PILOT FEASIBILTY TRIAL OF DOSE VOLUME ADJUSTED CHEMORADIOTHERAPY IN HPV-ASSOCIATED OROPHARYNGEAL CANCER OF THE ELDERLY (DACHOC-E)

Principal Investigator/Radiation Oncology
Omar Mahmoud, MD
omar.mahmoud@bmcjax.com

Co-Principal Investigator/Radiation Oncology
Mark Augspurger, MD
Mark.Augspurger@bmcjax.com

Head and Neck Surgical Oncology Chair
Faisal Ahmad, MD
faisal.ahmad@bmcjax.com

Head and Neck Surgical Oncology
Erica Mayland, MD
erica.mayland@bmcjax.com

Medical Oncology Chair
Ian Pinto, MD
ian.pinto@bmcjax.com

PILOT FEASIBILTY TRIAL OF DOSE VOLUME ADJUSTED CHEMORADIOTHERAPY IN HPV-ASSOCIATED OROPHARYNGEAL CANCER OF THE ELDERLY (DACHOC-E)

CONTENTS

SCHEMA

<table>
<tr>
<td rowspan="5">Register</td>
<td rowspan="5">P16 Positive</td>
<td rowspan="5">Stratify</td>
<td>Frailty G8 score < 14 vs. ≥14</td>
<td rowspan="5">ENROLL</td>
<td rowspan="5">RT 55Gy in 25 fractions to GTV
42.5 Gy to 3cm marginal region
+ weekly Cisplatin 40 mg /m2 in 5 weeks</td>
</tr>
<tr>
<td>Any T stage (T1, T2, T3, T4)</td>
</tr>
<tr>
<td>N positive (any N stage with positive regional lymph nodes: N1, N2, N3)</td>
</tr>
<tr>
<td>>65-≤75 vs. >75</td>
</tr>
<tr>
<td>Smoking History: ≤ 10 PY vs. >10 PY</td>
</tr>
</table>

1. OBJECTIVES

1.1 Primary Objective

1.1.1 To determine non-inferiority of hypofractionated short radiotherapy regimen in elderly patients in term of 2 years progressive free survival compared with published outcomes.

1.2 Secondary Objectives

1.2.1 To establish frailty index as a good discriminator on the patient who cannot tolerate aggressive long term chemoradiotherapy with its association to the need of PEG tube, hospitalization and treatment breaks compared with published outcomes.

1.2.2 To compare patterns of failure (locoregional vs. distant) with published outcomes.

1.2.3 To compare acute toxicity profiles (and overall toxicity burden) with published outcomes.

1.2.4 To compare long term toxicity CTCAE, v. 4 late toxicity at 1, 2 years with published outcomes.

2. BACKGROUND

2.1 Oropharyngeal Cancer: Current State of Practice and Purpose of This Trial

The recent rapid rise in the incidence of oropharyngeal human papilloma virus-associated carcinoma (HAOPC) and the increased prevalence in elderly patients above 65 years old have prompted the evaluation of treatment intensity de-escalation [1].

While the 3-year survival in low risk patients in RTOG 0129 was 93%, [2] the standard of care platinum based chemoradiotherapy with large radiation fields endorsed by NRG [2]and GORTEC [3] are associated with very high level of acute and long term toxicities as well as fatalities[4, 5].

First set of deintensification studies, DeESCALaTE and RTOG 1016, confirmed that Cisplatin cannot be substituted with Cetuximab without jeopardizing local control [6, 7]. University of Florida and North Carolina phase II studies reported 3-year locoregional control and survival of 100% and 93% with radiation dose reduction (60Gy to gross disease and 48-54Gy to elective neck)[8]. Currently, NRG-HN002 and HN005 are investigating 60Gy in 6 weeks.

More importantly, the evidence to treat elderly patients (> 65) and those with frailty is lacking. Frailty indices were shown to offer an important prognosticator for overall survival and overall tolerance to treatment [9].

2.2 Rationale for Lower Dose Radiation

As the recent studies demonstrated the superiority of combined chemoradiotherapy, the contribution of concurrent chemotherapy may be considered radiobiologically equivalent to approximately 8-9 Gy10 of biologic effective dose (BED)[10, 11]. With an effective concurrent radiosensitizer, the risks of reducing the radiation dose may be mitigated.

Phase II studies employing lower radiation dose are ongoing as shown in table 1. Indeed NRG HN002 met acceptability criterion of 2-year progression-free-survival exceeding 85% with either 60Gy in 6 weeks with Cisplatinum as well as 60Gy in 5 weeks without chemotherapy [12]. The most recent update confirmed 2-year overall survival of 96.7% for the cisplatin arm meeting both end points (PFS and OAS) to be advanced to the phase III arm[13].

Even at lower radiation doses (30Gy) investigators at MSKCC demonstrated that 30 Gy may result in complete response in selected patients based on response image guided phase II study [14]. In this study, PET guidance after 30 Gy allowed de-escalation of the dose from 70 to 30 Gy in 15 out of the 18 patients.

Achieving similar tumor outcome with a reduced dose is expected to be associated with higher therapeutic value through reducing grade 2-3 severe acute and late toxicities [4, 5] which in turn especially valuable in frail elderly patient population.

Table 1: Phase II studies employing lower radiation dose.

Institution Name	Systemic Agent	Dose to Gross Disease	Target Accrual	Primary Endpoint
Univ. North Carolina, Chapel Hill	Concurrent cisplatin 30 mg/m2 weekly	60 Gy	40	Pathologic response at 3 months
John Hopkins Univ.	Concurrent Cisplatin 40 mg/m2 weekly	63 Gy to pharyngeal constrictors, larynx, parotids, mandible, and masticatory muscles +8 mm expansion, 70 Gy to remainder of PTV	60	Local-regional control ≥ 80%, late toxicity at 2 years
Long Island Jewish Hosp.	Induction TPF x 3, then +/- concurrent chemotherapy	Responders: 70 Gy; non-responders: 70 Gy (with concurrent chemotherapy)	50	Response at 3 months
Dana Farber Cancer Institute	Induction TPF x 3, then concurrent chemotherapy	Responders receive "reduced dose"	50	Local-regional control at 2 and 5 years
ECOG 1308	Induction TP-cetuximab x 3, then	Responders: 54 Gy; non-responders: 70 Gy	90	PFS at 2 years in 54 Gy group

	concurrent chemotherapy			
Memorial Sloan Kettering	"Standard chemotherapy" (concurrent regimens)	70 Gy to primary, 60 Gy to nodes followed by neck dissection	100 HPV+, 50 HPV-	Feasibility of 18F-MISO PET to detect hypoxia, 3-month neck control ≥ 80%
Univ. of California, Davis	Induction carboplatin-paclitaxel x 2, then concurrent paclitaxel	Complete response: 54 Gy; non-responders: 60 Gy	50	PFS at 2 years

Reduction of radiation dose and volume is expected to reduce the long-term side effects of radiation therapy. The ability to reduce the low or intermediate-level doses further may allow lesser xerostomia, dysphagia, neuropathy and hypothyroidism through better sparing of salivary glands [15], thyroid gland [16], and brachial plexus [17].

2.3 Rationale for Reduced Size of Radiation Fields

Pattern of lymph node metastasis and consequent target volume definition are largely influenced by the seminal paper by Dr. Lindberg and Byers et al[18] [19]. However, extensive coverage based on risk of lymph node involvement led to excessive head and neck mucosa and organs at risk exposure to therapeutic radiation dose with consequent higher toxicity.

Reduction in target coverage was shown in multiple studies to result in same local control rate while reducing toxicity. In Chicago University experience, reducing field to contralateral level II and retropharyngeal lymph nodes during three phases of radiation planning (comprising 748 head and neck cancer patients) showed comparable locoregional control with improvement of swallowing scores and reduction of long-term dysphagia [20]. Princess Margret investigators updated their experience with the role of ipsilateral radiation in the HPV positive tonsillar cancer N0-N2b cases showing contralateral failure rates of 2% [21].

Similar findings were confirmed in 901 tonsillar cancer patients treated at MDACC where the contralateral recurrence was 2% [22].

After induction chemotherapy HPV positive oropharyngeal cancer patients were treated to the gross disease and the first echelon of lymph nodes with a 2-year PFS of 95% [23].

All of these studies confirm that a tighter radiation volume encompassing the primary disease with the next echelon of lymph nodes without needing to cover contralateral or low risk lymphatics with probability of harboring microscopic disease is less than 5% is justified and, more importantly, is expected to be associated with lower toxicity especially in frail elderly patient population.

2.4 Rationale for Hypofractionated Regimen

Hypofractionated radiotherapy was used successfully in laryngeal tumor with limited volume disease. The Japanese experience reported superior local control with 56.25 Gy in 25 fractions (2.25 Gy/fraction over 39 days compared to 60Gy in 30 fractions (2 Gy/fraction over 46 days)[24]. The radiobiological rational for this superior outcomes was postulated to be two folds: The first is shortening the overall treatment time in a rapidly populating tumor clone as head and neck squamous cell carcinoma [25] and the second due to associated increased radiosensitivity with higher dose per fraction [26].

The importance of overall time was recently validated in the RTOG 0129 study showing that 72Gy in 6 weeks with 2 cycles of chemotherapy provided the same survival as 70Gy in 7 weeks with 3 cycles of chemotherapy postulating that accelerated delivery of radiotherapy counteracted the rapid tumor repopulation (addressed by the third cycle of chemotherapy)[27].

To reduce overall treatment time effect, subsequent standard radiotherapy regimens in head and neck studies adopted a mildly hypofractionated dose prescription permitting the therapy to be completed in 33 fractions delivering 69.96 Gy, 59.4 Gy and 54.45Gy in 2.12 Gy, 1.8 Gy and 1.65Gy, respectively.

In our proposal, 55Gy in 25 fractions to gross tumor disease would be equivalent to 63 Gy in 2Gy per fraction and 42.5 Gy to subclinical microscopic disease would be equivalent to 41Gy in 2Gy per fraction adopting 21 day as time to accelerated tumor repopulation and 0.75Gy per day as dose of radiation needed to account for prolongation of overall treatment time per day as proliferative an alpha beta ratio of 3 and 10 for late reacting tissue and tumor, respectively. Form a normal tissue perspective, cell turnover kinetics are not typically included to estimate late radiation damage with 55Gy and 42.5Gy would be equivalent to 57.2 and 40 Gy, respectively, with standard fraction size [25].

A more intense hypofractionation with Cisplatin was shown to be feasible in a recent study employing 20 fractions to deliver 55Gy and 46Gy to gross and subclinical disease, respectively [28]. Moreover, MSKCC investigators reviewed a more intense hypofractionated regimen with fractions size >6Gy showing safety and efficacy of this approach [29]. Especially in elderly frail patients, reduction of grade 3 acute toxicity to 36% was observed with 40Gy in 16 factions indicating the potential clinical benefit of this approach [30].

The study hypothesizes that a dose reduction to sensitive HPV positive malignant clone delivered in a slightly hypofractionated regimen with a shorter overall time maybe not only feasible but expected to be more convenient with less acute mucosal toxicity and less financial toxicity with patient needing to commit to 5 week course instead of the 6 week course currently being tested in NRG. Moreover, reducing the radiation course by an extra week may lead to significant reduction in overall health expenditure especially for a vulnerable patient population highlighting the cost effectiveness of this approach [31].

