Protocol Title: A Pilot Single Arm Study of Intensity Modulated Radiation Therapy Elective Nodal Dose De-Escalation for HPV-Associated Squamous Cell Carcinoma of the Oropharynx

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PROTOCOL TITLE
A Pilot Single Arm Study of Intensity Modulated Radiation Therapy Elective Nodal Dose De-Escalation for HPV-Associated Squamous Cell Carcinoma of the Oropharynx

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A Pilot Single Arm Study of Intensity Modulated Radiation Therapy Elective Nodal Dose De-Escalation for HPV-Associated Squamous Cell Carcinoma of the Oropharynx

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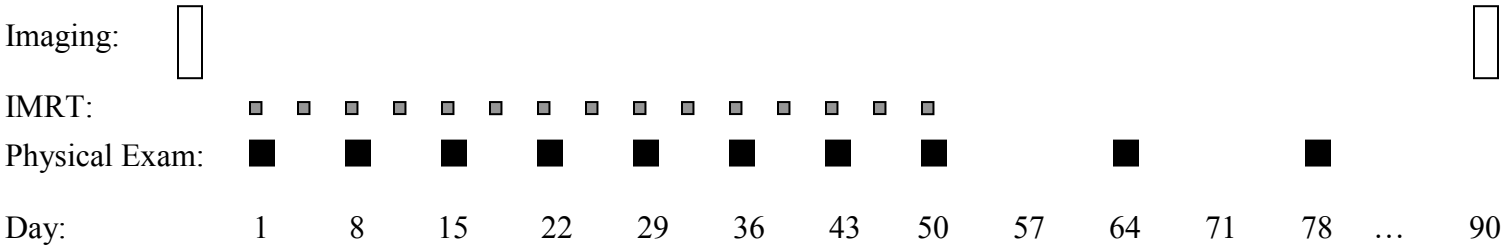

Study Design

This is a single arm, pilot study to estimate the toxicity, effectiveness and safety of intensity modulated radiation therapy in patients treated with $p16^{+}/HPV^{+}$ oropharyngeal squamous cell carcinoma with reduced radiation dose to the lymph nodes at risk for microscopic disease but clinically staged as N0.

Intensity Modulated Radiation Therapy

- Patients will be treated with intensity-modulated radiation therapy (IMRT). Planning Target Volume (PTV1) will include the gross disease with expansions for microscopic disease extension and 3 mm setup error expansion and will receive 70 Gy/35 fractions at 2.0 Gy/fraction/day for 5 days/week of a 7 week regimen.
- PTV2 will include the clinically uninvolved cervical lymph nodes (N0 lymph node volumes) with a 3 mm expansion for setup error and will be treated to 39.6 Gy/22 fractions at 1.8 Gy/fraction/day for 5 days/week.

ELIGIBILITY (see section 3)

- Confirmed histopathologic diagnosis of p16-positive tumor by immunohistochemistry.
- Must undergo pre-treatment tumor staging using the version 7 American Joint Cancer Committee Staging System.
- Patients must undergo a PET CT within 8 weeks prior to cancer treatment.
- Patients must have a contrast neck CT within 8 weeks to cancer treatment (this can be the CT simulation) or if they have a CT contrast allergy this can be a neck MRI scan.
- Tumor must be measurable by physical exam and/or endoscopy, and PET CT.
- Primary diagnosis is clinical stage I-IVb (T1-T4, N0-N3, M0).
- 18 years of age or older.

- Able to lie flat on the table for IMRT and tolerate aquaplast or other immobilization systems that reduces intra-fraction motion to 3 mm or less.
- Able to understand English (or a medical interpreter for their native language must be available for all study visits).
- Zubrod performance status 0-2.
- Nutritional and general medical condition must be considered compatible with the proposed radiotherapy treatment.
- No prior radiotherapy to the head and neck in the volumes to be irradiated for this malignancy.
- No other malignancy except non-melanomatous skin cancer or a carcinoma not of head and neck origin with the patient being disease free for ≥ 5 years.
- No major medical psychiatric or neurologic illness, which in the investigators' opinions would interfere with either completion of therapy or with full and complete understanding of the risks and potential complications of the therapy.
- Mentally reliable to follow instructions and to keep appointments.
- Pregnant and breastfeeding women are excluded from this study.
    - Women of childbearing potential (WOCBP) must have a negative pregnancy test within 14 days prior to cancer treatment.
    - WOCBP and men agree to use adequate contraception (hormonal or barrier method of birth control) for the duration of radiation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.
- Signed study-specific informed consent form.

TREATMENT (see section **Error! Reference source not found.**):

- Patients will be treated with IMRT. Planning Target Volume (PTV1) will receive 70 Gy/35 fractions at 2.0 Gy/fraction/day for 5 days/week.
- Clinically uninvolved cervical lymph nodes (N0 lymph nodes) will be treated to 39.6 Gy/22 fractions at 1.8 Gy/fraction/day for 5 days/week.

