions. PTV coverage has precedence over normal tissue constraints.

7.631 *Spinal Cord*: The PRVcord (as defined in Section 6.4.2.1) should not exceed 35 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm). The spinal cord PRV should not exceed 30 Gy to any volume in excess of 0.01 cc.

7.632 *Brainstem*: The PRVbrainstem (as defined in Section 6.4.2.2) should not exceed 35 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm).

7.634 *Lips:* Reduce the dose as much as possible. The mean dose should be < 15 Gy.

7.635 *Oral Cavity:* Reduce the dose as much as possible. The mean dose should be < 20 Gy.

7.636 *Parotid Glands*: In most cases, it will be easier to spare one parotid than the other. The treatment planning goal will be for this individual parotid gland to receive a mean dose of < 10 Gy. Otherwise, the goal will be for the total mean parotid dose to be < 15 Gy.

7.637 *Submandibular Glands:* If either submandibular gland is outside of the target volume, the goal will be for a mean dose for that gland to be <20 Gy. Otherwise reduce the dose as much as possible.

7.637 *OARpharynx*: Reduce the dose as much as possible.

7.638 *Cervical Esophagus*: Reduce the dose as much as possible.

7.639a *Glottic and Supraglottic larynx (GSL)*: Reduce the dose as much as possible.

7.639b *Mandible:* Reduce the dose as much as possible.

7.7 Compliance Criteria

Treatment breaks must be clearly indicated in the treatment record along with the reason(s) for the treatment break(s). Radiation breaks, if necessary, should not exceed one treatment day. Radiation breaks should be allowed only for resolution of severe acute toxicity and/or for intercurrent illness and not for social or logistical reasons. Any radiation break(s) exceeding one treatment day for reasons other than toxicity/illness will be considered a major protocol deviation.

7.8 **Radiation Therapy Adverse Events**

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4 will be utilized for grading all adverse events. All appropriate treatment areas should have access to a copy of the CTCAE, v. 4. A copy of the CTCAE, v. 4 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

Grade 3 therapy-induced mucositis and/or dysphagia are expected to develop in about one third of patients. Nutritional evaluation prior to the initiation of therapy for a prophylactic gastrostomy (PEG) tube placement is highly recommended. Placement of a feeding tube should be recorded on the appropriate case report form, as should use of a feeding tube during and after treatment (e.g., greater than or less than 50% of nutrition by tube).

Other common radiation adverse events include: fatigue, weight loss, regional alopecia, xerostomia, hoarseness, transient ear discomfort, dysgeusia, and skin erythema and desquamation within the treatment fields.

Less common long-term treatment adverse events include: hypothyroidism, loss of hearing, chronic swallowing dysfunction requiring permanent feeding tube, and cervical fibrosis.

Much less common radiation adverse events include: mandibular osteoradionecrosis (< 5% incidence with attention to dental recommendations), and cervical myelopathy (< 0.1% with restriction of spinal cord dose to ≤ 30 Gy).

8.0 Dosage Modification Based on Adverse Events

Strictly follow the modifications in this table. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions are based on adverse events observed since the prior dose.

ALERT: *ADR reporting may be required for some adverse events (See Section 10)*

8.1 Dose Levels (Based on Adverse Events in Tables 8.*2*)

Dose Level	DOCETAXEL (Day 1 or 8)
0*	15 mg/m2 IV
-1	10 mg/m2 IV
-2	5 mg/m2 IV

*Dose level 0 refers to the starting dose.
- If the patient requires one docetaxel delay (Day 1 or 8), start at Dose -1
- If patient requires more than one docetaxel delay (Day 1 or 8), start at Dose -2

8.2

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified* ← ←			
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
BASED ON INTERVAL ADVERSE EVENT			
Investigations, Other, Blood/ Bone Marrow	ANC < 1500/mm3 **OR** PLT < 75,000/mm3	docetaxel	Hold docetaxel. Resume treatment at one decreased dose level when ANC ≥ 1500/mm3 and PLT ≥ 75,000. If no recovery after 3 weeks despite institution of all clinically appropriate symptomatic treatment, discontinue docetaxel.
Investigations, Other, Liver	AST or ALT > 1.5 x ULN when AP > 2.5 x ULN **OR** AST or ALT > 3 x ULN **OR** Direct Bilirubin > 1.5 x ULN	docetaxel	Hold docetaxel. Resume treatment at one decreased dose level when AST/ALT ≤ 3 x ULN, AP < 2.5 x ULN, and Direct Bilirubin ≤ 1.5 x ULN. If no recovery after 3 weeks despite institution of all clinically appropriate symptomatic treatment, discontinue docetaxel.
Neurology	Grade 3+ peripheral neuropathy	docetaxel	Discontinue docetaxel.
All other non-hematologic adverse events	Grade 2-4 (exclude nausea/vomiting that has not been pre-medicated)	docetaxel	Hold docetaxel. Resume treatment at one decreased dose level when resolved to grade 0-1 adverse event. If no recovery after 3 weeks despite institution of all clinically appropriate symptomatic treatment, discontinue docetaxel.

* Located at http:/ctep.cancer.gov/protocolDevelopment/electronic_applications.ctc.htm

** Use the following to describe actions in the Action column:

- Omit = Treatment is not given for this cycle
- Hold/Delay = Treatment can be made up as part of this cycle
- Discontinue = Treatment is totally stopped

NOTE: If the patient experiences a significant adverse event requiring a dose reduction at the start of the next dose, then the dose will remain lowered for that entire cycle.

NOTE: Adverse events requiring a dose-reduction step for any or all drugs beyond the two dose-reduction steps (levels –1 and –2) will be at the discretion of the treating physician, if the decision is made for the patient to be kept on study. These dose reductions must be clearly recorded in reported clinical data.

9.0 Ancillary Treatment/Supportive Care

9.1 Antiemetics may be used at the discretion of the attending physician.

9.2 Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology (42) Update of Recommendations for the Use of Hematopoietic Colony-Stimulating Factors: Evidence-Based, Clinical Practice Guidelines. *Journal of Clinical Oncology, Vol 24, No 19 (July 1), 2006: pp. 3187-3205*.

9.3 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.4 Diarrhea: This could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

In the event of grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting **should be hospitalized** for intravenous hydration and correction of electrolyte imbalances.

9.5 For mucositis, esophagitis, and nutritional support: These may include analgesics, antiemetics, topical mouth rinses, skin creams/ointments, etc. The use of amifostine as a radioprotector is not allowed.

10.0 Adverse Event (AE) Reporting and Monitoring

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE version 4.0. Next, determine whether the event is expected or unexpected (see Section 10.2) and if the adverse event is related to the medical treatment or procedure (see Section 10.3). With this information, determine whether the event must be reported as an expedited report (see Section 10.4). Important: Expedited adverse event reporting requires submission of a MedWatch report(s). Expedited reports are to be completed within the timeframes and via the mechanisms specified in

Sections 10.4. All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.52 and 18.0).

10.12 Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT). Grade is an essential element of the Guidelines and, in general, relates to **severity** for the purposes of regulatory reporting to NCI.

NOTE: A severe AE, as defined by the above grading scale, is **NOT** the same as serious AE which is defined in the table in Section 10.4.

10.2 **Expected vs. Unexpected**

- The determination of whether an AE is expected is based on the agent-specific information provided in Section 15.0 of this protocol.

- Unexpected AEs are those not listed in the agent-specific information provided in Section 15.0 of this protocol.

NOTE: "Unexpected adverse experiences" means any adverse experience that is neither identified in nature, severity, or frequency of risk in the information provided for IRB review nor mentioned in the consent form.

10.3 **Assessment of Attribution**

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the agent(s).
Probable - The adverse event *is likely related* to the agent(s).
Possible - The adverse event *may be related* to the agent(s).
Unlikely - The adverse event *is doubtfully related* to the agent(s).
Unrelated - The adverse event *is clearly NOT related* to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug and the adverse event.