2.5 Rationale for Frailty Index Selection and Stratification

Frail elderly patient population displays multiple competing mortality hazards ranging from cancer related (tumor recurrence and mortality), treatment-related morbidity and mortality (mucositis associated infection, immunocompromised infection, aspiration pneumonia, malnutrition and dehydration), and increased age intercurrent non-cancer mortality are all well known to complicate the interpretation of treatment effects[32].

In addition, the magnitude of benefit from treatment intensification is not the same across all age strata and such intensification is controversial as survival advantage was not seen in elderly individuals[33].

While Frailty models have been adopted to predict chemotherapy toxicity in the cancer management in general [34], the formal adoption in radiation patients in general and in head and neck cancer patient in particular has not been formalized or in wide use as expected [35].

Multiple models showed good prediction of frailty in elderly population to identify a patient subpopulation that might benefit from selective treatment deintensification [36-38].

Multiple factors were found to be associated with morbidity and mortality in elderly frail head and neck cancer patients undergoing chemoradiotherapy and typically assessed in the comprehensive geriatric assessment (CGA) model [39]:

a. The presence of more than 2 comorbidities [40] on Charlson comorbidity score
b. Depressed mood with score 9 or more on Geriatric Depression Scale Short form 33(GDS-SF33)[41]
c. More than 2 falls in the last 3 months [42]
d. Lowered cognitive performance on mini mental examination with score 23 or less [42]
e. Body mass index < 18.5 or loosing $\geq$ 5% of body weight in the last 6 months [43, 44]
f. Intake of more than 5 medications [43]
g. Score 7 or higher in Lawton scale of instrumental activity of daily living (IADL)[41]

In a prospective cohort of 461 head and neck cancer patients, vulnerable group defined as impairment of 2 of more domain in GCA model as defined above- was detected in almost one third of the cohort and this group showed lower survival at 12 and 18 months of 76% and 66%, respectively versus 89% and 81% observed in the non-vulnerable group [39]. Another study confirmed frailty using GCA (present in 43.6% of the patients) was a good predictor of 2 year mortality (P=0.27); however incorporating voice handicap index (VHI)$\geq$8, MD Anderson Dysphagia Inventory (MDADI) <70 were highly significant predictors of mortality and morbidity at 2 years [37]. In this study, high risk patients (14% of the patient population) with more than 5 factors (age >75, >220 PPY smoking, body weight loss, ECOG$\geq$2, CCI $\geq$1, dental problem, VHI$\geq$8, MDADI <70 and Beck depression inventory $\geq$14) displayed 60% 2-year mortality rate compared with 16% in patients with 2 to 4 risk factors. In addition, another study validated a

prognostic model based on Karnofsky Performance Status ≤ 70, Charlson Comorbidity Index (CCI) ≥ 6 and C-reactive protein (CRP) ≥ 5 and, in this cohort of 284 head and neck cancer patients older than 75 year old, the median survival was 9 months versus 130 months (p=0.005) in unfavorable versus favorable risk group, respectively [9].

While GCA is the gold standard and the most comprehensive, adoption in regular clinic is hampered by documentation of 7 domains with some domains involving extensive questionnaire. Also, its discrimatory impact on identifying those patients who would benefit from deescalated regimen was inferior to newer models [37]. Therefore, alternate more practical assessment tools were compared with GCA including vulnerable elders-survey 13 (VES13) and G8 [45]. The G8 was found to provide superior correlation with GCA in the ONCODAGE study evaluating these screening tools in 1435 patients [46]. Although ongoing studies are still employing GCA in prospective studies: ELAN-RT (NCT01864850) testing different definitive radiotherapy regimens in older adults aged ≥70 years, G8 practicality was assessed and shown to provide an equivalent precision [47, 48]. In anticipating widespread adoption in the clinic is one of the main study hypotheses confirming the validity of this screening tool and the 14 cut point used for stratification.

2.6 Toxicity and Quality of Life (QOL)

In addition to showing the non-inferiority of radiation dose deescalation in HPHNC elderly patients and in addition to establishing the frailty index G8 in identifying those at high risk of morbidity and mortality with standard radiation doses, the study aim to show that the reduction in radiation dose and fields will substantially reduce the burden of acute toxicity, improve swallowing function which will reflect on QOL.

The protocol-specific Toxicity Assessments are defined as evaluations performed by the clinical team and will include clinician-reporting and grading of CTCAE (v. 4) symptoms, findings on physical examination, and laboratories.

The tools and time points selected are designed to capture most of the short- and longer-term effects of the treatment. Short term assessments include baseline status, end of treatment at week 5 or 7 when maximum acute toxicity is expected, as well as tracking of subacute toxicity and/or recovery at 3 and 6 months. The late changes usually more obvious between 6 months and 2 years when certain late effects such as dry mouth, incomplete return of taste, persistent weight loss, pain syndromes, soft tissue necrosis and/or, bone necrosis may be predominant.

Protocol-specific Toxicity assessments will evaluate and compare events in patients regarding the following:

- Reduction in 10 key acute toxicity rates by > 50%.
- Reduction in acute high-grade (3-4) dysphagia by > 50%.
- Reduction in feeding tube usage by > 50%.

- Reduction in 4 key late effects by > 50%.

Assuming the primary endpoint (non-inferior 2-year locoregional control) is met, and both toxicity outcome goals are met, then concurrent short course radiotherapy would be considered an effective and less toxic alternative to concurrent standard arm, in locally advanced HPV-associated carcinoma of the oropharynx.

2.6.1 Schedule of Toxicity Assessments

Toxicity assessments will occur on a limited schedule over the first 2 years. Routine follow up and cancer status evaluations will occur as per the traditional follow-up schedule during and after completion of the 2-year. Beyond 2 years, CTCAE late effects will revert to standard collection methods.

Toxicity will be collected at only 6 time-points, all follow-up evaluations performed over the first 2 years (baseline, end treatment, 1, 3, 6, 9 12, 15, 18, 21, and 24 months) will include the same case report forms (CRFs) instructing sites regarding collection of hard coded CTCAE terms.

2.6.2 Clinician-reported Toxicity Assessment Tools

Toxicity-related tools will be collected and reported by clinical staff. Collectively, completion of these forms requires < 30 minutes for the patient-clinician-research associate interaction.

- CTCAE events (10-15 minutes);
- Nutrition/feeding tube
- Dental status

2.6.3 Swallowing Function

Swallowing limitation heavily impact QOL [49]. Similarly, the persistent need of feeding tube support hinders social functioning with its resultant psychological distress, and cost. Measuring swallowing toxicity can be performed using diet assessment, video fluoroscopy, and patient questionnaires. In the absence of gold standard for barium swallow interpretation [49], several measurement methods for swallowing will be used:

- Hard-coded CTCAE events (Dysphagia);
- Feeding tube use;
- Weight loss;

2.6.4 Acute and Late Toxicity Profiles

Cisplatin enhances radiation-related epithelial reactions, causes life-threatening neutropenia, and carries high gastrointestinal effects. Chemoradiation has been shown to impact QOL and head and neck specific domains for up to 1 year. Functional outcomes from chemoradiation (dry mouth, dental effects, swallowing disorders, neurosensory, and mood disorders) can persist for the remainder of survivorship, which is expected to be > 70% at 5 years in the HPV-associated head and neck population.

Estimated differences in acute toxicity rates extrapolated from RTOG 1016 and RTOG 0522 (using identical chemoradiation to the standard arm in this study), specifically for a cohort of oropharynx cancers treated with IMRT (N=278 for acute, and N= 270 for late toxicity). The median follow-up on this cohort is 1.9 years (range: 0.3- 4.0).

Based on comparative review of these data, detectable reductions are anticipated in 10 specific acute effects item:

-grade 3+ dysphagia (26% versus 61%),

- pain (28% versus 71%),

Estimated Difference in Overall Acute Toxicity Burden (T-score) routine reporting of adverse events will be performed using the CTCAE v. 4.0 terminology and grading system. Data will be reported, including a summary of lower toxicity (grade 1-2) versus higher toxicity (grade 3-4) events.

Early Deaths due to toxicity or within 30 days of completing radiation were reported in RTOG 0522; 6 patients (2.2%) died from toxicity or within 30 days of completing treatment (2 patients died of treatment-related causes and 4 additional patients died within 30 days of treatment from other causes). Similar figures were reported in RTOG 0129 (2.8%). Deaths due to toxicity will be reported separately as well as G5 side effects. Death from non-related comorbidities or other causes will be reported but not counted as treatment related mortality.

A simple 5-point global health dental scale was created in RTOG 1016 and will be used in this study due to absence of global dental instrument: edentulous, excellent, good, fair, or poor (see Appendix 4). In addition to overall assessment of dental health changes over time, a dental “count” will be performed at each of the designated outcome assessments (Appendix 5) which involve simply counting the number of native teeth at each visit, not including bridges or partial or full dentures. A diagram of 32 teeth will be provided to assist in dental count. The percent change from baseline in number of teeth over time will be reported. Loss of teeth (up to 10 years follow up) should give a quantitative measure of changes in dental health in the HPV associated population treated with IMRT.

3. ELIGIBILITY AND INELIGIBILITY CRITERIA

For questions concerning eligibility or radiation therapy-related questions, please contact the principal investigator.

3.1 Eligibility Criteria

A patient cannot be considered eligible for this study unless ALL the following conditions are met.

3.1.1 Pathologically proven diagnosis of squamous cell carcinoma (not including the neuroendocrine phenotype) of the oropharynx (tonsil, base of tongue, soft palate, or oropharyngeal walls); cytologic diagnosis from a cervical lymph node is sufficient in the presence of clinical evidence of a primary tumor in the oropharynx. Clinical evidence should be documented, may consist of palpation, imaging, or endoscopic evaluation, and should be sufficient to estimate the size of the primary (for T stage).

3.1.2 Patients must have clinically or radiographically evident measurable disease at the primary site or at nodal stations. Simple tonsillectomy or local excision of the primary without removal of nodal disease is not permitted, as is excision removing gross nodal disease prior to chemoradiotherapy.

3.1.3 P16-positive based on local site immunohistochemical tissue staining (defined as greater than 70% strong diffuse nuclear or nuclear and cytoplasmic staining of tumor cells). Fine needle aspiration (FNA) biopsy specimens may be used as the sole diagnostic tissue.

3.1.4 Clinical stage Any T as long as N+ and M0 AJCC, 8th ed.) including no distant metastases based on the following diagnostic workup:

- General history and physical examination within 56 days prior to registration.
- Exam with laryngopharyngoscopy (mirror or in office direct procedure acceptable) within 70 days prior to registration.
- One of the following imaging studies is required within 56 days prior to registration:

Chest and neck CT with contrast or FDG-PET/CT of the neck and chest (with or without contrast); FDG-PET/CT scan is strongly preferred and highly recommended to be used for eligibility.