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1 BACKGROUND AND RATIONALE

1.1 Study Synopsis

Oropharyngeal squamous cell carcinoma (OPSCC) is commonly treated with platinum-based chemoradiation followed by neck dissection(s) for locally advanced nodal disease. Radiation schedules conventionally include 70 Gray (Gy) in 35 fractions to macroscopic disease and 60 Gy to the clinically uninvolved cervical lymphatics at high risk for microscopic metastatic disease and 50-54 Gy to the clinically uninvolved cervical lymphatics at low risk for microscopic metastatic disease(1). Despite advances in technology and the utilization of intensity-modulated radiotherapy (IMRT), treatment still causes significant acute toxicity, long term morbidity, reduced functional status, and a poor quality of life for many patients. Since the expected toxicities for radiation for this group of patients is extremely high (See Expected Toxicities Table in section 8.1.2) there is a great need to develop less toxic radiation regimens with equivalent efficacy to current standard of care regimens. Specifically, strategies for personalized cancer care which reduce the toxicity of treatment for those patients with more sensitive disease are needed. Oropharyngeal carcinoma is increasing in incidence in the United States in non-traditional populations, i.e. non-ethanol and non-tobacco user groups, secondary to human papilloma virus (HPV) infection. HPV-associated tumors over-express p16, a protein easily detected by immunohistochemistry, and are more sensitive to chemotherapy and radiation than non-HPV-associated tumors. We recently reported a retrospective analysis of 112 oropharyngeal cancer patients treated with definitive IMRT +/- chemotherapy with 70 Gy to PTV1 and 50.4 Gy to PTV2 showing that p16-positive tumors are highly curable with 100% primary tumor local control, 90% sterilization of pathologic lymph nodes based on pathologic analysis of neck dissection data, and 100% control of the clinically uninvolved (N0) cervical nodes(2). Given that 100% of the N0 nodes are sterilized by 50 Gy with or without chemotherapy we propose reducing the radiation dose to the N0 cervical nodal volumes in patients with HPV-associated tumors, as determined by p16 immunohistochemical staining. We hypothesize that we can deliver 39.6 Gy to the N0 nodes in OPSCC patients with p16 positive tumors and reduce toxicity without compromising N0 nodal control, disease-free survival, or overall survival.

UVA treats approximately 20-25 oropharyngeal cancer patients annually with definitive radiation or chemoradiation. We anticipate an accrual rate of 15-20 cases per year over 3 years (n=45). We will recruit a total of 45 patients with Stage I-IVb, p16-positive OPSCC who are candidates for radiotherapy. All patients will receive IMRT as part of their cancer treatment and will be followed on this study for 3 years after treatment.

The purpose of this study is to test the overall hypothesis that reduced intensity radiation treatment (39.6 Gy) to the N0 nodes in OPSCC patients with p16 positive tumors can reduce toxicity without compromising treatment efficacy. This represents a 10% reduction from 44 Gy (the minimum dose that the current NCCN guidelines recommend for the elective treatment of N0 nodes of patients with squamous cell carcinoma of the head and neck) and a 20% reduction from out institutional standard of care of 50.4 Gy. Efficacy endpoints will include N0 nodal control, disease-free survival, and overall survival. Safety will be assessed by grading of acute and late radiation-induced toxicity including acute radiation dermatitis and late subcutaneous fibrosis, neck dissection complication rate, xerostomia and dysphagia.

1.2 Disease Background

1.2.1 Epidemiology of Head and Neck Cancer

Although head and neck cancer is relatively rare, accounting for roughly 5% of adult cancers(3), it is a devastating disease with significant treatment-associated toxicities. The American Cancer Society reports approximately 40,000-50,000 cases of head and neck cancer are diagnosed annually in the United States(4). Head and neck cancer represents a diverse set of tumors originating in the head and neck region that include squamous cell carcinomas of the upper aerodigestive tract above the thoracic inlet, salivary gland tumors, thyroid tumors, sarcomas, and rare sinus tumors(5). Squamous cell carcinomas make up the vast majority of head and neck cancers and can develop in the mucosa of various upper aerodigestive anatomic sites including the oral cavity, oropharynx, nasopharynx, nasal cavity, paranasal sinuses, larynx, and hypopharynx(5). The development of these tumors is often related to patient use of tobacco products and/or ethanol, but viruses (HPV and Epstein-Barr Virus) and immunosuppression are also etiologic factors(5). The most common head and neck cancer treated at UVA with radiation is squamous cell carcinoma of the oropharynx (OPSCC).

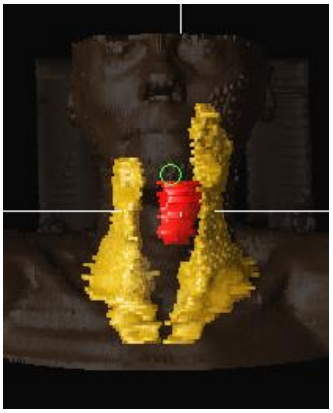
1.2.2 Standard Radiotherapy for OPSCC

Head and neck cancer can metastasize to cervical lymph nodes and do so in a predictable pattern with initial involvement of the first nodal echelon and sequential involvement in lower cervical and contralateral nodal regions(6-8). The Seventh Edition of the American Joint Committee on Cancer Staging Manual published in 2010 is the current staging system used by most physicians to stage head and neck cancer patients(9). Patients with stage I and II disease have a small primary tumor without clinical evidence of lymph node metastases and are managed with surgery or radiation therapy alone. Patients with stage III and IV

are generally considered to have locally advanced disease that is manifest by large primary tumors and/or clinically involved cervical lymph nodes. Therapy for these patients frequently involves multi-modality therapy based on the volume and location of both the primary tumor and lymph node disease and may include various combinations of surgery, radiation, cytotoxic chemotherapy (cisplatin, carboplatin, taxol, taxotere, 5-fluorouracil, capecitacbine), and/or biologic therapy (Cetuximab, an anti-epidermal growth factor receptor antibody)(10).