10.4 **Expedited Reporting Requirements for CIP Studies using Commercial Agent(s) ONLY:**

Expedited Reporting Requirements for Adverse Events that Occur in a Non-IND/IDE trial within 30 Days of the Last Administration of a Commercial Agent [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the sponsor within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">7 Calendar Days</td><td rowspan="2">24-Hour 3 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>7 Calendar Days</td></tr>
</table>

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported via MedWatch within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

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Additional Instructions:

1. An increased incidence of an expected adverse event (AE) is based on the patients treated for this study at their site. A list of known/expected AEs is reported in the package insert or the literature, including AEs resulting from a drug overdose.
2. Complete and submit all appropriate sections of the three page of the FDA MedWatch 3500A, (Mandatory reporting form) available at: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf
   Instructions on how to complete the form may be found at the following website:

http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/UCM387002.pdf

Mayo Clinic Cancer Center (MCCC) Institutions:

Submit copies, along with the Event Reporting coversheet, to the following email address: CANCERCROSAFETYIN@mayo.edu. This email will be managed by the SAE, IND and Safety Reporting Coordinators.

EVENT TYPE	REPORTING PROCEDURE
Other Grade 4 or 5 Events and/or Any Hospitalizations During Treatment Not Otherwise Warranting an Expedited Report	Complete a Notification Form: Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form electronically via the MCCC Remote Data Entry System or paper form within 5 working days of the date the clinical research associate (CRA) is aware of the event(s) necessitating the form. If an expedited written report has been submitted, this form does not need to be submitted.

10.5 Other Required Reporting

10.51 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital abnormities or birth defects, must be reported immediately if they occur at any time following treatment with an agent under an IND/IDE since they are considered to be a serious AE and must be reported to the sponsor as specified in 21 CFR 312.64(b).

10.52 Death

Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

Reportable categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

- Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.53 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

- All secondary malignancies that occur following treatment with an agent under an IND/IDE be reported. Three options are available to describe the event:

  - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])

  - Myelodysplastic syndrome (MDS)

  - Treatment-related secondary malignancy

- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.54 Second Malignancy

- A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting.

10.6 Required Routine Reporting

Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per the CTCAE v4.0 grading unless otherwise stated in the table below:.

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation	Grading scale (if not CTCAE)
Gastrointestinal disorders	Dry mouth	X	X	CTCAE
	Dysphagia	X	X	CTCAE
	Mucositis oral	X	X	CTCAE
	Nausea	X	X	CTCAE
	Esophagitis	X	X	CTCAE
	Oral Pain	X	X	CTCAE
General disorders and administration site conditions	Fatigue	X	X	CTCAE
Musculoskeletal and connective tissue disorders	Superficial soft tissue fibrosis	X	X	CTCAE
Vascular disorders	Lymphedema	X	X	CTCAE

10.61 Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.6

10.611 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.612 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.613 Grade 5 AEs (Deaths)

10.6131 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.6132 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

11.0 Treatment Evaluation

11.1 Patients will be evaluated at baseline, 14 days post XRT, 1 month post-XRT, then every 3 months for 2 years post-XRT followed by every 6 months during year 3, then annually for years 4 & 5. Once patients go off treatment or observation for recurrence, they will be followed per the Section 18.0 criteria.

11.2 At the time of reevaluation, patients will be classified in the following manner:

11.21 No evidence of disease (NED).

11.22 Recurrence of disease (REC). Recurrence must be confirmed by imaging and/or

biopsy, with supporting materials submitted per Section 18.0. If recurrence occurs, the report documenting recurrence is to be submitted per Section 18.0.

11.221 The site of recurrence (or failure) will also be collected and classified as local vs. regional vs. distant recurrence. The specific site of failure will also be collected as well.

11.222 Secondary Treatment. The date of the first retreatment and extent of retreatment post-recurrence (i.e. secondary resection or re-irradiation for primary disease), will be collected. Pathology, if available, and operative reports are required to be submitted per Section 18.0.

12.0 Descriptive Factors

-
- Primary tumor site: Tonsil vs. Tongue Base vs. Soft palate vs. Pharyngeal Wall vs. Other. (Can choose multiple)
- Neck Radiation: Bilateral vs. Unilateral.
- T Stage: 1 vs. 2 vs. 3 vs. 4a vs. 4b
- N Stage: 0 vs. 1 vs. 2a vs. 2b vs. 2c vs. 3.
- HPV-positivity by HPV-ISH: Yes vs. No

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Patients who have a recurrence while receiving therapy or during observation will go to the event-monitoring phase and be followed per Section 18.0.

13.2 Patients who go off protocol treatment or observation for reasons other than recurrence will go to the event-monitoring phase and be followed per Section 18.0.

13.3 Patients that complete all adjuvant treatment will then be followed during the observation phase at 14 days post-XRT, 1 month post-XRT, followed by every 3 months post-XRT for 2 years, followed by every 6 months for year 3, then annually for years 4 & 5.

13.4 A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly to the event-monitoring phase of the study (or off study, if applicable).

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.
- If the patient never received treatment, on-study material must be submitted.

13.5 A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study. The patient may continue treatment off-protocol at the discretion of the physician as long as

there are no safety concerns, and the patient was properly registered. Event monitoring will be required per Section 18.0 of the protocol.

13.6 A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens:

14.1 Summary Table of Research Blood and Body Fluid Specimens to be Collected for this Protocol

NOTE: This blood collection system will only be collected for Mayo Clinic Rochester patients.

Correlative Study (Section for more information)	Mandatory or Optional	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect per tube (# of tubes to be collected)	Pre-registration (Pre surgery)	Pre-Treatment	Three Month Post XRT	Process at site? (Yes or No)	Temperature Conditions for Storage /Shipping
CfDNA for Mayo Clinic Rochester patient only	Optional	Whole Blood	Streck	Two 10 mL whole blood samples in Streck Cell Free DNA BCT tubes	X	X	X	Yes	Ambient BAP Lab

14.2 Collection and Processing

14.21 Circulating Cell Free DNA (cfDNA)

14.21.1 Specimens will be collected at the following time points

- Prior to surgery as a pre-registration collection
- Post-surgery prior to radiation therapy
- 3 months post radiation therapy

14.22 Two 10 mL blood samples will be collected in Streck Cell Free DNA BCT tubes. The tubes should be gently inverted 7 to 10 times to thoroughly mix the samples. These samples will be processed within 7 days of collection for cfDNA extraction using the Qiagen QIAmp Circulating Nucleic Acid kit according to manufacturer's specifications. Evaluation for prespecified gene mutations will be performed using digital droplet PCR with the RainDrop platform (raindancetech.com). All of these samples must be labeled for immediate processing. The Streck Cell Free DNA BCT tubes will be provided for this study.

14.3 Shipping and Handling

14.31 Shipping Specimens

The Streck tubes for cfDNA should be kept at 6°C (42.8°F) to an ambient temperature of 37°C (98°F) during shipping. Ship cfDNA sample and CTC samples together to:

BAP Freezer
Mayo Clinic
[redacted]

Samples for the cfDNA studies should be collected and shipped Monday – Thursday. However, if the study participant can only be seen on Fridays, please contact the Biospecimen Resource Manager [redacted] for additional instructions Tel: [redacted] Email: [redacted]

14.4 Background and Methodology

14.41 Circulating Cell Free DNA (cfDNA): Several studies indicate that circulating cell free DNA (cfDNA) includes representation of key genetic alterations related to cancer progression or resistance to systemic therapy; these alterations include mutations of tumor suppressor genes (e.g., *TP53*) and oncogenes (e.g., *PIK3CA*, *KRAS* and *BRAF*). Commercially available platforms exist with a predefined set of genes and point mutations of interest for use across multiple malignancies. A more flexible system for individualized monitoring is needed. Mayo Clinic Rochester has developed an internal assay for this purpose.

15.0 Drug Information

15.1 Docetaxel (Taxotere®, TATER) Commercial Supply

15.11 **Background**: Antineoplastic Agent, Antimicrotubular, Taxane derivative. Docetaxel promotes the assembly of microtubules from tubulin dimers, and inhibits the depolymerization of tubulin which stabilizes microtubules in the cell. This results in inhibition of DNA, RNA, and protein synthesis. Most activity occurs during the M phase of the cell cycle.

15.12 **Formulation**: **Note:** Docetaxel is now available as a one-vial formulation in two concentrations: 10 mg/mL and 20 mg/mL. The older formulation included 2 vials which consisted of a concentrated docetaxel vial and a diluent vial, resulting in a reconstituted concentration of 10 mg/mL. Admixture errors could occur due to the concentration difference between the new formulations of 10 mg/mL and 20 mg/mL and the old formulation (10 mg/mL). Do not use the two-vial formulation with the one-vial formulation for the same admixture product.