3.1.5 Patients must provide their personal smoking history prior to registration. The following formula is used to calculate the pack-years during the periods of smoking in the patient's life; the cumulative total of the number of pack-years during each period of active smoking is the lifetime cumulative history.
Number of pack-years = [Frequency of smoking (number of cigarettes per day) × duration of cigarette smoking (years)] / 20

3.1.6 Age ≥ 65.

3.1.7 Normal organ and marrow function within 14 days prior to registration defined as follows:

- Absolute neutrophil count ≥ 1,500/mcL
- Platelets ≥ 100,000/mcL
- Hemoglobin ≥ 8.0 g/dL (Note: use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dL is acceptable)
- Total bilirubin ≤ 1.5× institutional upper limit of normal (ULN)
- AST(SGOT) or ALT(SGPT) ≤ 3.0 × institutional ULN
- Serum creatinine ≤ 1.5× institutional ULN

3.1.8 Patients with known Human immunodeficiency virus (HIV)-infection on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

3.2 Ineligibility Criteria

3.2.1 Metastatic disease

3.2.2 Recurrent disease after primary management

3.2.3 Cancers with center of mass is outside the oropharyngeal boundaries (i.e. laryngeal, hypopharyngeal, nasopharyngeal or oral cavity tumors)

3.2.4 Synchronous double primaries

3.2.5 Prior radiotherapy for lymphoma or other malignancy

3.2.6 Prior systemic therapy including immunotherapy

3.2.7 Severe active comorbidity where life expectancy is <1 year.

3.2.8 Autoimmune disease

3.2.9 Patient with known Uncontrolled HIV

4. REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP

4.1 Assessments: Pre-Treatment:

Time Point	Procedure	Notes
Prior to registration	• Pathologically confirmed oropharyngeal HPV	

	positive squamous cell carcinoma • Smoking history	
70 days prior to registration	Endoscopic evaluation of tumor	
56 days prior to registration	• H&P • FDG PET Scan • Diagnostic CT or MRI neck if clinically indicated	
14 days prior to registration	CBC CMP(NA, K, Ca, Glu, Cr, BUN, AST, ALT, Bil, Alb)	
Prior to treatment	• G8 • MDADI Dental assessment VHI	

4.2 Assessments: On Treatment

Time Point	Procedure	Notes
Cycles 1 to 5 (weekly)	-CBC +Diff -CMP (NA, K, Ca, Glu, Cr, BUN, AST, ALT, Bil, Alb) -Physical Exam -Weekly RT assessment -Adverse events evaluation -Cisplatin 40 mg/m2 given over 60 minutes	

Week 5	• H&P • Adverse events evaluation PEG tube existence, documentation if in active use. • Weight • MDADI • VHI • G8	

4.3 Assessments: Follow Up

Time Point	Procedure	Notes
At 12-16 weeks from RT end	• FDG PET scan	
1, 3, 6, 9 12, 15, 18, 21, and 24 months	• H&P • Adverse events evaluation • PEG tube existence, documentation if in active use. • Weight • MDADI • VHI • G8 • Dental assessment if medically necessary	

<u>Definition of Disease Assessments</u>

• Response versus "Tumor Clearance" versus Cancer Progression

Response and confirmation of local (primary site) or regional (neck) "tumor clearance" are not endpoints in this study. Clinical or radiographic evidence of progressive local-regional disease beyond 20 weeks should be documented in the clinical record and ideally confirmed by local or regional biopsy, neck dissection, or salvage surgery. CT or MRI (of head and neck region, with

Chest CT), or PET/CT (including chest anatomy) may be used as radiographic evaluation of overall cancer status. The primary, neck and chest portions of the scans should be evaluated and reported separately. The CT portion of a PET/CT may serve as sufficient radiographic evaluation of the chest. If CT or MRI is used for evaluation of the head and neck region, CT of chest will be needed to rule out distant disease or second primaries at the designated evaluation intervals.

• Local or Regional Progression

Local (primary site) or regional (neck) progression is defined as clinical or radiographic evidence of progressive disease at the primary site or neck. The location of progressive disease should be separately distinguished (local vs. neck) to document the precise pattern of failure if possible. Progression of local or regional disease should be confirmed by biopsy when possible but may be clinically assessed and documented in the clinical record at the judgment of the treating clinicians. Suspicion of disease progression exclusively on the basis of indeterminate or positive PET/CT scan should be confirmed with continued clinical follow-up or pathologically.

• Distant Metastasis

Clear evidence of distant metastases (lung, bone, brain, etc.); biopsy is recommended where possible. A solitary, spiculated lung mass/nodule is considered a second primary neoplasm unless proven otherwise.

- **Second Primary Neoplasm**

Tumor reappearing with the initial and immediate adjoining anatomical region of the primary will be considered local recurrence. Multiple lung nodules/masses are considered distant metastases from the index cancer unless proven otherwise.

5. TREATMENT PLAN

Protocol treatment must begin within 30 days from signing informed consent. .

5.1 Systemic Therapy: Cisplatin

5.1.1 Intravenous Cisplatin Administration Concurrent with Radiation

Cisplatin: 40 mg/m2/week, every week during radiation.
Dose should be based on actual body weight.
The first cisplatin infusion should be started within 24 hours before or after the first scheduled radiation treatment.
Cisplatin is administered concurrent with radiation therapy.
Doses of cisplatin that are not given or which are held for toxicities may be made up.
Aiming to deliver 5 cycles is the preferred goal.

Cisplatin should be administered on Mondays or Tuesdays to maximize overlap of daily radiation with cisplatin exposure.

Administration on Wednesday prior to that day's radiation dose is acceptable but not preferred.
Cisplatin should be administered before or after radiation.
Investigators should strive to administer cisplatin on schedule, but if the dose is not being held for toxicity reasons, a variance of 1 day is acceptable for vacations, holidays, etc.
If radiation treatments are held for toxicity, cisplatin dosing should also be held.

5.1.2 Cisplatin Concurrent with Radiation Administration Guidelines

- Cisplatin is highly ematogenic and can cause both acute and delayed nausea (occurring > 24 hours after chemotherapy administration).
    - Investigators should be prepared to use aggressive prophylactic antiemetics and hydration.
    - Many institutions will have standard guidelines for the administration of cisplatin at the doses used in this study.
    - **For purposes of this protocol, individual investigators may use their local guidelines for Cisplatin administration.**
    - The anti-emetic and hydration regimen and schedule is to be determined by the local investigator medical oncologist.

- All patients receiving cisplatin chemotherapy should be offered a combination of anti-emetics. Examples of appropriate anti-emetic choices are provided.
  o Neurokinin 1 (NK1) receptor antagonist
- Aprepitant 125 mg PO on day of cisplatin and 80 mg PO on days 2 and 3, or
- Fosaprepitant 150 mg IV on day of cisplatin

  o Serotonin (5-HT3) receptor antagonist
- Granisetron 1 mg IV on day of cisplatin, or
- Ondansetron up to 16 mg IV on day of cisplatin, or
- Palonosetron 0.25 mg IV on day of cisplatin

  o Steroid
- Dexamethasone up to 20 mg IV on day of cisplatin
  o Olanzapine
- 10 mg PO on day of cisplatin

  • Dexamethasone (up to 8 mg PO daily) and olanzapine may be continued on days 2 to 4 of cisplatin administration to prevent delayed nausea.
  • A 5-HT3 receptor antagonist may also be used as needed for delayed nausea.
  • *Cisplatin pre-hydration guidelines*: Pre-hydration with 1 liter D5 ½ NS and 40 meq KCL/ liter x 1 liter prior to cisplatin. Mannitol 12.5 gm IV immediately prior to cisplatin.
  • *Cisplatin administration*: Cisplatin, 100 mg/m2 over 30-60 minutes IV in 250 cc NS. Infusion rate not to exceed 2 mg/min. See Section 6.2 for dose modifications. See above discussion on scheduling and number of doses concurrent with radiation.

• *Cisplatin post-hydration guidelines*: Following the end of the cisplatin administration, an additional liter of ½ NS with 10 meq KCL/L, 8 meq MgSO4/L, and 25 g mannitol should be infused over 2 hours. On the second- and third-day following cisplatin, patient should be encouraged to take at least 2 liters of fluid per day orally. Patients unable to orally self-hydrate should be considered for additional IV hydration on these days with normal saline.

- *Low-dose Cisplatin pre-hydration guidelines*:

Pre-hydration with 1 liter D5 ½ NS and 40 meq KCL/ liter x 1 liter prior to cisplatin should be given.
Mannitol 12.5 gm IV immediately prior to cisplatin may be given. Use of mannitol is left to the discretion of the investigator.

- *Low-dose Cisplatin administration*:

Standard administration is cisplatin, 40 mg/m2 over 30-60 minutes IV in 250 cc NS.
Infusion rate not to exceed 2 mgs per min.

- *Low-dose Cisplatin post-hydration guidelines*:

Following the end of the cisplatin administration, an additional liter of D5½ NS with 10 meq KCL/L, 8 meq MgSO4/L, and 25 g mannitol should be infused over 2 hours.
On the second- and third-day following cisplatin, patient should be encouraged to take at least 2 liters of fluid per day orally.
Patients unable to orally self-hydrate should be considered for additional IV hydration on these days with NS. The amount of pre- and post-hydration is left to the discretion of the investigator.

5.2 Radiation Therapy

Intensity Modulated Radiation Therapy (IMRT) and Image-Guided Radiation Therapy (IGRT) are mandatory for this study.

Arm 1: 55 Gy radiation in 5 weeks using 5 fractions per week + Cisplatin every week

5.2.1 Treatment Technology

Megavoltage energy photon beam irradiation with energy ≥ 4MV is required (6MV energy is preferred).

Proton therapy is not allowed.

IMRT techniques including static field IMRT, and VMAT are allowed.

Matched conventional anterior neck field is not allowed.

Treatment machine must be equipped to provide daily kV, or MV image guidance.

The minimum requirements for image guidance are given in Section 5.2.10.

5.2.2 Immobilization and Simulation

Patients will be treated supine and must have a secure head and neck immobilization (e.g. aquaplast mask) made prior to the treatment planning CT scan.
The treatment planning CT scan should be performed with IV contrast or fused with IV contrast CT images with a slice thickness of 3 mm or less.

5.2.3 Imaging for Structure Definition, Image Registration/Fusion and Follow-up

A diagnostic CT or MRI for structure delineation is recommended. These may be fused to the planning CT scans to facilitate target and structure definition.

When available FDG PET/CT images may also be fused to the planning CT data set.

5.2.4 Definition of Target Volumes and Margins

All specified target volumes and organs-at-risk (OAR) will be contoured on the planning CT scan data sets and named according to the nomenclature described below. For the purposes of contouring, MRI and PET images, if available and clinically indicated, may be fused with the planning CT data set.

Target volumes and OARs will be labeled according to published guidelines:

- **Gross Tumor Volume (GTV)**

The GTV represents clinically or radiographically grossly involved regions of primary tumor or involved nodes designated GTVp_5500 and GTVn_5500, respectively.

These volumes are defined based on physical exam and review of available imaging.

FDG-PET may assist in GTV identification, but specific GTV border delineation should not rely exclusively on PET signal given the known variable association between gross tumor extent and PET signal cutoff and image fusion uncertainty.

- **Nodal Definitions**

- Clinicians are highly encouraged to request radiologist review if the determination is unclear.
- Grossly Positive Nodes (GTVn_5500) are defined as those greater than 1.5 cm in long axis and/or > 1 cm in short axis, a cluster of 3 or more borderline size nodes, radiographic evidence of extracapsular extension (ECE), or a node of any size with evidence of necrosis.
- Smaller nodes may be determined to be gross disease objects depending on clinical suspicion (based on proximity to the primary site or other involved nodes) or demonstration of significant uptake of FDG on PET scanning.
- Extracapsular extension (ECE): is defined as radiographic evidence of irregular borders and/or perinodal fat stranding, invasion of adjacent structures, or both. Any areas of potential involvement should be included within the GTV.
- Matted Nodes: Three or more abutting nodes with loss of the intervening fat planes.

- **Clinical Target Volume (CTV)**

- CTVs are defined and contoured in relation to the targets they are intended to encompass and the dose they are intended to receive. For gross targets (GTVs), the CTVs are defined by 3D isotropic expansions that should then be limited by potential barriers to tumor spread such as air cavities, external contours and bony or fascial planes through which tumor spread is not possible or apparent. Similarly, CTVs may be expanded beyond the limits defined in this protocol in order to cover areas deemed at risk of tumor extension (e.g. neck musculature invaded by nodal disease, or pterygoid regions of infratemporal fossa in superiorly extending tonsillar cancers). For nodal regions of potential microscopic involvement CTVs are defined according to normal anatomic landmarks.

- **CTV_5500: Primary Tumor and Involved Nodes**

    - A CTV_5500 will be defined for primary tumor and involved nodes as a 0.5 cm isotropic expansion of the GTVs defined for these structures.

- **CTV: High-Risk conventional can be contoured but not mandatory per protocol. This volume will not be prescribed any dose and can be used for future dosimetric comparative studies**

    - High-risk subclinical sites are defined as:

        i) Areas of potential subclinical tumor infiltration beyond the primary site CTVp_5500

        ii) The first echelon node levels to the primary site irrespective of gross nodal involvement and all node levels containing gross nodes.

- The value of this intermediate dose level is questionable in HAOPC typically defined as:
  i) 1.0 cm isotropic expansion of GTVp_5500
  ii) 1st echelon node levels based on standard anatomic definitions. In most cases 1st echelon would be ipsilateral level II, but in cases of midline primary site involvement this should include bilateral level II. In cases with soft palate or posterior pharyngeal wall involvement this should include the lateral retropharyngeal lymph nodes.
  iii) All node levels containing a CTVn_5500 that has been assigned to involved nodes (all grossly involved nodal levels).
  iv) Other high-risk subclinical sites may include nodes < 1cm not thought to harbor gross disease yet thought to be at risk of containing more than

- **CTV_4250: Node Levels at risk of microscopic spread**
  - CTV_4250 will be defined to treat node levels without evidence of gross disease yet at risk of microscopic spread. These levels are defined anatomically according to published Intergroup consensus guidelines [50]. The levels to be treated will depend on the site and extent of the primary tumor and any grossly involved lymph nodes and are indicated in Table 2. It will only include 3cm superior and inferior expansion of the CTV5500 and the radial extension will respect fat plan. Committing to entire nodal level is not recommended and contralateral delineation of nodal region is not indicated in contralateral N0 disease. The probability of neck failure outside of that 3cm boundary is typically below 5% and typically addressed with the tumoricidal effect of chemotherapy while permitting more sparing of organs at risk.

Table 2: Nodal Levels to Receive Prophylactic Microscopic Dose Not required per protocol	Ipsilateral Neck	Contralateral Neck**
N0-1 (in level II – IV)	• Ib (for primary oral cavity extension), • II-IV • RP (lateral retropharyngeal LN) for primary extension to posterior pharyngeal wall or soft palate	• II-IV • RP (lateral retropharyngeal LN) for primary extension to posterior pharyngeal wall or soft palate
N2a-b	• Ib, II, III, IV, V, RP	• II-IV • RP (lateral retropharyngeal LN) for primary extension to posterior pharyngeal wall or soft palate

- **Contralateral Neck not required for N0**
  - It is recognized that the evidence as to the efficacy and safety of a unilateral neck radiotherapy approach within specific patient groups is largely retrospective, yet increasingly compelling evidence has led some centers to consider unilateral radiotherapy standard practice.
  - Unfortunately, the data for patients with selected N2b or lateralized tongue base cancers is less well defined in the literature than that for N0-N2a tonsillar cancer, and additionally, substantial disparities in opinions remain related to the effect of extracapsular extension [51]. Although unilateral or bilateral radiation is optional to the discretion of treating physician, 3 groups of patients with respect to laterality of neck irradiation were defined:

a) Group 1: Unilateral treatment is recommended.

T1 to T3 tonsil primaries with < 1cm clinical or radiographic extension into tongue base and/or palate, no posterior pharyngeal wall extension, N0-N2a (no ECE)

b) Group 2: Unilateral treatment is optional in standard therapy but required per protocol

T1 to T3 tonsil primaries with < 1cm clinical or radiographic extension into tongue base and/or palate, no posterior pharyngeal wall extension, N2b (no ECE) with involved adenopathy confined to ipsilateral level 2 of the neck

Table 3: Clinical Target Volume Nomenclature and Description.

Standard Name	Description	Detailed Specification
GTVp_5500	GTV to receive 55 Gy at the primary site Required	Equivalent to GTVp as defined above

GTVn_5500	GTV to receive 55 Gy at involved nodes **Required**	Equivalent to GTVn as defined above
CTVp_5500	CTV to receive 55 Gy at the primary site **Required**	0.5 cm isotropic expansion of GTVp_55 limited by potential anatomic barriers to tumor spread such as air cavities, external contours and bony or fascial planes through which tumor spread is not possible or apparent
CTVn_5500	CTV to receive 55 Gy at involved nodes **Required**	0.5 cm isotropic expansion of GTVn_55 limited by potential anatomic barriers to tumor spread such as air cavities, external contours and bony or fascial planes through which tumor spread is not possible or apparent
CTV_4250	CTV to receive 42.5 Gy at low-risk volume at the primary site and applicable node levels **Required**	Arm1: Defined anatomically according to consensus guidelines [50]. The levels to be treated will depend in the site and extent of the primary tumor and any grossly involved lymph nodes. more Arm2: Defined as 3cm isotropic expansion around CTV5500 limited by potential anatomic barriers to tumor spread such as air cavities, external contours and bony or fascial planes through which tumor spread is not possible or apparent

5.2.5 Definition of Organs at Risk

Table 4: Organ at Risk Nomenclature

OAR Standard Name	Description
SpinalCord	Spinal cord **Required**
SpinalCord_05	PRV = 5 mm expansion on spinal cord **Required**
BrainStem	Brain stem **Required**
BrainStem_03	PRV= 3 mm expansion on brainstem **Required**
Lips	Lips **Required**
OralCavity	Oral cavity **Required**
Parotid_R	Right parotid gland **Required**
Parotid_L	Left parotid gland **Required**
Mandible	Mandible **Required**
Esophagus_Up	Cervical esophagus **Required**
Larynx	Larynx

	Required

- **Spinal Cord**: The cord begins at the cranial-cervical junction (ie, 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 volume will be defined at approximately T3-4 (ie, 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 as: SpinalCord_05 = cord + 5 mm in each dimension.
- **Brain Stem**: 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 as: BrainStem_03 = brainstem + 3 mm in each dimension.
- **Lips**: The definition of lips is self-explanatory.
- **Oral Cavity**: The oral cavity will be defined as a composite structure posterior to lips consisting of the anterior ½ to 2/3 of the oral tongue/floor of mouth, buccal mucosa, and superiorly the palate, and inferiorly to the plane containing the tip of the mandible.
- **Parotid Glands**: Parotid glands will be defined in their entirety (superficial and deep lobes) based on the treatment planning CT scan.
- **Esophagus**: This will be defined as the cervical (upper) esophagus, a tubular structure that starts at the bottom of pharynx (cricopharyngeal inlet) and extends to the thoracic inlet.
- **Larynx**: This will be defined as the glottic and supraglottic larynx, including the tip of the epiglottis, the aryepiglottic folds, arytenoids, false cords, and true cords, bounded by the thyroid cartilage laterally, anteriorly including the anterior edge of the pre-epiglottic fat, and posteriorly bounded by the anterior edge of the pharyngeal wall or the posterior edge of the arytenoid and/or cricoid cartilage.
- **Mandible**: This includes the entire bony structure of the mandible from TMJ through the symphysis.

5.2.6 Planning Target Volumes

All CTVs will have associated PTVs which represent the volumes to which radiation dose will be prescribed, delivered, and evaluated.
The PTVs are isotropic expansions of the CTVs to account for internal motion and residual set-up error.
PTVs are defined as a 3 mm expansion of the CTV in all planes

The PTVs may be modified in the following situations:
1) When a PTV overlaps a critical OAR (spinal cord and/or brainstem) and its associated PRV, the PTV should be modified to exclude the PRV so as to limit the dose delivered to the PRV within constraints defined in table 5.
2) The PTVs should be constrained 3 mm within the external contour. The multiple beam entry tangential angles characteristic of intensity modulated arc therapy is typically delivering higher than calculated surface dose not accounted with planning software algorithms. These software dose calculation algorithms model tissue air interface overestimating the skin sparing effects of

electronic equilibrium which may give the impression of dose undercoverage and/or not meeting planning dosimetric goals.

Table 5: Planning Target Volume Nomenclature and Description

Standard Name	Description	Detailed Description
PTVp_5500	PTV to receive 55Gy at the primary site **Required**	3-5mm expansion of CTVp_5500
PTVn_5500	PTV to receive 55 Gy at involved nodes **Required**	3-5mm expansion of CTVn_5500
PTV_5500	PTV to receive 55 Gy **Required**	Sum of PTVp_5500 and PTVn_5500
PTV_4250	PTV to receive 42.5 Gy at the primary site and applicable node levels **Required**	3-5mm expansion of CTV_4250

5.2.7 Dose Prescription

The prescribed radiotherapy dose to gross disease for all patients will be 55Gy over 25 fractions delivered once daily, 5 fractions per week Monday to Friday for 25 consecutive treatment days (5 weeks), with weekly concurrent cisplatin at 40 mg/m2.

The primary tumor and involved nodes will receive 55 Gy (2.2 Gy per fraction for 25 fractions), and low-risk subclinical sites will receive 42.5 Gy (1.7Gy per fraction for 25 fractions).

Doses prescribed are indicated in Table 6 below. All PTVs are to be treated concurrently within a single IMRT plan of 25 fractions.

Table 6: Doses Prescribed to PTVs

Target Standard Name	**Dose (Gy)**	**Fraction Size** (Gy)	**# of fractions**	**Dose specification technique**
PTV_5500	55	2.2	25	Covering ≥ 95% of PTV_5500
PTV_4250	42.5	1.7	25	Covering ≥ 95% of PTV_4250

5.2.8 Treatment Planning Priorities and Instructions

IMRT Dose Prescription to PTVs

Doses are prescribed to PTVs as outlined in Table 6. The treatment goal is that 95% of the volume of all PTVs must receive the prescribed dose with a minimum dose (defined as dose to 99% of PTVs) greater than 93% of the prescription dose and a maximum dose (defined as dose encompassing 0.03 cc of the PTV) less than 110-115% of the highest prescription dose.

It is recognized that portions of PTVs close to the skin or critical PRVs (spinal cord and brainstem) may receive significantly less than the prescription doses. This is acceptable in these regions if cold spots within these PTVs do not exist within the GTV.

It is also recognized that PTVs abutting or enclosing higher dose PTVs will have regions of maximum dose that may exceed their prescribed dose to achieve acceptable minimal doses to the higher dose PTVs which are considered a higher priority target.

Prioritization for IMRT Planning

1. Spinal Cord
2. Brainstem
3. PTV_5500
4. PTV_4250
5. Parotid gland contralateral to primary tumor site
6. Larynx
7. Oral Cavity
8. Esophagus
9. Parotid gland ipsilateral to primary tumor site
10. Mandible

5.2.9 Doses to Normal Structures

Dose limitations to normal structures are described below. For the critical structures of spinal cord and brainstem these are mandatory. For other structures recommended limits are provided, but the doses delivered should always be as low as reasonably achievable without compromising doses to PTVs.