15.13 Drug procurement:

Preparation, storage, and stability: Storage conditions: Store the packaged docetaxel between 2 and 25°C (36 and 77°F). Retain in the original package to protect from bright light. Freezing does not adversely affect the product.

One-vial formulation: Note: One-vial formulation is available in two concentrations: 10 mg/mL and 20 mg/mL. Further reconstitution with diluent is not required. Further dilute for infusion in 250-500 mL of NS or D_5W in a non-DEHP container (e.g., glass, polypropylene, polyolefin) to a final concentration of 0.3-0.74 mg/mL. Gently rotate to mix thoroughly. Solutions prepared from the one-vial formulation and diluted for infusion should be used within 4 hours of preparation (infusion should be completed within 4 hours).

Two-vial formulation: Vials should be diluted with 13% (w/w) ethanol/water (provided with the drug) to a final concentration of 10 mg/mL. Do not shake. Further dilute for infusion in 250-500 mL of NS or D_5W in a non-DEHP container (e.g., glass, polypropylene, polyolefin) to a final concentration of 0.3-0.74 mg/mL. Gently rotate to mix thoroughly. Diluted solutions of the two-vial formulation are stable in the vial for 8 hours at room temperature or under refrigeration. Solutions prepared with the two-vial formulation and diluted for infusion in D_5W or NS are stable for up to 4 weeks (Thiesen, 1999) at room temperature of 15ºC to 25ºC (59ºF to 77ºF) in polyolefin containers; however, the manufacturer recommends use within 4 hours (infusion should be completed within 4 hours).

15.14 **Administration:** Administer IV infusion over 1-hour through nonsorbing polyethylene lined (non-DEHP) tubing; in-line filter is not necessary. **Note:** Premedication with dexamethasone 8 – 10 mg orally twice daily for 3-5 days, beginning the day before docetaxel administration is recommended to decrease the incidence and severity of fluid retention and prevent hypersensitivity reactions and pulmonary/peripheral edema. When administered as sequential

infusions, taxane derivatives should be administered before platinum derivatives (cisplatin, carboplatin) to limit myelosuppression and to enhance efficacy.

15.15 **Pharmacokinetic information**: Docetaxel exhibits linear pharmacokinetics at the recommended dosage range.
Distribution: Extensive extravascular distribution and/or tissue binding; $V_{d:}$ 80-90 L/m2, V_{dss}: 113 L (mean steady state)
Protein binding: ~94% to 97%
Metabolism: Hepatic; oxidation via CYP3A4 to metabolites
Half-life elimination: Terminal: ~11 hours
Excretion: Feces (~75%, <8% as unchanged drug); Urine (<5%)

15.16 **Potential Drug Interactions**:
Cytochrome P450 Effect: Substrate (major) of CYP3A4; **Inhibits** CYP3A4 (weak).
Increased Effect/Toxicity: CYP3A4 inhibitors may increase the levels/effects of docetaxel. Concomitant use of docetaxel with a potent CYP3A4 inhibitor should be avoided. If systemic administration of a potent CYP3A4 inhibitor cannot be avoided, a 50% reduction in docetaxel dose should be considered along with close monitoring for docetaxel toxicity. Refer to the package insert or LexiComp[1] for example inhibitors. When administered as sequential infusions, observational studies indicate a potential for increased toxicity when platinum derivatives (carboplatin, cisplatin) are administered before taxane derivatives (docetaxel, paclitaxel). Taxane derivatives may enhance the adverse/toxic effect of anthracyclines.
Decreased Effect: CYP3A4 inducers may decrease the levels/effects of paclitaxel. Refer to the package insert or LexiComp[1] for example inducers.
Ethanol/Herb/Nutraceutical Interactions: Avoid ethanol (due to GI irritation). Avoid St John's wort (may decrease docetaxel levels).

15.17 **Known potential adverse events:** Consult the package insert for the most current and complete information. Percentages reported for docetaxel Monotherapy; frequency may vary depending on diagnosis, dose, liver function, prior treatment, and premedication. The incidence of adverse events was usually higher in patients with elevated liver function tests.

Common known potential toxicities, > 10%:
Cardiovascular: Fluid retention
Central nervous system: Neurosensory events including neuropathy, fever, neuromotor events.
Dermatologic: Alopecia, cutaneous events, nail disorder
Gastrointestinal: Stomatitis, diarrhea, nausea, vomiting
Hematologic: Neutropenia, leukopenia, anemia, thrombocytopenia, febrile neutropenia
Hepatic: Transaminases increased
Neuromuscular & skeletal: Weakness, myalgia
Respiratory: Pulmonary events
Miscellaneous: Infection, hypersensitivity

Less common known potential toxicities, 1% - 10%:

Cardiovascular: Left ventricular ejection fraction decreased, hypotension
Dermatologic: Rash/erythema
Gastrointestinal: Taste perversion
Hepatic: Bilirubin increased, alkaline phosphatase increased
Local: Infusion-site reactions including hyperpigmentation, inflammation, redness, dryness, phlebitis, extravasation, swelling of the vein
Neuromuscular and skeletal: Arthralgia
Ocular: Epiphora associated with canalicular stenosis

Rare known potential toxicities, <1% (Limited to important or life-threatening):
Acute myeloid leukemia, acute respiratory distress syndrome, anaphylactic shock, angina, ascites, atrial fibrillation, atrial flutter, bleeding episodes, bronchospasm, cardiac tamponade, chest pain, chest tightness, colitis, conjunctivitis, constipation, cutaneous lupus erythematosus, deep vein thrombosis, dehydration, disseminated intravascular coagulation, drug fever, duodenal ulcer, Dyspnea, dysrhythmia, ECG abnormalities, erythema multiforme, esophagitis, gastrointestinal hemorrhage, gastrointestinal obstruction, gastrointestinal perforation, hand and foot syndrome, hearing loss, heart failure, hepatitis, hypertension, ileus, intestinal pneumonia, ischemic colitis, lacrimal duct obstruction, loss of consciousness (transient), MI, multiorgan failure, Myelodysplastic syndrome, neutropenic enterocolitis, ototoxicity, pleural effusion, pruritus, pulmonary edema, pulmonary embolism, pulmonary fibrosis, radiation pneumonitis, radiation recall, renal insufficiency, seizure, sepsis, sinus tachycardia, Stevens-Johnson syndrome, syncope, toxic epidermal necrolysis, tachycardia, thrombophlebitis, unstable angina, visual disturbances (transient)

15.18 Nursing guidelines -

15.181 Monitor CBC closely, as neutropenia, and thrombocytopenia are common and may be life threatening, and dose limiting. Instruct patient to report any signs or symptoms of infection, any unusual bruising, or bleeding.

15.182 Administer antiemetics as ordered. Evaluate for their effectiveness.

15.183 Monitor for signs/symptoms of hypersensitivity reactions that may include chills, rigors, dyspnea, bronchospasms, etc. Stop infusion immediately and administer proper emergency treatment.

15.184 Because of the risk of anaphylaxis and development of edema, instruct patient that is imperative to take steroid premedications as ordered.

15.185 Instruct patient on proper oral care, as mucositis may occur.

15.186 Advise patient about alopecia.

15.187 Monitor liver function tests.

15.188 Drug is a vesicant. Monitor infusion site frequently for signs of irritation or infiltration. Drug extravasation causes acute streaking, burning pain, and discoloration at the site. Skin may be reddened for several weeks and occasionally blister and/or peel. Reactions are usually reversible over time. Because of this central venous access may be necessary. Discuss with MD if patient has poor peripheral venous access. If docetaxel concentrate or diluted solution comes into contact with skin, wash with soapy water immediately. If it comes into contact with mucosa, wash with warm water immediately.

15.189a Instruct patient to report any signs of peripheral neuropathy to the health care team (pain, numbness, tingling).

15.189b Monitor for signs and symptoms of fluid retention, weight gain, ascites and CHF.

15.189c Instruct patient about possible facial flushing, rash, and skin and nail changes. Monitor for signs and symptoms of hand/foot syndrome. However premedication with steroids can minimize this side effect. Discuss with MD possible ways to manage itching and skin changes that may occur up to a week after docetaxel administration. Advise patients that nails may crack, peel, or fall off all together. This may be a chronic toxicity. Instruct patient to keep nails clean, short and to avoid wearing nail polish or artificial nails.