• **Spinal Cord***:* The PRV for spinal cord (SpinalCord_05) should not exceed 48 Gy to any volume more than 0.03 cc (approximately 3 mm x 3 mm x 3 mm). In treatment planning, the spinal cord PRV should be given the highest priority.

• **Brainstem**: The PRV for brainstem (BrainStem_03) should not exceed 50 Gy to any volume more than 0.03 cc (approximately 3 mm x 3 mm x 3 mm). In treatment planning, the BrainStem_03 should be given less priority than the SpinalCord_05, but more than the critical structures listed below.

• **Oral Cavity***:* Reduce the dose as much as possible. The mean dose should be < 32 Gy for the oral cavity. Efforts should also be made to avoid hot spots (> 60 Gy) within the non-involved oral cavity.

• **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 < 26 Gy, but efforts should be made to reduce this further if possible without compromising dose to PTVs.

• **Esophagus**: Reduce the dose as much as possible; recommended (but not mandatory) treatment goal: mean dose < 30 Gy.
• **Larynx***:* Reduce the dose as much as possible. The larynx mean dose is recommended to be ≤ 35 Gy if whole-neck IMRT is used.
• **Mandible***:* Reduce the dose as much as possible. Hot spots within the mandible should be avoided. It is recommended that maximum dose within the mandible be < 63 Gy.

5.2.10 Dose Compliance Criteria

The compliance criteria listed in Table7 will be used to evaluate each case.

The Per Protocol and Variation Acceptable categories are both considered to be acceptable.

The Per Protocol cases can be viewed as ideal plans, and the Variation Acceptable category can include more challenging plans that do not fall at or near the ideal results.

A final category, called Deviation Unacceptable, results when cases do not meet the requirements for either Per Protocol or Variation Acceptable.

Plans falling in this category are suboptimal and additional treatment planning optimization is recommended to avoid protocol deviation.

Table 7: Planning Target Volume and Critical OAR Constraints and Compliance Criteria

Name of Structure	**Dosimetric parameter***	**Per Protocol Dose (Gy)**	**Variation Acceptable**
PTV_5500	D95%*(Gy)	55	> 55 and ≤ 58
	D99%(Gy)	≥ 51	≥ 50
	Dmax**(Gy)	≤ 60	≤ 63
CTV_5500	V55 Gy (%)	≥ 99 %	95 to 99 %
PTV_4250	D95%*(Gy)	≥ 42.5	≥ 40
	D99%(Gy)	≥ 39.5	≥ 38
	Dmax**(Gy)	≤ 52	≤ 56
CTV_4250	V42.5 Gy (%)	99 %	95 to 99 %
SpinalCord_05	Dmax**(Gy)	≤48	≤50
Spinal Cord	Dmax**(Gy)	≤45	≤48
BrainStem_03	Dmax**(Gy)	≤ 50	≤52
Recommended dose acceptance criteria for other normal tissue, but not to be used for plan score			
Parotid		Mean dose to one parotid ≤ 26 Gy	
Larynx		Mean dose ≤ 35 Gy	
OralCavity (excluding PTV's)		Mean dose ≤ 32 Gy	
Esophagus_Up		Mean dose ≤ 30 Gy	
Mandible		D0.03cc < 63 Gy	

A **Deviation Unacceptable** will be scored when the Variation Acceptable limits are not met.
*D95%(Gy) = dose to 95% of volume
**Dmax = maximum dose to 0.03 cc of the volume

5.2.11 Delivery Compliance Criteria

Protocol treatment must begin within 30 days of signing informed consent. Treatment breaks must be clearly indicated in the treatment record along with the reason(s) for the treatment break(s). Treatment breaks, if necessary, should not exceed 3 treatment days at a time and 5 treatment days total.

Treatment breaks should be allowed only for resolution of severe acute toxicity and/or for intercurrent illness and not for social or logistical reasons. Any treatment break(s) exceeding 2 treatment days for reasons other than toxicity/illness will be considered a protocol deviation.

Given the importance of timeliness of treatment delivery in this study, it is strongly recommended that patients receive twice-daily treatments with a minimum 6-hour inter-fraction interval to compensate for missed days including holidays and those for toxicity or illness once sufficiently recovered with the goal of keeping the overall treatment time within the limits defined in Table 8.

Table 8: Delivery Compliance Criteria

	Per Protocol	Variation Acceptable	Deviation Unacceptable
Overall Treatment time	<37 days	38-42 days	>42 days without a medically appropriate indication for delay
Interruptions (without medical indication)	0-2 days	2-4 days	>4 days

5.2.12 Dose Calculations

The primary data set for dose calculation is CT. In the case in which contrast is present during the treatment planning CT, the density of the contrast should be overridden to a representative background electron density. The dose grid size should be ≤ 3 mm in all directions, which means that the CT slice thickness should be ≤ 3 mm.

5.2.13 Daily Treatment Localization/IGRT

Daily image guidance (IGRT) of IMRT is required to meet PTV margins of 0.3 cm, and IGRT credentialing is also required. (Section 8.3).
IGRT may be achieved using any one of more of the following techniques:

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

The institution's procedure to register the 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 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 surgical clips and 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, reimaging is not mandatory.

If one or more of the corrections are larger than 5 mm, the imaging must be repeated in addition to performing table/positioning adjustments.

5.2.14 Replanning

In cases of weight loss > 10% or substantial shrinkage of lymphadenopathy during therapy, it is recommended that the immobilization mask be adjusted or re-made to preserve adequate immobilization, and that a repeated simulation CT be performed to assess the dose distributions in the current anatomy.

Whether or not a new IMRT plan will be generated is at the discretion of the treating physician. If a new plan is made, the targets should be the same as those used for the initial plan and not adjusted in cases of disease regression, except to respect clear anatomic barriers such as skin or fascial or muscle planes initially uninvolved by disease.

The new CT dataset should be used for IGRT image registration when the patient's shape changes significantly.

5.2.15 Radiation Therapy Adverse Events

Grade 3-4 (CTCAE, v. 4) therapy-induced mucositis and/or dysphagia, which are enhanced by cisplatin, are expected to develop in about two thirds of patients.

Nutritional evaluation prior to the initiation of therapy to decide on the use of a prophylactic gastrostomy (PEG) tube placement is recommended, but in the absence of significant pretreatment dysphagia and associated weight loss of < 10% body weight the insertion of a prophylactic PEG is not recommended.
If done the placement of a feeding tube should be recorded, as should proportion of 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 the dental recommendations provided in Appendix V), and cervical myelopathy (< 1% with restriction of spinal cord dose to ≤ 45 Gy).

5.3 Surgery

Surgery is expected to play only a limited role in the favorable risk HPV-associated cancers included in this study. Locoregional progression is expected in <10% of patients. The role of neck dissection has been declining in recent years, in part due to a high rate of negative specimens when planned neck dissections are performed in cancers of the oropharynx.

5.3.1 Post-Treatment Imaging/Timing

While centers are allowed to follow their institutional policies in conducting earlier post-treatment imaging evaluations, the major initial post-radiation imaging evaluation for the purposes of this study is required at 12-14 weeks after the completion of radiotherapy with diagnostic quality, contrast-enhanced CT or MRI of the neck.

PET/CT may be conducted in this timeframe as well, based on the preference of treating clinicians, but does not substitute for the mandatory anatomic imaging. The required diagnostic CT may be performed as part of the integrated PET/CT but only if the CT is considered diagnostic quality and is contrast enhanced.

PET/CT may facilitate pre-and post-treatment evaluation of metabolic response and the need for post-treatment neck dissection.

If physical examination and imaging suggest residual disease at the primary site, a biopsy will be performed to confirm residual disease; otherwise, patients will undergo serial follow up.

Annual chest imaging is required to a maximum of 3 annual imaging sets and thereafter should be performed based on clinical judgment.

5.3.2 Post-Treatment Surgical Salvage of Residual Disease

Treatment of residual disease at the primary site will be determined by the treating clinicians and the clinical situation, and surgical resection, re-irradiation, chemotherapy, or palliative care will be done.

If the primary site is cleared of residual disease yet residual disease at the cervical nodal basin is strongly suggested by imaging/clinical evaluation, then selective neck dissection will be performed unless a cytologic sampling (biopsy) of the node is negative.

Post-treatment "planned" neck dissection will be defined as being performed for residual disease and within 20 weeks (140 days) of completion of radiotherapy.

Positive neck specimens removed within 140 days will be considered part of the initial treatment plan and not considered as failures of initial management; positive specimens upon neck dissection beyond 140 days will be considered regional failures.

Note that this is relaxed from the traditional definition of 105 days (15 weeks) to permit resolution of HPV-associated adenopathy, which is commonly cystic and may have a somewhat slower regression rate.

Such post-treatment consolidation neck dissections will encompass only the areas (typically only levels 2 and 3) initially involved in the side of the neck in question.

The extent of neck dissections performed for nodal recurrence, nodal progression, or salvage of disease at the primary ultimately will be determined by the treating surgeon.

In the case of negative PET/CT in patients who did not achieve clinical or CT/MRI-based radiological nodal CR, a minimum of careful clinical examination is required at 3 months, and further imaging is highly recommended, such as follow-up imaging every 3-4 months for at least 24 months, as well as careful recording of the clinical dimensions of the residual abnormality.

5.4 General Concomitant Medication and Supportive Care Guidelines

5.4.1 Permitted Supportive/Ancillary Care and Concomitant Medications

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

These may include analgesics, antiemetics, topical mouth rinses, skin creams/ointments, etc. In general, HIV-positive patients who are on a stable Highly Active Anti-Retroviral Therapy (HAART) regimen should continue HAART while receiving chemotherapy.

However, for patients who are newly diagnosed with HIV but with laboratory parameters meeting the eligibility criteria, it is preferable to defer initiation of HAART until after

chemotherapy is completed. HAART regimens containing zidovudine and stavudine should be avoided during chemotherapy due to concerns for overlapping toxicity with chemotherapy. In addition, the protease inhibitor atazanavir (Rayataz) can cause a physiologically unimportant hyper-hyperbilirubinemia; however, in the setting of chemotherapy, some experts suggest switching that drug for another equally effective one.

If HAART is withheld during chemotherapy, it should be resumed promptly after conclusion of the last cycle of chemotherapy.

5.4.2 Participation in Other Trials

Patients may not participate in other clinical trials that are intended to treat the diagnosed oropharyngeal cancer or intended to reduce toxicity of therapy.

5.5 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue as specified in the above treatment modality sections or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.6 Measurement of Response/Progression

- Response versus “Tumor Clearance” versus Cancer Progression

Response and confirmation of local (primary site) or regional (neck) “tumor clearance” are not endpoints in this study.
Clinical or radiographic evidence of progressive local-regional disease beyond 20 weeks should be documented in the clinical record and ideally confirmed by local or regional biopsy, neck dissection, or salvage surgery.
CT or MRI (of head and neck region, with Chest CT), or PET/CT (including chest anatomy) may be used as radiographic evaluation of overall cancer status. The primary, neck and chest portions of the scans should be evaluated and reported separately.
The CT portion of a PET/CT may serve as sufficient radiographic evaluation of the chest. If CT or MRI is used for evaluation of the head and neck region, CT of chest will be needed to rule out distant disease or second primaries at the designated evaluation intervals.

- Local or Regional Progression

Local (primary site) or regional (neck) progression is defined as clinical or radiographic evidence of progressive disease at the primary site or neck. The location of progressive disease should be separately distinguished (local vs. neck) to document the precise pattern of failure if possible.

Progression of local or regional disease should be confirmed by biopsy when possible but may be clinically assessed and documented in the clinical record at the judgment of the treating clinicians. Suspicion of disease progression exclusively on the basis of indeterminate or positive PET/CT scan must be pathologically confirmed.

- Distant Metastasis

Clear evidence of distant metastases (lung, bone, brain, etc.); biopsy is recommended where possible. A solitary, spiculated lung mass/nodule is considered a second primary neoplasm unless proven otherwise.

- Second Primary Neoplasm

Tumor reappearing with the initial and immediate adjoining anatomical region of the primary will be considered local recurrence. Multiple lung nodules/masses are considered distant metastases from the index cancer unless proven otherwise.

6. TREATMENT MODIFICATIONS/MANAGEMENT

6.1 Chemotherapy Dose Modifications:

If adverse events prevent the administration of chemotherapy, the patient may continue to receive radiation therapy.

6.1.1 Cisplatin Dose Modifications during Concurrent Radiation

Note: Substitution of carboplatin for cisplatin during adverse events is NOT allowed.

Patients will be examined and graded for subjective/objective evidence of developing toxicity weekly according to CTCAE, v. 4 while receiving concurrent cisplatin with radiotherapy. Treatment interruptions are allowed if there is symptomatic mucositis or skin reaction that, in the judgment of the clinician, warrants a break. For chemotherapy-attributable AEs requiring a break in treatment, resumption of concurrent cisplatin may begin when AEs have recovered to the levels specified below. Chemotherapy should be discontinued in the event of more than 2 events requiring dose reduction (e.g. if grade 3 or greater non-hematologic or hematologic event occurs at the reduced dose of cisplatin, at 23 mg/m2/week.

If an AE does not resolve to the levels specified in the sections below prior to the calendar week of the last radiation treatment (See Section 5.1 for details concerning parameters for timing of last allowable concurrent cisplatin dose), then chemotherapy should be discontinued.

There will be no dose re-escalation for concurrent cisplatin.

Chemotherapy dosage modifications are based upon lab values obtained within the 24 hours prior to cisplatin and interim non-hematologic toxicities during the week prior to a particular cisplatin dose.

The dose modifications for cisplatin (below) are intended to be permanent (i.e., if the patient's dose is reduced to dose level -1, it remains at the reduced dose level).

6.1.2 Cisplatin Dose Modifications for Hematologic Adverse Events during Concurrent Radiation

Starting Dose	Dose Level -1	Dose Level -2
40 mg/m2	30 mg/m2	23 mg/m2

Chemotherapy must not be administered until the ANC is ≥ 1,000 mm3 and platelets are ≥ 75,000 mm3. If not, delay 7 days. Cisplatin should be held every week until the above ANC and

platelet parameters are met. Dose reductions when cisplatin is resumed after delay for low ANC or platelets will be as follows, based upon counts at time cisplatin was held.

ANC		Platelets	Reduction
< 1000 mm3	or	< 75,000	One dose level

Note: **Hematologic growth factors for neutropenia or anemia are not allowed during concurrent cisplatin and radiation treatment.**

Neutropenic Fever: Grade 3 (CTCAE, v 4) neutropenic fever (ANC < 1000/mm3 with a single temperature of > 38.3 degrees C [101 degrees F] or a sustained temperature of ≥ 38 degrees C [100.4 degrees F] for more than 1 hour) is an expected potential complication of concurrent chemotherapy and radiotherapy or chemotherapy alone. If neutropenic fever is noted, the chemotherapy dose reduction will be determined by the weekly blood counts.

6.1.3 Cisplatin Dose Modifications for Non-Hematologic Adverse Events during Concurrent Radiation

Renal Adverse Events: Dose will be modified based on the serum creatinine prior to each cisplatin dose. If the serum creatinine is ≤ 1.5 mg/dL, creatinine clearance is not necessary for treatment with full dose. If the serum creatinine is > 1.5 mg/dL, a creatinine clearance should be obtained by urine collection or nomogram calculation (valid only if serum creatinine is not changing rapidly).

Cisplatin must not be administered until creatinine is ≤ 1.5 or creatinine clearance ≥ 50.
Once the creatinine has met the above parameters, cisplatin may be restarted with the below modifications based on the creatinine at the time the cisplatin was held: In general, cisplatin should be held for weekly intervals (rather than restarting cisplatin later in the same week that a dose limiting AE is seen).

Cisplatin dose modifications for creatinine during concurrent radiation			
Creatinine (mg/dL)		Creatinine clearance, measured or calculated ml/min	Cisplatin dose reduction
≤ 1.5	or	> 50	No change
> 1.5	and	40-50	One dose level
		< 40	Hold drug

Neurologic (neuropathy) Adverse Events:

Grade (CTCAE, v. 4)	**Dose Reduction**
0-1	None
2	One dose level
3-4	Hold drug

Ototoxicity: Should patients develop clinical evidence of ototoxicity, further audiometric evaluation is required. A neurologic deficit should be distinguished from a conductive loss from obstruction of the Eustachian tube leading to a middle ear effusion. Because no AE scale,

including the CTCAE, v. 4, has been validated in terms of correlation with clinically relevant hearing loss, there are no protocol mandates requiring dose reduction for audiogram-determined sensorineural hearing loss without an analogous clinical high grade (> grade 2) hearing loss. However, for clinical grade 3 or higher hearing loss, cisplatin should be held and for grade 2 clinical hearing loss, one dose level reduction should be implemented.

All Other Non-Hematologic Adverse Events Attributable to Cisplatin during Concurrent Radiation: For all other non-hematologic adverse events in which toxicity is ≥ grade 2 (CTCAE v. 4), investigators are advised to evaluate and manage correctable issues promptly to prevent worsening of toxicity. For these events in which toxicity is ≥ grade 3, investigators should hold cisplatin, with weekly re-evaluation until AE grade falls to 0-1, then restart cisplatin at one lower dose level. Note: Grade 3 mucositis is commonly experienced by head and neck cancer patients; the investigator generally would not hold the cisplatin dosing in this case, unless there is unusual concern for progression to grade 4 mucositis.

7. ADVERSE EVENTS REPORTING REQUIREMENTS

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for adverse event (AE) reporting. The CTCAE version 4.0 is located on the CTEP web site at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

7.1 Adverse Events (AE)

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6). [CTEP, NCI Guidelines: Adverse

According to Baptist policy, Adverse Events (AEs) must be reported to the IRB, sponsor, and regulatory bodies according to the study protocol and regulatory timelines. Serious Adverse Events (SAEs) must be reported immediately to the Sponsor, IRB, and regulatory bodies, within 24 hours if expedited reporting criteria are met. Initial reports should include basic event details, followed by more detailed updates as additional information becomes available.

7.2 Serious Adverse Events (SAEs)

Serious adverse events (SAEs) that meet expedited reporting criteria will be reported to the PI and IRB via email within 24 hour include the following:

Any adverse drug event (experience) occurring at any dose that results in any of the following outcomes:

• Death;
• A life-threatening adverse drug experience.
• Inpatient hospitalization or prolongation of existing hospitalization.
• A persistent or significant disability/incapacity.
• Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

8. REGISTRATION, STUDY ENTRY, AND WITHDRAWAL PROCEDURES

8.1 Site Registration Requirements

IRB Approval
IRB approval must be obtained for this protocol and submit IRB approval and supporting documentation to the Regulatory Office before they can be approved to enroll patients.

The following documents will be needed:
-
- IRB Approved Informed Consent and protocol.

8.1.1 Radiotherapy Plan Evaluation and Storage

The radiotherapy plan will be reviewed by radiotherapy principal investigator before patient radiotherapy start using direct email communication and deidentified data with final DICOMRT plan using unique patient protocol ID stored in BMDA Aria data repository. The same plan can still be presented for Peer review committee.

8.2 Patient enrollment

Patient registration can occur only after evaluation for eligibility is complete and documented.

Patients must have signed and dated all applicable consents and authorization forms.

9. DRUG THERAPY

9.1 Investigational Study Agent

Not applicable for this study.

9.2 Commercial Agent: Cisplatin

Adverse Events: Sites must refer to the package insert for detailed pharmacologic and safety information.

10. DATA COLLECTION

10.1 Data Management/Collection and Storage

Data collection for this study will be via secured email correspondence with the PI and his delegates.

Upon initial site registration approval for the study, all persons with data handling and collection roles will be identified as contact persons for this site.

All the data related electronic communication will be secured in BMDA firewall protected and password encrypted server.

10.2 Data Submission

Folder	Item
Registration	Subject enrollment form with checklist 1 & 2
Baseline	• Consultation note • Pathology • Labs • G8
RT data	DICOM RT
End of RT	RT specifics Supportive care documentation Hospitalization PEG tube existence, documentation if in active use. AAdverse events forms (if any)
Follow up at 3, 6, 9 12, 15, 18, 21, and 24 months	Follow up PET scan: Disease, new primary Supportive care documentation Hospitalization PEG tube existence, documentation if in active use. Adverse events forms (if any) protocol or non-protocol related

11. STATISTICAL ANALYSIS

11.1 Study Design

11.1.1 Stratification

Frailty index using G8 score < 14 versus ≥ 14 will be the main stratifying factor used for this study

11.1.2 Accrual Number

20 patients

11.2 Study Endpoints

11.2.1 Primary Endpoint

Two-year progression free survival

11.2.2 Secondary Endpoint

- Frailty index G8 score 14 as major determinant of benefit and tolerance to treatment through:
  - 2-year overall survival in frail versus non-frail elderly (versus published outcomes)
- Acute and late toxicity in frail versus non-frail elderly (versus published outcomes)
- Acute toxicity (Grade 3 or higher) (versus published outcomes)
- Late toxicity (Grade 3 or higher) (versus published outcomes)
- Pattern failure (versus published outcomes) (local in field, local marginal miss, local regional failure, distant failure, combination of the above).

11.3 Primary Objectives Study Design

11.3.1 Primary Hypothesis and Endpoints

In HAOPC patients, the favorable risk group will achieve a 2-year progression-free survival (PFS) rate of ≥ 85% with standard chemoradiotherapy based on HN002, RTOG 0522 and RTOG1016 studies, without unacceptable swallowing toxicity. Although the patient population in our study is older, the age is not expected to affect the oncologic outcomes.

11.3.2 Definition of Primary Endpoint

Progression free survival is defined as time from day 1 of therapy to local- failure, distant metastasis, or deaths due to any causes. PFS rates will be estimated for all treatment arms using the Kaplan-Meier method. Multivariate analysis will be performed using the Cox proportional hazards model.

11.3.3 Study Monitoring of Primary Objectives

Interim Safety Analysis with Early Stopping Rules

At 18 months, the estimated enrollment would be 20 patients. As 10 patients reach 6 months follow up period, the interim analysis will be conducted aiming to achieve progression free survival of 90% with 90% confidence interval 80- 99.9%.

The interim analysis is expected to occur at 1.5 years from the start of the study allowing IRB approval and 6 months of follow up. If 3 events are encountered among the first 10 patients, the study will be suspended. With 2-year progression free survival exceeding 80%, the total number of events during the whole study period is 8 events per arm explaining the 3 events cut off in the interim analysis.

11.3.4 Accrual Logistics

11.3.4.1 Accrual Rate

The accrual rate is expected to be 1-2 patients per month

11.3.4.2 Accrual Goal

The total sample size is 20 patients.

11.3.4.3 Study Duration

The accrual is expected to occur in 2 years, allowing for 2 year follow up, the study is expected to extend for 4 years.