15.189d In case of overdose, patient should be hospitalized and vital signs monitored. Patient should receive therapeutic G-CSF ASAP after discovery of the overdose.

15.2 Neck radiation

15.21 Nursing guidelines

15.211 Assess for increased fatigue. Instruct patient in energy saving lifestyle.

15.213 Monitor for nutritional status. Advise patient accordingly.

15.214 Assess for skin reaction.

15.215 Assess for possible mouth/throat soreness, dry mouth, thick secretions, nausea, and treat as necessary.

16.0 Statistical Considerations and Methodology

Note: The first patient enrolled will be excluded from all analyses because they received Docetaxel (15 mg/m2) on days 1, 8 and Docetaxel 75 mg/m2 on day 15 as well. All other patients will only receive Day 1 and 8 of Docetaxel (15 mg/m2 each day). This first patient was still eligible per protocol. Per Addendum 1, day 15 was removed for all subsequent patients.

In addition, this study will be stratified into two patient cohorts: patients who do not have ECE (“cohort A”) and patients who have ECE (“cohort B”). Cohort B patients will be treated with a slightly higher

radiation dose (36 rather than 30 Gy), but will be followed and evaluated in the same fashion as patients in Cohort A. Each cohort will be independently evaluated for all the endpoints described below

16.1 Overview: This phase II study, with a feasability analysis in the first 5 pts, will evaluate adjuvant hyperfractionated radiation and docetaxel for HPV-associated Oropharynx Cancer using a 1-stage design. Standard therapy for this disease yields a 2-year cumulative incidence of local/regional failure of approximately 10% (Ang KK, Harris J, Wheeler R, et al.), but it also has high rates of grade 3 or worse adverse events (Bernier J, Domenge C, Ozsahin M, et al). Given the high rates of severe or worse functional mucosal adverse events (AEs), especially, it is of high interest to find a chemo/RT combination that can still yield low rates of local/regional failure with reduced AE rates. If this new treatment combination can achieve a 2-year cumulative incidence of local/regional failure of no more than 20% (primary endpoint), while significantly reducing the acute grade 3+ functional mucosal AE rate as compared to historical controls (key secondary endpoint), further study would be warranted. In addition to the 2-year cumulative incidence rate and the acute functional mucosal adverse event rate, this study will assess many additional secondary endpoints, including, overall survival, disease-free survival, distant failure rates, quality of life (QOL) measures, swallowing studies, other acute adverse events, and late adverse events and translational studies.

16.2 Primary Endpoint: The 2-year cumulative incidence of local/regional failure associated with adjuvant hyperfractionated radiation and docetaxel in patients with intermediate risk HPV+ Associated Oropharynx Cancer. All patients meeting the eligibility criteria who have signed a consent form, and begun treatment will be considered evaluable for the 2-year cumulative incidence rate.

16.21 Analysis plans: Given that the current standard therapy yields a 2-year cumulative incidence of local/regional failure of around 10% (Ang KK, Harris J, Wheeler R, et al.), this study treatment will be of interest for further study if the 2-year cumulative incidence of local/regional failure does not exceed 20%, while also significantly reducing AE rates (see 16.3, key secondary endpoint). The 2-year cumulative incidence of local/regional failure will be estimated by the competing risk method (Gooley, et al.), where the competing risks are distant failures and deaths from other causes (i.e. deaths from distant failure or non-Oropharynx Cancer). If the 2-year cumulative incidence of local/regional failure does not exceed 20%, this will give evidence that a 2-year local/regional failure rate of around 10% can not be ruled out, since the 2-sided 85% confidence interval would contain 10% (85% CI: 10 – 30%) with 35 evaluable patients using nQuery Advisor version 6.01 for confidence intervals for a single proportion.

16.3 Key Secondary Endpoint: To characterize the acute grade 3 or higher functional mucosal adverse events (up to 1 month post-XRT) associated with adjuvant hyperfractionated radiation and docetaxel in patients with intermediate risk HPV+ Associated Oropharynx Cancer. All patients meeting the eligibility criteria who have signed a consent form, and begun treatment will be considered evaluable for this key secondary endpoint.

16.31 Definition of success: A success will be defined as a patient who does

not experience a grade 3+ functional mucosal adverse event in the first month post- XRT.

16.32 Power, Sample Size: The current standard of care yields acute grade 3+ functional mucosal AE rates of approximately 40% (Bernier J, Domenge C, Ozsahin M, et al.). This regimen will be of high interest based on safety if the acute grade 3+ functional mucosal AE rate could be reduced to around 20% or lower.

With 35 evaluable patients per cohort, this study would have 85% power to detect an acute grade 3+ functional mucosal AE-free rate of 80%, with a 0.06 level of significance if the true grade 3+ AE-free rate is 60%. The decision rule for this trial is as follows: If 25 or fewer patients are grade 3+ AE-free after 1 month post-XRT, we will conclude that the AE rate is not significantly reduced in this patient population. If 26 or more patients are grade 3+ AE-free, this will be considered adequate evidence of safety for this treatment and it may be recommended for further testing in subsequent studies, especially if the primary endpoint discussed above meets criteria as well (see 16.21).

16.4 Sample Size: We will enroll 35 evaluable patients per cohort to the combination of adjuvant hyperfractionated radiation and docetaxel (total patients = 70 evaluable patients.) We anticipate accruing an additional 5 patients per cohort to account for ineligibilities, cancellations, major violations, or other reasons. Therefore, maximum accrual will be 80 patients. Following the approval of addendum 6, overall accrual will increase to 81 patients so that additional patient data can be used for analysis.

16.5 Accrual Time and Study Duration: The anticipated accrual rate is approximately 1 patient per month or 12 patients per year per cohort. Therefore, the accrual period for this Phase II study is expected to be around 3 years. The final analysis can begin approximately 5 years after the trial begins, i.e., as soon as the last patient registered has been observed for 24 months.

16.6 Safety Analysis in First 5 patients: In the first 5 patients, acute adverse events (up to 1 month post-XRT) will be closely monitored to make sure that nothing unusual occurs. Based on the current standard of care, we expect that no more than 50% of patients will have a grade 3+ non-hematologic AE (regardless of attribution). If 3 or more patients in the first 5 have a grade 3+ non-hematologic AE, we will consider lowering the dose even further for further evaluation. In addition, if 1 or more of the first 5 patients has a local or distant failure or expires from this cancer during the first 6 months, the dose for the study may be modified going forward. Accrual will continue while we wait for the first 5 patients to be followed for a minimum of 6 months. As long as the dose remains the same, the first 5 patients will be included in the final analysis as well.

16.7 Definitions and Analyses of Secondary Endpoints:

16.71 Overall Survival (OS) is defined as the time from registration to death due to any cause. The distribution of OS will be estimated using the method of Kaplan-Meier (Kaplan E, Meier P).

16.72 Disease-free survival (DFS) is defined as the time from registration to the first of either disease recurrence or death. The distribution of DFS will be estimated using the method of Kaplan-Meier (Kaplan E, Meier P).

16.73 Distant Failure Rates: The 2-year cumulative incidence of distant failure will be estimated by the competing risk method (Gooley, et al.), where the competing risks are local/regional failures and deaths from other causes (i.e. deaths from local/regional failure or non-Oropharynx Cancer).

16.74 Quality of Life (QOL): The patient QOL will be measured using the following tools: 1) XeQOLS form, 2) Eq-5D, 3) FACT H & N (Version 4), 4) Dermatology Life Quality Index; and QLQ H&N35 (see QOL Booklet). These QOL measures will be assessed at baseline, 14 days post-XRT and 3, 12 and 24 months post-XRT. These QOL scores will be explored descriptively to detect patterns and substantial changes over time. In addition, differences between post-baseline and baseline QOL scores will be analyzed using a paired-sample t-test or the nonparametric equivalent to see if the QOL tends to improve over time with treatment.

16.75 Patient Assessment Form (Appendix V): The data from this form will be analyzed descriptively, using frequencies and percentages for each timepoint (baseline, 14 days post-XRT, and 3, 12 and 24 months post-XRT).

16.76 Swallowing Studies: Swallowing will be scored (yes, no) for aspiration, penetration, velopharyngeal incompetence, epiglottic everson, tongue base retraction, and pharyngeal swallow response using the metric outlined by Eisbruch et al. (Eisbruch A, Teresa L, Bradford CR, et al.) Swallowing assessments will be completed at baseline, along with 1and 12 months after the completion of protocol XRT. The swallowing questions will be explored descriptively to detect patterns and substantial changes over time. In addition, McNemar's test for paired samples will be used to see if the swallowing questions significantly change over time for each post-baseline timepoint.

16.77 Acute Adverse Events (up to 1 month post-XRT): All eligible patients that have initiated treatment will be considered evaluable for assessing acute adverse events, defined as any adverse event that occurs in the 1st month post-XRT. The maximum grade for each type of acute adverse event will be recorded for each patient, and frequency tables will be reviewed to determine patterns, especially focusing on grade 3+ adverse events, regardless of attribution to the study treatment.

16.78 Late Adverse Events (up to 2 years post-XRT): All eligible patients that have initiated treatment will be considered evaluable for assessing adverse event rate(s). The maximum grade for each type of adverse event will be recorded for each patient for up to 2 years post-treatment, and frequency tables will be reviewed to determine patterns, especially focusing on grade 3+ non-hematologic adverse events, regardless of attribution to the study treatment. Hematologic adverse events will not be followed closely long-term given that adjuvant treatment is only given for 1 month.

16.79 Translational studies: Due to the limited sample size in this study, the proposed translational studies are considered exploratory and hypothesis generating. Tumor specimens (at baseline) will be assessed for E6/E7 mRNA of HPV16 and other high-risk serotypes on a chromogenic RNA ISH assay called RNAscope (see 17.4). In addition, serum collected before and one week post-radiation will be assessed for changes in TGF-beta1 levels (see 14.3). We will also assess the pre-surgery blood samples as well for patients that are pre-registered to the trial. We plan to correlate these markers with clinical endpoints like acute adverse events, cumulative incidence rates of local/regional failure, overall survival, and disease-free survival. Statistical and graphical techniques will be used to explore the relationships between tumor markers and clinical data. For time-to-event endpoints, we will use Cox proportional hazards models, and for binary endpoints we will use Logistic regression models. In addition, we will use the Chi-square or Fisher's exact tests to test the association between categorical marker data and binary endpoints. All these statistical techniques will allow us to explore whether these tumor markers are potentially related to the clinical endpoints of acute adverse events, cumulative incidence rates of local/regional failure, overall survival, and disease-free survival.

16.8 Data & Safety Monitoring:

16.81 The principal investigator(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The trial is monitored continually by the study team who are notified of every grade 4 and 5 event in real time. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office. Any safety issues requiring protocol changes are communicated through protocol amendments.

16.82 Adverse Event Stopping Rules: The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Based on data from previous studies, we expect about 50% of patients to experience Grade 3+ non-hematologic adverse events within 1 month post-treatment. Accrual will be temporarily suspended to this study if at any time we observe adverse events that satisfy any of the following criteria:

- If at any time 12 or more patients in the first 20 treated patients experience a Grade 3 or 4 non-hematologic adverse event (regardless of attribution).
- If at any time 2 or more Grade 5 events occur in the first 20 treated patients (regardless of attribution).
- If after the first 20 patients have been treated:

- 60% or more of all patients experience a Grade 3 or 4 non-hematologic adverse event (regardless of attribution).
- 10% or more of all patients experience a Grade 5 adverse event (regardless of attribution).

We note that we will review all Grade 5 adverse events on a case-by-case basis as well (regardless of attribution), and may suspend accrual after just one Grade 5 event, if we feel it is necessary for patient safety.

16.9 Results Reporting on ClinicalTrials.gov: At study activation, this study will have been registered within the "ClincialTrails.gov" website. The Primary and Secondary Endpoints (i.e., "Outcome Measures") along with other required information for this study will be reported on ClinicalTrials.gov. For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 60 months after the study opens to accrual. The definition of "Primary Endpoint Completion Date" (PECD) for this study is when the last patient registered has been followed for at least 2 years for the 2-year cumulative incidence rate.

16.10 Inclusion of Women and Minorities

16.11 This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

16.12 There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.13 The geographical region served by the Mayo Clinic, has a population which includes approximately 5% minorities. We expect about 5% of patients will be classified as minorities by race and about 40% of patients will be women. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Estimates by Gender/Ethnicity/Race for All Phase II and III Studies
(Updated March 22, 2002, for January 1, 2002, Requirements)

Ethnic/Racial Categories	Sex/Gender			
	Females	**Males**	**Unknown**	**Total**
Hispanic or Latino	0	0	0	0
Not Hispanic or Latino	32	48	0	80
Unknown	0	0	0	0
Ethnic Category: Total of all subjects*	32	48	0	**80***
Racial Category				
American Indian or Alaskan Native	0	0	0	0
Asian	0	2	0	2
Black or African American	2	0	0	2
Native Hawaiian or other Pacific Islander	0	0	0	0
White	30	46	0	76
More than one race	0	0	0	0
Unknown	0	0	0	0
Racial Category: Total of all subjects*	32	48	0	**80***

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Article I. Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens:

17.1 Summary Table of Research Tissue Specimens to be Collected for this Protocol

Correlative Study (Section for more information)	Mandatory or Optional	Type of Tissue to Collect	Block, Slides, Core, etc.	Prior to Radiation Treatment	Temperature Conditions for Storage /Shipping
Tumor Genetic Analyses	Optional	FFPE\fresh frozen	2 to 6 curls	Yes	Ambient

17.2 Diagnostic Slides from Original Tissue

Either 2-6 FFPE tissues curls or samples from fresh frozen tumor will be collected from original tumor biopsy, tumor removed during surgery, or recurrent tumor specimens. This tissue is already being collected and shared through [redacted] protocol 50-97. This tissue will be used for determining tumor-specific genetic alterations. Detected alterations may be compared to upwards of 50 samples of normal tissue from IRB 13-000883.

Additionally, we may examine tumor specimens from Tissue Registry through our collaborators either within Mayo Clinic or at Memorial Sloan Kettering Cancer Center (MSKCC). This may include whole genome sequencing, whole exome sequencing, focused exome sequencing, mate-pair analysis, HPV-subtyping, immunologic profiling, RNA sequencing, in situ hybridization, cytogenetics, molecular testing, protein expression, or immunohistochemistry. Towards this end, up to 30 slides (5 microns thick) will be retrieved from tissue blocks from the primary tumor, nodal disease, and/or sites of metastatic/ recurrent disease. If slides need to be obtained from FNA or core biopsy specimens, particular care will be taken to minimize the slides taken so that the block is not exhausted. Slides sent to MSKCC will be de-identified of patient data and labelled with the patient study number from MC1273.

Samples may be sent to:

[redacted]

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Pre-Registration Material(s)

Case Report Form (CRF)	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)
Pre-Registration Screening Failure Form	Complete only if patient is NOT registered after he/she is pre-registered
Research Blood Submission	≤30 days after pre-registration

Initial Material(s) -

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)
On-Study Form	≤2 weeks after registration
Baseline Adverse Events Form	
OP and Path Reports (see Section 17.0)	
Baseline Swallowing Function Assessment Form	≤2 weeks after registration but prior to treatment
Pathology Assessment Form	≤7 weeks prior to treatment
End of Active Treatment/Cancel Notification Form	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy
Patient Questionnaire Booklet	≤2 weeks after registration but prior to treatment- Patient questionnaire booklet **must** be used; copies are not acceptable for this submission.
Patient Questionnaire Booklet Compliance Form	This form must be completed **only** if the patient Questionnaire Booklet contains absolutely **NO** patient provided assessment information.
Patient Assessment Form	≤2 weeks after registration
Research Blood Submission	≤2 weeks after registration

Test Schedule Material(s)

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)		
	At each evaluation during treatment	At end of treatment	Observation
Evaluation/Treatment Form	X	X	
Adverse Events Form	X	X	X
Disease Status Form[4]	X	X	X
End of Active Treatment/Cancel Notification		X	

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)		
	At each evaluation during treatment	At end of treatment	Observation
Form			
Evaluation/Observation Form			X
Swallowing Function Assessment Form			X[3]
Patient Questionnaire Booklet			X[1]
Patient Questionnaire Booklet Compliance Form			X[2]
Patient Assessment Form			X[5]
Notification Form – Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form	At each occurrence (see Section 10.0)		
ADR/AER	At each occurrence (see Section 10.0)		
Research Blood Submission			X[6]

1. At 14 days post-XRT, and 1, 3, 12, and 24 months from the end of radiation treatment. Patient questionnaire booklet **must** be used; copies are not acceptable for this submission.
2. This form must be completed ONLY if the patient questionnaire contains absolutely NO patient provided assessment information.
3. One month post treatment, and one year post treatment (see section 4.0)
4. As needed to report NED or disease recurrence.
5. At 14 days post-XRT, and 1, 3, 12 and 24 months post-XRT.
6. This will only occur 3 months post-XRT

Follow-up Material(s)

CRF	Event Monitoring Phase[1]				
	q. 6 months until recurrence	At recurrence	After recurrence q. 6 mos.	Death	New Primary
Event Monitoring Form	X[2]	X[2]	X	X	At each occurrence

1. If a patient is still alive 5 years after registration, no further follow-up is required.
2. Submit copy of documentation of response or progression to the MCCC Operations Office, Attention: QAS for MC1273.