11.3.5 Secondary Elements Statistical Analysis

The Kaplan Meyer curve for 2-year survival and log rank test will compare survival in Frail elderly using G8 score 14 cut off.

Two sample T test will be conducted between mean toxicity scores.

REFERENCES:

1. Windon, M.J., et al., *Increasing prevalence of human papillomavirus-positive oropharyngeal cancers among older adults.* Cancer, 2018. **124**(14): p. 2993-2999.
2. Ang, K.K., et al., *Human papillomavirus and survival of patients with oropharyngeal cancer.* N Engl J Med, 2010. **363**(1): p. 24-35.
3. Bourhis, J., et al., *Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): an open-label phase 3 randomised trial.* Lancet Oncol, 2012. **13**(2): p. 145-53.
4. Trotti, A., et al., *TAME: development of a new method for summarising adverse events of cancer treatment by the Radiation Therapy Oncology Group.* Lancet Oncol, 2007. **8**(7): p. 613-24.
5. Machtay, M., et al., *Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis.* J Clin Oncol, 2008. **26**(21): p. 3582-9.

6. Gillison, M.L., et al., *Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial.* Lancet, 2019. **393**(10166): p. 40-50.
7. Mehanna, H., et al., *Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomised controlled phase 3 trial.* Lancet, 2019. **393**(10166): p. 51-60.
8. Chera, B.S., et al., *Mature results of a prospective study of deintensified chemoradiotherapy for low-risk human papillomavirus-associated oropharyngeal squamous cell carcinoma.* Cancer, 2018. **124**(11): p. 2347-2354.
9. Ruhle, A., et al., *Development and validation of a novel prognostic score for elderly head-and-neck cancer patients undergoing radiotherapy or chemoradiation.* Radiother Oncol, 2020. **154**: p. 276-282.
10. Lee, I.H. and A. Eisbruch, *Mucositis versus tumor control: the therapeutic index of adding chemotherapy to irradiation of head and neck cancer.* Int J Radiat Oncol Biol Phys, 2009. **75**(4): p. 1060-3.
11. Fowler, J.F., *Correction to Kasibhatla et al. How much radiation is the chemotherapy worth in advanced head and neck cancer? (Int j radiat oncol biol phys 2007;68:1491-1495).* Int J Radiat Oncol Biol Phys, 2008. **71**(2): p. 326-9.
12. Yom SS, T.-S.P., Caudell JJ, Waldron JN, Gillison ML, Truong MT, Jordan R, Subramaniam R, Yao M, Chung C, Geiger JL, *NRG-HN002: a randomized phase II trial for patients with p16-positive, non-smoking-associated, locoregionally advanced oropharyngeal cancer.* International Journal of Radiation Oncology Biology Physics, 2019. **105**(3): p. 684-685.
13. Yom, S.S., et al., *Reduced-Dose Radiation Therapy for HPV-Associated Oropharyngeal Carcinoma (NRG Oncology HN002).* J Clin Oncol, 2021: p. JCO2003128.
14. Riaz, N., et al., *A personalized approach using hypoxia resolution to guide curative-intent radiation dose-reduction to 30 Gy: A novel de-escalation paradigm for HPV-associated oropharynx cancers (OPC).* Journal of Clinical Oncology, 2017. **35**(15_suppl): p. 6076-6076.
15. Gabrys, H.S., et al., *Parotid gland mean dose as a xerostomia predictor in low-dose domains.* Acta Oncol, 2017. **56**(9): p. 1197-1203.
16. Chyan, A., et al., *Dosimetric predictors of hypothyroidism in oropharyngeal cancer patients treated with intensity-modulated radiation therapy.* Radiat Oncol, 2014. **9**: p. 269.
17. Chen, A.M., et al., *Dose--volume modeling of brachial plexus-associated neuropathy after radiation therapy for head-and-neck cancer: findings from a prospective screening protocol.* Int J Radiat Oncol Biol Phys, 2014. **88**(4): p. 771-7.
18. Byers, R.M., P.F. Wolf, and A.J. Ballantyne, *Rationale for elective modified neck dissection.* Head Neck Surg, 1988. **10**(3): p. 160-7.
19. Lindberg, R., *Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts.* Cancer, 1972. **29**(6): p. 1446-9.
20. Spencer, C.R., et al., *Eliminating radiotherapy to the contralateral retropharyngeal and high level II lymph nodes in head and neck squamous cell carcinoma is safe and improves quality of life.* Cancer, 2014. **120**(24): p. 3994-4002.

21. Huang, S.H., et al., *Re-evaluation of Ipsilateral Radiation for T1-T2N0-N2b Tonsil Carcinoma at the Princess Margaret Hospital in the Human Papillomavirus Era, 25 Years Later.* Int J Radiat Oncol Biol Phys, 2017. **98**(1): p. 159-169.
22. Chronowski, G.M., et al., *Unilateral radiotherapy for the treatment of tonsil cancer.* Int J Radiat Oncol Biol Phys, 2012. **83**(1): p. 204-9.
23. Seiwert, T.Y., et al., *OPTIMA: a phase II dose and volume de-escalation trial for human papillomavirus-positive oropharyngeal cancer.* Ann Oncol, 2019. **30**(10): p. 1673.
24. Yamazaki, H., et al., *Radiotherapy for early glottic carcinoma (T1N0M0): results of prospective randomized study of radiation fraction size and overall treatment time.* Int J Radiat Oncol Biol Phys, 2006. **64**(1): p. 77-82.
25. Bentzen, S.M. and M.C. Joiner, *The linear-quadratic approach in clinical practice.* Basic clinical radiobiology, 2009. **4**: p. 120-34.
26. Baumann, M. and V. Gregoire, *Modified fractionation.* Basic clinical radiobiology, 2009. **4**: p. 135-148.
27. Ang, K.K., et al., *Randomized phase III trial of concurrent accelerated radiation plus cisplatin with or without cetuximab for stage III to IV head and neck carcinoma: RTOG 0522.* J Clin Oncol, 2014. **32**(27): p. 2940-50.
28. Jacinto, A.A., et al., *Feasibility of concomitant cisplatin with hypofractionated radiotherapy for locally advanced head and neck squamous cell carcinoma.* BMC Cancer, 2018. **18**(1): p. 1026.
29. Teckie, S., et al., *High-dose hypofractionated radiotherapy is effective and safe for tumors in the head-and-neck.* Oral Oncol, 2016. **60**: p. 74-80.
30. Bonomo, P., et al., *Elderly patients affected by head and neck squamous cell carcinoma unfit for standard curative treatment: Is de-intensified, hypofractionated radiotherapy a feasible strategy?* Oral Oncol, 2017. **74**: p. 142-147.
31. Gupta, T., S. Ghosh-Laskar, and J.P. Agarwal, *Resource-sparing curative-intent hypofractionated-accelerated radiotherapy in head and neck cancer: More relevant than ever before in the COVID era.* Oral Oncol, 2020. **111**: p. 105045.
32. Mell, L.K., et al., *Predictors of competing mortality in advanced head and neck cancer.* J Clin Oncol, 2010. **28**(1): p. 15-20.
33. Pignon, J.P., et al., *Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients.* Radiother Oncol, 2009. **92**(1): p. 4-14.
34. Hurria, A., et al., *Validation of a Prediction Tool for Chemotherapy Toxicity in Older Adults With Cancer.* J Clin Oncol, 2016. **34**(20): p. 2366-71.
35. Maggiore, R., et al., *The Older Adult With Locoregionally Advanced Head and Neck Squamous Cell Carcinoma: Knowledge Gaps and Future Direction in Assessment and Treatment.* Int J Radiat Oncol Biol Phys, 2017. **98**(4): p. 868-883.
36. Carmona, R., et al., *Improved Method to Stratify Elderly Patients With Cancer at Risk for Competing Events.* J Clin Oncol, 2016. **34**(11): p. 1270-7.
37. Kwon, M., et al., *An Introduction to a Head and Neck Cancer-Specific Frailty Index and Its Clinical Implications in Elderly Patients: A Prospective Observational Study Focusing on Respiratory and Swallowing Functions.* Oncologist, 2016. **21**(9): p. 1091-8.
38. Ruhle, A., et al., *Development and validation of a novel prognostic score for elderly head-and-neck cancer patients undergoing radiotherapy or chemoradiation.* Radiother Oncol, 2021. **154**: p. 276-282.

39. Chou, W.C., et al., *Clinical Significance of Vulnerability Assessment in Patients with Primary Head and Neck Cancer Undergoing Definitive Concurrent Chemoradiation Therapy.* Int J Radiat Oncol Biol Phys, 2020. **108**(3): p. 602-611.
40. Boje, C.R., *Impact of comorbidity on treatment outcome in head and neck squamous cell carcinoma - a systematic review.* Radiother Oncol, 2014. **110**(1): p. 81-90.
41. Rieke, K., et al., *Depression and survival in head and neck cancer patients.* Oral Oncol, 2017. **65**: p. 76-82.
42. Pottel, L., et al., *Serial comprehensive geriatric assessment in elderly head and neck cancer patients undergoing curative radiotherapy identifies evolution of multidimensional health problems and is indicative of quality of life.* Eur J Cancer Care (Engl), 2014. **23**(3): p. 401-12.
43. Pottel, L., et al., *G-8 indicates overall and quality-adjusted survival in older head and neck cancer patients treated with curative radiochemotherapy.* BMC Cancer, 2015. **15**: p. 875.
44. Loser, A., et al., *Head and neck cancer patients under (chemo-)radiotherapy undergoing nutritional intervention: Results from the prospective randomized HEADNUT-trial.* Radiother Oncol, 2021. **159**: p. 82-90.
45. Bellera, C.A., et al., *Screening older cancer patients: first evaluation of the G-8 geriatric screening tool.* Ann Oncol, 2012. **23**(8): p. 2166-2172.
46. Soubeyran, P., et al., *Screening for vulnerability in older cancer patients: the ONCODAGE Prospective Multicenter Cohort Study.* PLoS One, 2014. **9**(12): p. e115060.
47. Hamaker, M.E., et al., *Frailty screening methods for predicting outcome of a comprehensive geriatric assessment in elderly patients with cancer: a systematic review.* Lancet Oncol, 2012. **13**(10): p. e437-44.
48. Neve, M., et al., *Impact of geriatric assessment on the management of older adults with head and neck cancer: A pilot study.* J Geriatr Oncol, 2016. **7**(6): p. 457-462.
49. Langendijk, J.A., et al., *Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy.* J Clin Oncol, 2008. **26**(22): p. 3770-6.
50. Gregoire, V., et al., *Delineation of the neck node levels for head and neck tumors: a 2013 update. DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines.* Radiother Oncol, 2014. **110**(1): p. 172-81.
51. Expert Panel on Radiation, O.-H., et al., *ACR Appropriateness Criteria(R) ipsilateral radiation for squamous cell carcinoma of the tonsil.* Head Neck, 2012. **34**(5): p. 613-6.