19.0 Budget

19.1 Costs charged to patient: routine clinical care

19.2 Tests to be research funded by Mayo Clinic Institutional funding.

19.3 Other budget concerns:

20.0 References

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Appendices

Appendix I

ECOG PERFORMANCE STATUS

Grade	
0	Fully active, able to carry on all pre-disease activities without restriction (Karnofsky 90-100).
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work (Karnofsky 70-80).
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50 percent of waking hours (Karnofsky 50-60).
3	Capable of only limited self-care, confined to bed or chair 50 percent or more of waking hours (Karnofsky 30-40).
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).
5	Dead

Appendix II

Guidelines for the use of IMRT (including Intra-Thoracic Treatments)

3/2009

1. For all patients, as outlined in Section 7.0, the prescription isodose must cover 100% of the PTV volume; therefore, the total dose in the PTV_LOW volume will be 3000 cGy. The minimum acceptable dose within PTV_LOW will be 3000 cGy. If the minimum dose falls below these parameters, an unacceptable deviation will be assigned. At least 98% of PTV_HIGH should be covered by 36 Gy. The maximum dose for the PTV should not exceed 115%. If the maximum doses exceed these parameters, an unacceptable deviation will be assigned.

2. Up to 1 day of radiation treatment interruption is permitted for any reason. For interruptions of 2 days or greater, an unacceptable deviation will be assigned. In the case of toxicity there should be no deviation for breaks greater than one day.

Appendix III

Radiation Therapy Quality Control Guidelines

1. Tumor Volume Coverage
   a. No deviation -- coverage + ≤ 1 cm of specified.
   b. Minor deviation -- coverage + > 1 to 2 cm of specified or failure to cover tumor volume + ≥ 1/2 specified margin.
   c. Major deviation -- > 2 cm of specified or no CT and/or MRI scans available to assess treatment volume appropriateness (if not initially available should be requested) or failure to cover the target (tumor or tumor + edema) as defined in the protocol.

2. Isodoses - initial volume isodose plots are required on a minimum of three contours; one at central axis (CA), one superior to CA (2 cm below the superior field edge) and one inferior to CA (2 cm above the inferior field edge). Boost volume isodose plot required at CA.
   a. No deviation -- isodoses submitted as required, and inhomogeneity across the target volume shall be no greater than ± 5%.
   *b. Minor deviation -- isodose information incomplete or inhomogeneity across the target volume > 5 but ≤ 10%.
   *c. Major deviation -- no isodoses submitted or inhomogeneity across the target volume > 10%.
   * Deviations would occur only if isodose information is incomplete or not submitted after there has been a request to submit complete isodose information.

3. Normal Tissues
   Normal structures are only to be included within the radiation field in as much as this is necessary to treat the primary tumor volume. A minor deviation will result when normal structures are unnecessarily included, but this is not felt to result in unacceptable toxicity that would interfere with the scientific aims of the protocol. A major deviation will result when normal structures are unnecessarily included in the radiation therapy field and such inclusion is felt likely to result in a major increase in toxicity which would potentially compromise the scientific goals of the study.

4. Other parameters: (dose per fraction, total dose, overall treatment time and portal films).
   a. No deviation -- +/- < 5% of protocol specification.
   b. Minor deviation -- +/- > 5% to 10% of protocol specification.
   c. Major deviation -- +/- > 10% of protocol specification or incomplete data (i.e. no portal or sim films, etc.) available for review (after additional request has been made).

5. Any individual minor deviation will result in an overall score of minor deviation; any major deviation will result in an overall score of a major deviation. Multiple minor deviations will not add up to a major deviation.

Appendix IV

Known inducers & inhibitors of isoenzyme CYP3A4

Inducers	
Carbamazepine Dexamethasone Ethosuximide Glucocorticoids Griseofulvin Nafcillin Nelfinavir Nevirapine Oxcarbazepine Phenobarbital Phenylbutazone	Phenytoin Primidone Progesterone Rifabutin Rifampin Rofecoxib (mild) St John's wort Sulfadimidine Sulfinpyrazone Troglitazone
Inhibitors	
Amiodarone Anastrozole Azithromycin Cannabinoids Cimetidine Clarithromycin Clotrimazole Cyclosporine Danazol Delavirdine Dexamethasone Diethyldithiocarbamate Diltiazem Dirithromycin Disulfiram Entacapone (high dose) Erythromycin Ethinyl estradiol Fluconazole (weak) Fluoxetine Fluvoxamine Gestodene Grapefruit juice lndinavir lsoniazid ltraconazole	Ketoconazole Metronidazole Mibefradil Miconazole (moderate) Nefazodone Nelfinavir Nevirapine Norfloxacin Norfluoxetine Omeprazole (weak) Oxiconazole Paroxetine (weak) Propoxyphene Quinidine Quinine Quinupristin and dalfopristin Ranitidine Ritonavir Saquinavir Sertindole Sertraline Troglitazone Troleandomycin Valproic acid (weak) Verapamil Zafirlukast Zileuton

Appendix V

Patient Assessment Form

INSTRUCTIONS:
This form is completed by the investigator (rater) and submitted at each time point specified by the protocol, whether or not any of the patient assessment items (Q's 6,7,8) are answered.

SUGGESTIONS FOR ADMINISTRATION:
These performance scales must be rated by health professionals such as physicians, nurses, nutritionists, etc. Ratings are determined through use of an unstructured interview format.

1 SCHEDULED DATA POINT (CHECK ONE)(1)

- ☐ 1 = Pre-treatment assessment
- ☐ 2 = At completion of radiotherapy
- ☐ 3 = Four weeks followup
- ☐ 4 = ___other followup (specify calendar date or followup interval, e.g., 3 months, 2 years, etc.)(2)
- ☐ 5 = Other, specify_____(3)

2 IF NO PATIENT ASSESSMENT, SPECIFY REASON (CHECK ONE)(4)

- ☐ 0 = Not applicable, questionnaire was completed
- ☐ 1 = Patient was too ill
- ☐ 2 = Patient unable to be contacted
- ☐ 3 = Questionnaire not completed due to institutional error
- ☐ 4 = Patient refused, including attempts by telephone interview, specify reason for refusal _____(5)
- ☐ 5 = Patient refused, telephone interview not attempted, specify reason for refusal _____(6)
- ☐ 6 = Other reason, specify _____(7)

3 WAS INFORMATION OBTAINED BY TELEPHONE INTERVIEW

(CHECK ONE)(8)

- ☐ 1 = No
- ☐ 2 = Yes

4 _____-_____-_____DATE OF EVALUATION(9)

5 RATER'S NAME_____(10)

6 NORMALCY OF DIET (CHECK ONE) **RATING**(11)
Begin by asking the patient what kind of foods are difficult for him/her to eat. Based on patient's response, choose an item at the low end of the scale. Move up the scale giving examples of foods in each category and ask patient if s/he can eat those food items. The patient's score is the highest number to which an affirmative response is received.

- ☐ 100 = Full diet (no restrictions)
- ☐ 90 = Peanuts
- ☐ 80 = All meat
- ☐ 70 = Carrots, celery
- ☐ 60 = Dry bread and crackers
- ☐ 50 = Soft, chewable foods (e.g., macaroni, canned/soft fruits, cooked vegetables, fish, hamburger, small pieces of meat)
- ☐ 40 = Soft foods requiring no chewing (e.g., mashed potatoes, apple sauce, pudding)
- ☐ 30 = Pureed foods (in blender)
- ☐ 20 = Warm liquids
- ☐ 10 = Cold liquids
- ☐ 0 = Non-oral feeding (tube fed)

7 PUBLIC EATING (CHECK ONE) **RATING**(12)
Score the Public Eating scale by asking the patient where s/he eats, with whom s/he eats and whether s/he alters his/her diet according to where s/he is eating. Choose the score beside the description that best fits the patient.

- ☐ 100 = No restriction of place, food or companion (eats out at any opportunity)
- ☐ 75 = No restriction of place, but restricts diet when in public (eats anywhere, but may limit intake to less "messy" foods, e.g., liquids)
- ☐ 50 = Eats only in presence of selected persons in selected places
- ☐ 25 = Eats only at home in presence of selected persons
- ☐ 0 = Always eats alone

8 UNDERSTANDABILITY OF SPEECH (CHECK ONE) **RATING**(13)
This scale is scored based on the interviewer's ability to understand the patient during conversation (in this case, based on conversation regarding the Normalcy of Diet and Public eating scale. Choose the score beside the description that best fits the patient.

- ☐ 100 = Always understandable
- ☐ 75 = Understandable most of the time; occasional repetition necessary
- ☐ 50 = Usually understandable; face-to-face contact necessary
- ☐ 25 = Difficult to understand
- ☐ 0 = Never understandable; may use written communication

COMMENTS(14)_____
_____

Appendix VI
QOL
Patient Information Sheet

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. This booklet contains the EORTC-QLQ H&N 35 form, the FACT H & N (Version 4), the XeQOLS form, the Dermatology Life Quality Index form, and the EQ-5D form.

2. Directions on how to complete each set of questions are written at the top of each set.

3. You will be given the nurse's name and telephone number. You can call them any time with any concerns or questions.

4. It is very important that you return the booklet with us, whether you finish the study or not.

Please complete and return to the study staff as soon as possible.

Thank you for taking the time to help us.

EORTC QLQ - H&N35

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		**Not at all**	**A little**	**Quite a bit**	**Very much**
31.	Have you had pain in your mouth?	1	2	3	4
32.	Have you had pain in your jaw?	1	2	3	4
33.	Have you had soreness in your mouth?	1	2	3	4
34.	Have you had a painful throat?	1	2	3	4
35.	Have you had problems swallowing liquids?	1	2	3	4
36.	Have you had problems swallowing pureed food?	1	2	3	4
37.	Have you had problems swallowing solid food?	1	2	3	4
38.	Have you choked when swallowing?	1	2	3	4
39.	Have you had problems with your teeth?	1	2	3	4
40.	Have you had problems opening your mouth wide?	1	2	3	4
41.	Have you had a dry mouth?	1	2	3	4
42.	Have you had sticky saliva?	1	2	3	4
43.	Have you had problems with your sense of smell?	1	2	3	4
44.	Have you had problems with your sense of taste?	1	2	3	4
45.	Have you coughed?	1	2	3	4
46.	Have you been hoarse?	1	2	3	4
47.	Have you felt ill?	1	2	3	4
48.	Has your appearance bothered you?	1	2	3	4

Please go on to the next page

During the past week:		Not at all	A little	Quite a bit	Very much
49.	Have you had trouble eating?	1	2	3	4
50.	Have you had trouble eating in front of your family?	1	2	3	4
51.	Have you had trouble eating in front of other people?	1	2	3	4
52.	Have you had trouble enjoying your meals?	1	2	3	4
53.	Have you had trouble talking to other people?	1	2	3	4
54.	Have you had trouble talking on the telephone?	1	2	3	4
55.	Have you had trouble having social contact with your family?	1	2	3	4
56.	Have you had trouble having social contact with friends?	1	2	3	4
57.	Have you had trouble going out in public?	1	2	3	4
58.	Have you had trouble having physical contact with family or friends?	1	2	3	4
59.	Have you felt less interest in sex?	1	2	3	4
60.	Have you felt less sexual enjoyment?	1	2	3	4

During the past week:		No	Yes
61.	Have you used pain-killers?	1	2
62.	Have you taken any nutritional supplements (excluding vitamins)?	1	2
63.	Have you used a feeding tube?	1	2
64.	Have you lost weight?	1	2
65.	Have you gained weight?	1	2

FACT-H&N (Version 4)

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you <u>during the past 7 days</u>**.

<u>PHYSICAL WELL-BEING</u>	Not at all	A little bit	Some-what	Quite a bit	Very much
I have a lack of energy	0	1	2	3	4
I have nausea	0	1	2	3	4
Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
I have pain	0	1	2	3	4
I am bothered by side effects of treatment	0	1	2	3	4
I feel ill	0	1	2	3	4
I am forced to spend time in bed	0	1	2	3	4

<u>SOCIAL/FAMILY WELL-BEING</u>	Not at all	A little bit	Some-what	Quite a bit	Very much
I feel close to my friends	0	1	2	3	4
I get emotional support from my family	0	1	2	3	4
I get support from my friends	0	1	2	3	4
My family has accepted my illness	0	1	2	3	4
I am satisfied with family communication about my illness	0	1	2	3	4
I feel close to you partner (or the person who is my main support)	0	1	2	3	4
Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box ☐ and go to the next section.					
I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

<u>EMOTIONAL WELL-BEING</u>	Not at all	A little bit	Some-what	Quite a bit	Very much
I feel sad	0	1	2	3	4
I am satisfied with how I am coping with my illness	0	1	2	3	4
I am losing hope in the fight against my illness	0	1	2	3	4
I feel nervous	0	1	2	3	4
I worry about dying	0	1	2	3	4
I worry that my condition will get worse	0	1	2	3	4

<u>FUNCTIONAL WELL-BEING</u>	Not at all	A little bit	Some-what	Quite a bit	Very much
I am able to work (including work in home)	0	1	2	3	4
My work (include work in home) is fulfilling	0	1	2	3	4
I am able to enjoy life	0	1	2	3	4
I have accepted my illness	0	1	2	3	4
I am sleeping well	0	1	2	3	4
I am enjoying the things I usually do for fun	0	1	2	3	4
I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

<u>ADDITIONAL CONCERNS</u>	Not at all	A little bit	Some-what	Quite a bit	Very much
I am able to eat the foods that I like	0	1	2	3	4
My mouth is dry	0	1	2	3	4
I have trouble breathing	0	1	2	3	4
My voice has its usual quality and strength	0	1	2	3	4
I am able to eat as much food as I want	0	1	2	3	4
I am unhappy with how my face and neck look	0	1	2	3	4
I can swallow naturally and easily	0	1	2	3	4
I smoke cigarettes or other tobacco products	0	1	2	3	4
I drink alcohol (e.g. beer, wine, etc.)	0	1	2	3	4
I am able to communicate with others	0	1	2	3	4
I can eat solid foods	0	1	2	3	4
I have pain in my mouth, throat or neck	0	1	2	3	4

University of Michigan Xerostomia – Related Quality of Life Scale (XeQOLS)

These questions are concerned with your oral health and how it affects your life. Please answer the questions by checking the box that describes best how true each statement has been for you during the **past 7 days.**

1. My mouth/throat dryness limits the kinds or amounts of food I eat.
☐Not at all ☐A little ☐Somewhat ☐Quite a bit ☐Very much

2. My mouth/throat dryness causes discomfort.
☐Not at all ☐A little ☐Somewhat ☐Quite a bit ☐Very much

3. My mouth/throat dryness causes a lot of worry or concern.
☐Not at all ☐A little ☐Somewhat ☐Quite a bit ☐Very much

4. My mouth/throat dryness keeps me from socializing (going out).
☐Not at all ☐A little ☐Somewhat ☐Quite a bit ☐Very much

5. My mouth/throat dryness makes me uncomfortable eating in front of other people.
☐Not at all ☐A little ☐Somewhat ☐Quite a bit ☐Very much

6. My mouth/throat dryness makes me uncomfortable speaking in front of other people.
☐Not at all ☐A little ☐Somewhat ☐Quite a bit ☐Very much