APPENDICES

APPENDIX 1: G8 SCREENING TOOL

	Items	Possible answers (score)
A	Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?	0 : severe decrease in food intake
		1 : moderate decrease in food intake
		2 : no decrease in food intake
B	Weight loss during the last 3 months	0 : weight loss > 3 kg
		1 : does not know
		2 : weight loss between 1 and 3 kgs
		3 : no weight loss
C	Mobility	0 : bed or chair bound
		1 : able to get out of bed/chair but does not go out
		2 : goes out
D	Neuropsychological problems	0 : severe dementia or depression
		1 : mild dementia or depression
		2 : no psychological problems
E	Body Mass Index (BMI (weight in kg) / (height in m^2)	0 : BMI < 19
		1 : BMI = 19 to BMI < 21
		2 : BMI = 21 to BMI < 23
		3 : BMI = 23 and > 23
F	Takes more than 3 medications per day	0 : yes
		1 : no
G	In comparison with other people of the same age, how does the patient consider his/her health status?	0 : not as good
		0.5 : does not know
		1 : as good
		2 : better
H	Age	0 : >85
		1 : 80-85
		2 : <80
	TOTAL SCORE	0 – 17

APPENDIX 2: STAGING SYSTEM

American Joint Committee on Cancer (AJCC)
TNM Staging System for HPV-Mediated (p16+) Oropharyngeal Cancer (8th ed., 2017)
(Not including: P16-negative (p16-) cancers of the oropharynx)

Primary Tumor (T)
T0 No primary identified
T1 Tumor 2 cm or smaller in greatest dimension
T2 Tumor larger than 2 cm but not larger than 4 cm in greatest dimension
T3 Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4 Moderately advanced local disease
Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible or beyond*

Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of the larynx.

Regional Lymph Nodes (N)
Clinical N (cN)
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 One or more ipsilateral lymph nodes, none larger than 6 cm
N2 Contralateral or bilateral lymph nodes, none larger than 6 cm
N3 Lymph node(s) larger than 6 cm

Pathological N (pN)
NX Regional lymph nodes cannot be assessed
pN0 No regional lymph node metastasis
pN1 Metastasis in 4 or fewer lymph nodes
pN2 Metastasis in more than 4 lymph nodes

Distant Metastasis (M)
M0 No distant metastasis
M1 Distant metastasis

Histologic Grade (G)
No grading system exists for HPV-mediated oropharyngeal tumors

Prognostic Stage Groups

Clinical

Stage I	T0,T1,T2	N0,N1	M0
Stage II	T0,T1,T2	N2	M0
	T3	N0,N1,N2	M0
Stage III	T0,T1,T2,T3	N3	M0
	T4	N0,N1,N2,N3	M0
Stage IV	Any T	Any N	M1

Pathological

Stage I	T0,T1,T2	N0,N1	M0
Stage II	T0,T1,T2	N2	M0
	T3,T4	N0,N1	M0
Stage III	T3,T4	N2	M0
Stage IV	Any T	Any N	M1

APPENDIX 3: RTOG DENTAL EFFECTS HEALTH SCALE

0 Normal: Edentulous, with no gingival disease; native teeth in place with gingiva in excellent condition.

1 Mild changes/good dental health: mild periodontal inflammation-routine cleaning indicated; < 5 restorations indicated; no extractions indicated.

2 Moderate/fair dental health: moderate periodontal inflammation; deep periodontal cleaning indicated; 6 or more restorations indicated; less than full mouth extractions indicated.

3 Severe changes in dental health: widespread periodontal disease with extensive procedure/surgery indicated; full mouth extractions indicated.

4 Life-threatening dental condition: extensive abscess, extensive soft issue or bone infection, sepsis; urgent intervention indicated.

APPENDIX 4: MANAGEMENT OF DENTAL PROBLEMS IN IRRADIATED PATIENTS

Dental Care for Irradiated Patients:

Goals for a dental care program include:

1. To reduce incidence of bone necrosis.
2. To reduce incidence of irradiation caries.
3. To allow proper fitting of dentures following treatment.

Pre-irradiation Care and Procedures

The patients may be grouped into four groups in accordance with the problems they present prior to irradiation.

Group 1

Includes edentulous patients. They may require surgical removal of any symptomatic cysts, infected retained root tips, or alveolar hyperplasia. These patients require hygiene instruction and precautionary instruction about trauma with premature use of a prosthesis.

Group 2

Includes those with poor dental hygiene, including those patients whose teeth are beyond repair by ordinary dental procedure, those with generalized oral sepsis, those with generalized periodontal disease, and those with chronic periapical abscesses or granulomas. Procedures performed on this group include removal of all remaining teeth prior to irradiation with primary closure and surgical preparation of the alveolar ridges to laterally support a prosthesis. There should be antibiotic coverage during the healing stage and adequate time prior to the start of radiation therapy. These patients need complete hygiene instruction and precautionary instruction about premature use of a prosthesis.

Group 3

Includes those in whom dental condition is fair, including those patients whose teeth are restored, ordinary dental procedures, periodontal pockets are less than 3 mm deep, carious lesions are not in proximity to the pulp, and no more than 20 restorable carious lesions are present. X-ray examinations show at least 1/2 of the bone still present around root surfaces. These patients require removal of any teeth that are non-salvageable in accordance with the above and restorations of the remaining teeth as required. The patients are instructed for dental prophylaxis and the patients utilize custom-made fluoride carriers.

Group 4

Includes those in whom dental hygiene is good. This includes patients who do not have severe malocclusion in whom few carious lesions are present. Carious lesions are not in close proximity to the pulp and are correctable by conventional methods. These patients require periodontal evaluation and dental prophylaxis training, restorations as needed, no extractions prior to radiation therapy, and fitting for custom carriers. Extraction of Teeth If extraction of teeth is necessary prior to radiation therapy, the bone must be contoured so that closure at the extraction site is possible. All loose spicules and sharp projections must be removed. The approximation of the gingival tissue must be such that the closure is neither too loose nor too tight. At least 10 days are required for adequate healing prior to initiation of therapy.

Causative Factors

The major causative factors appear to be the reduction of the amount of saliva and secondarily, reduced pH in the mouth. This occurs following high dose radiation to the major salivary glands using parallel opposed fields. The decay process usually occurs in the first year following radiation therapy. It tends to occur more quickly in teeth which have a large amount of root cementum exposed to those teeth with large amounts of plaque formation present. Doses of radiation more than 20 Gy to salivary tissue place the teeth at risk.

Preventive Program

The rationale behind the use of fluoride treatments is to make the tooth surfaces less susceptible to the decay process. This is accomplished by a combination of increasing fluoride concentration on the tooth surface and by the effect of fluoride on the plaque and flora that are present in the oral cavity. Adequate results are obtained by:
1) cleansing the teeth thoroughly, followed by a good home care dental prophylaxis program,
2) construction of fluoride carriers, custom-made mouth guards, which provide local application of fluoride solution to the gingiva and tooth surfaces. Fluoride carriers are made individually with the use of casts. Material used for making a mouth guard is "Sta-Guard" plastic used in conjunction with vacutrole unit produced by Jelrus Technical Products, Corp., both of which are available through local dental supply. This material is molded to the cast impression and allowed to harden. A fluoride solution prepared at the M.D. Anderson Hospital is now available from the Emerson Laboratories, Inc., Dallas, Texas 75221. It has been used to coat the plastic carrier for use in the mouth. The patients are instructed to cleanse their teeth prior to placement of the carrier. It is then worn in place for 5 minutes each day. The patients are instructed to rinse their mouths thoroughly following the use of the carrier. This will be continued for an indefinite period of time. Close follow-up is necessary.

Results

In the 5-1/2 year program at the M.D. Anderson Hospital beginning in 1966, a study of 304 patients shows that the incidence of necrosis of the jaw was reduced to approximately 21% compared to 37% prior to initiation of the study. Groups 3 and 4 patients randomized with and without fluoride treatment showed reduction in radiation carries from 67% to 34% among Group 3 patients, and from 65% to 22% among Group 4 patients.

Failure to Control Decay

Management of failure to control radiation decay includes silver fillings with continued use of fluoride treatments. If the decay process is sufficiently advanced that a filling will no longer stay in place, these teeth are merely smoothed so that there will be no sharp, irritating edges. The mere existence of such a decayed tooth is not necessarily reason for extraction, for it must be remembered that extraction could lead to complications such as bone necrosis. Pulp exposure resulting from the decay process can usually be handled by use of antibiotics and/or root-canal therapy.

Hypersensitivity of Teeth

Occasionally, a patient will exhibit extreme sensitivity of the teeth secondary to diminished amounts of saliva. This has been shown to be reduced in incidence with the fluoride treatments.

Should this problem become manifest, increasing the fluoride treatment to 10 to 15 minutes 3 times a day is recommended.

Infections

Infections occurring in patients under or after radiation therapy are best managed conservatively with good oral hygiene, irrigation and flushing procedures, and systemic antibiotics.

Bone Necrosis

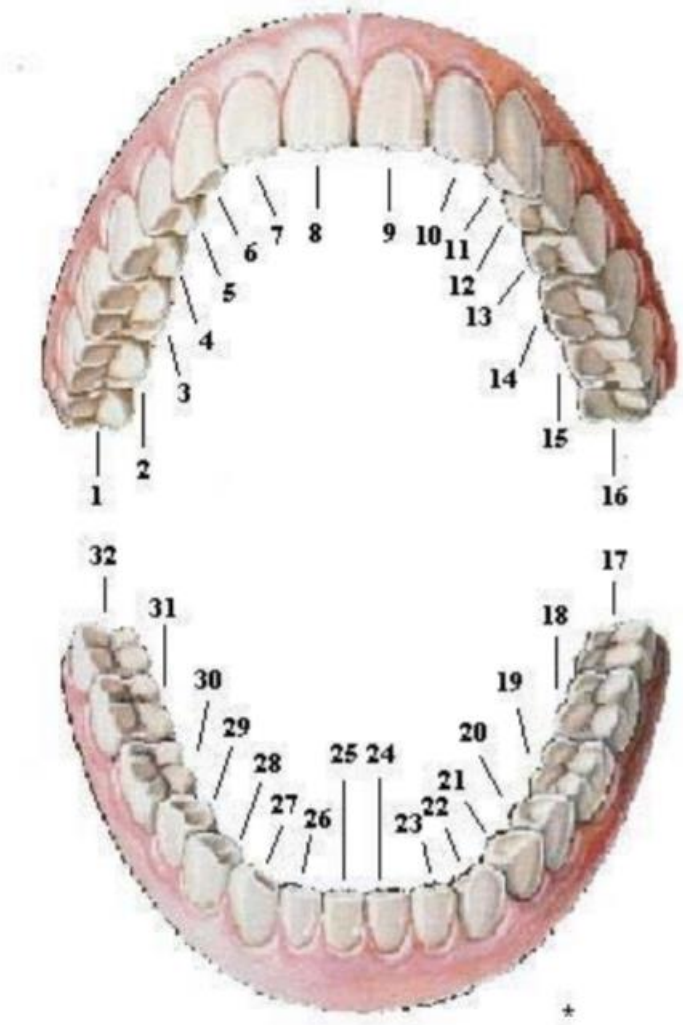
The patients receiving radiation therapy to a high dose to the head and neck region have increased susceptibility to bone necrosis for several reasons including impairment of normal metabolism, increased susceptibility to infection and severely limited repair process. Bone necrosis occurs most often after dental or oral surgery in patients who have been previously radiated. Conservative management should be tried first, though in more aggressive lesions a more radical approach may ultimately be necessary.

APPENDIX 5: DENTAL TOOTH COUNT DIAGRAM

Use the diagram below as a guide to count the number of native teeth in place, not including full or partial dentures or bridges.

The exact location of teeth does not need to be recorded, only the total number of native teeth in place (attached to bone in mandible or maxilla) on the day of evaluation.

This exam should be completed by a physician or designee, such as a physician's assistant, nurse or nurse practitioner, or a dentist/hygienist. Date of evaluation:



APPENDIX 6: Registration Check List