7. My mouth/throat dryness make me nervous.
☐Not at all ☐A little ☐Somewhat ☐Quite a bit ☐Very much

8. My mouth/throat dryness makes me concerned about the looks of my teeth and mouth.
☐Not at all ☐A little ☐Somewhat ☐Quite a bit ☐Very much

9. My mouth/throat dryness keeps me from enjoying life.
☐Not at all ☐A little ☐Somewhat ☐Quite a bit ☐Very much

10. My mouth/throat dryness interferes with my daily activities.
☐Not at all ☐A little ☐Somewhat ☐Quite a bit ☐Very much

11. My mouth/throat dryness interferes with my intimate relationships.
☐Not at all ☐A little ☐Somewhat ☐Quite a bit ☐Very much

12. My mouth/throat dryness has a bad effect on tasting food.
☐Not at all ☐A little ☐Somewhat ☐Quite a bit ☐Very much

13. My mouth/throat dryness reduces my general happiness with life.
☐Not at all ☐A little ☐Somewhat ☐Quite a bit ☐Very much

14. My mouth/throat dryness affects all aspects of life.
☐Not at all ☐A little ☐Somewhat ☐Quite a bit ☐Very much

15. If you were to spend the rest of your life with your mouth/throat dryness just the way it is now, how would you feel about this?
☐Delighted ☐Mostly satisfied ☐Mixed: equally satisfied/dissatisfied ☐Mostly dissatisfied ☐ Terrible

DERMATOLOGY LIFE QUALITY INDEX

Hospital No: Date:
Name: Score: Address:
Diagnosis:

The aim of this questionnaire is to measure how much your skin problem has affected your life
OVER THE LAST WEEK. Please tick ⌢ one box for each question.

1.	Over the last week, how itchy, sore, painful or stinging has your skin been?	Very much A lot A little Not at all	⌢ ⌢ ⌢ ⌢	
2.	Over the last week, how embarrassed or self conscious have you been because of your skin?	Very much A lot A little Not at all	⌢ ⌢ ⌢ ⌢	
3.	Over the last week, how much has your skin interfered with you going shopping or looking after your home or garden?	Very much A lot A little Not at all	⌢ ⌢ ⌢ ⌢	Not relevant ⌢
4.	Over the last week, how much has your skin influenced the clothes you wear?	Very much A lot A little Not at all	⌢ ⌢ ⌢ ⌢	Not relevant ⌢
5.	Over the last week, how much has your skin affected any social or leisure activities?	Very much A lot A little Not at all	⌢ ⌢ ⌢ ⌢	Not relevant ⌢
6.	Over the last week, how much has your skin made it difficult for you to do any sport?	Very much A lot A little Not at all	⌢ ⌢ ⌢ ⌢	Not relevant ⌢
7.	Over the last week, has your skin prevented you from working or studying?	Yes No	⌢ ⌢	Not relevant ⌢
	If "No", over the last week how much has your skin been a problem at work or studying?	A lot A little Not at all	⌢ ⌢ ⌢	
8.	Over the last week, how much has your skin created problems with your partner or any of your close friends or relatives?	Very much A lot A little Not at all	⌢ ⌢ ⌢ ⌢	Not relevant ⌢
9.	Over the last week, how much has your skin caused any sexual difficulties?	Very much A lot A little Not at all	⌢ ⌢ ⌢ ⌢	Not relevant ⌢

10.	Over the last week, how much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	⌒ ⌒ ⌒ ⌒	Not relevant ⌒

Please check you have answered EVERY question. Thank you.

EQ 5-D

By placing a checkmark in one box in each group below, please indicate which statement best describe your own health state today.

Mobility

☐ I have no problems in walking about

☐ I have some problems in walking about

☐ I am confined to bed

Self-Care

☐ I have no problems with self-care

☐ I have some problems washing or dressing myself

☐ I am unable to wash or dress myself

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

☐ I have no problems with performing my usual activities

☐ I have some problems with performing my usual activities

☐ I am unable to perform my usual activities

Pain/Discomfort

☐ I have no pain or discomfort

☐ I have moderate pain or discomfort

☐ I have extreme pain or discomfort

Anxiety/Depression

☐ I am not anxious or depressed

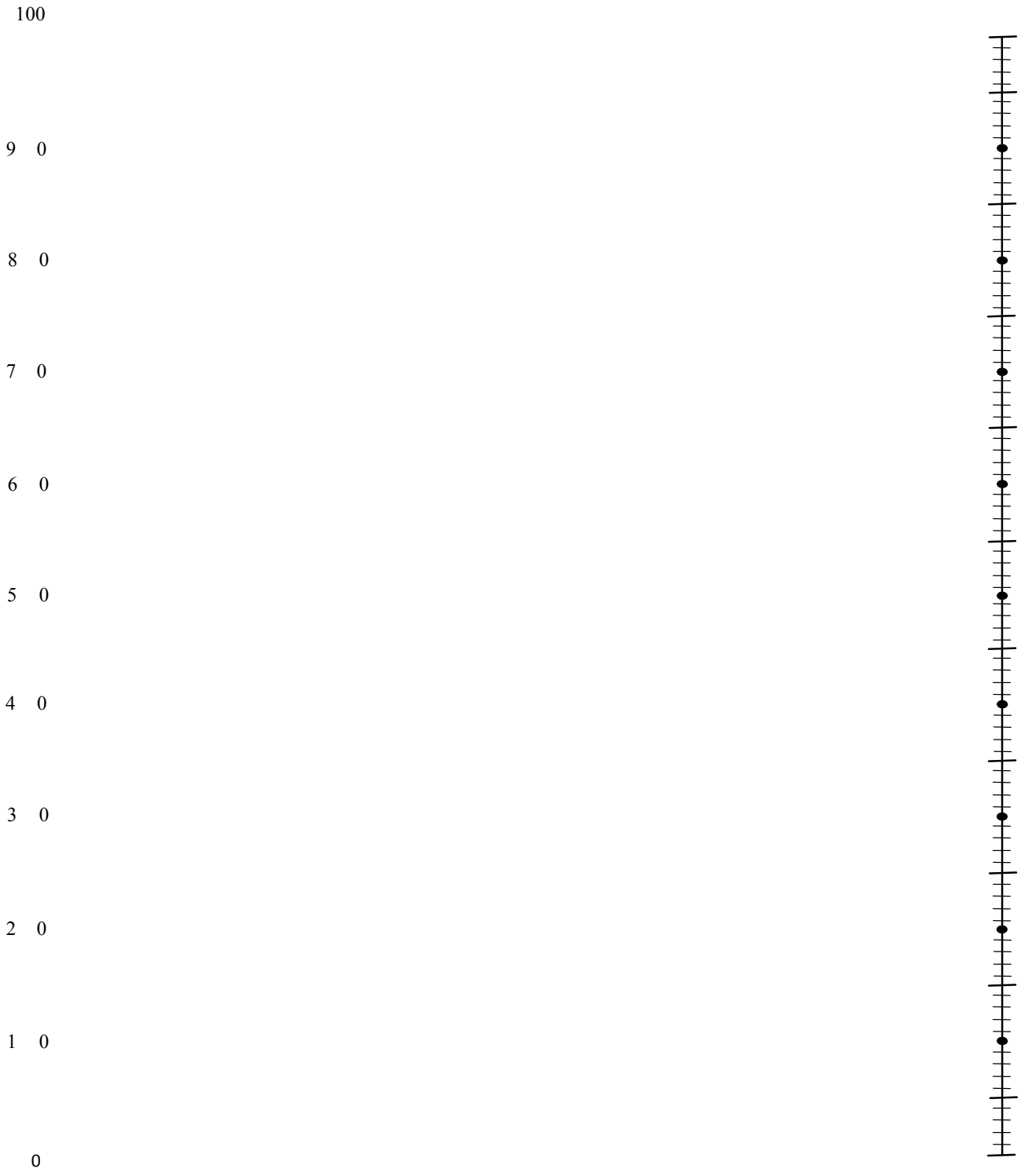
☐ I am moderately anxious or depressed

☐ I am extremely anxious or depressed

Best imaginable
health state

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.


100
9 0
8 0
7 0
6 0
5 0
4 0
3 0
2 0
1 0
0
Worst imaginable health state