Radiation therapy for oropharyngeal cancer can conceptually be thought of as treating two separate regions to be targeted by the radiation (target volumes). The first target volume is the planning target volume 1 (PTV1) which contains all known gross cancer including the primary tumor and all pathologic lymph nodes (See Figure 1). Planning target volume 2 (PTV2) contains all of the clinically uninvolved cervical lymphatics at risk for microscopic disease spread (termed the N0 neck). Standard treatment for oropharyngeal carcinoma is definitive radiation therapy with 70 Gy delivered to PTV1 and 44-64 Gy (commonly 50Gy) delivered to PTV2(11). Concurrent chemotherapy is delivered for patients with Stage III-IV disease, and patients with N2 and N3 cervical nodal disease may also undergo neck dissection(s) to resect the nodal disease at the completion of chemoradiation if this is still palpable or appears pathologic on post-treatment imaging. Irradiation of these large volumes spanning the base of skull to the clavicles results in significant acute toxicity (fatigue, skin redness and blistering, sore mouth and throat, mucosal ulceration, loss of taste, dry mouth, thick secretions, cough, hoarseness, dehydration, and nausea) and late toxicity (dental decay, permanent dry mouth, swallowing difficulties, middle ear effusions, altered taste, osteonecrosis of the mandible, and hypothyroidism)(5). Given the significant toxicity associated with current treatment techniques for OPSCC, translational advancements that would reduce dose and toxicity are highly desirable.

Figure 1: Diagram of PTV1 and PTV2



Red = PTV1 Yellow= PTV2

1.2.3 HPV-associated OPSCC: A sensitive patient sub-population

OPSCC is increasing in incidence in the United States in non-traditional populations, i.e. non-ethanol and non-tobacco user groups, secondary to HPV-associated malignancies(12). Data from multiple studies reveal that oropharyngeal HPV-associated tumors account for 20-75% of oropharyngeal tumors(13, 14). HPV16 is the most common viral subtype associated with malignant transformation, as it is found in 90-95% of HPV-associated OPSCC(13). Over 86% of HPV-associated tumors over-express $p16^{INK4A}$ (p16), a cyclin-dependent kinase inhibitor, and only 3% of HPV-non-associated tumors over-express p16(15). P16 status can be identified easily by standard immunohistochemical techniques. Based on our own tissue microarray p16 immunohistochemical analysis, approximately 60% of oropharyngeal SCCs in central Virginia are HPV-associated(16).

Malignant transformation of HPV-associated malignancies involves the E6 and E7 oncoprotein pathways which functionally inactivate two human tumor-suppressor proteins, p53 and pRb respectively, leading to cellular proliferation, loss of cell cycle regulation, impaired cellular differentiation, increased frequency of spontaneous and mutagen-induced mutations, impaired apoptosis, and chromosomal instability(15, 17-19). The E6 oncoprotein binds to the cellular ubiquitin-protein ligase E6-AP and uses E6-AP to target the tumor suppressor protein p53 for ubiquitination and subsequent proteasome-mediated degradation. As a result of this degradation, p53 cannot initiate the apoptosis cascade or activate p21 to arrest the cell cycle. The overall effect is the abrogation of both the p53 and p21 pathways leading to impaired apoptosis and uncontrolled cellular growth(15, 17-19). The E7 oncoprotein can associate with both pRb and p21. In normal, non-proliferating cells, pRb blocks cell cycle progression by complexing with transcription factors such as E2F(18). When pRb is phosphorylated by cyclin-dependent kinase (CDK) complexes, it disassociates with E2F, enabling the cell to advance through the cell-cycle and divide. The p16 protein is a tumor suppressor that inactivates CDK4- and CDK6-cyclin D complexes and therefore suppresses the phosphorylation of pRb and protects against unregulated cell proliferation(15, 17). The binding of pRb by E7 prevents the pRb/E2F complex formation and leads to uncontrolled cell division(18). pRb acts as an inhibitor of p16 transcription, so pRb inactivation by E7 results in highly increased p16 expression in HPV-positive SCC(15). P16 is frequently inactivated epigenetically in HPV-non-associated tumors by means of hypermethylation(20).

HPV-associated tumors in the head and neck have been reported to be more sensitive to chemotherapy and radiation than non-HPV-associated tumors, and p16 status is a highly significant independent prognostic indicator for disease-free survival (DFS) with reported 5-year DFS of 84% for p16 positive (p16+)

tumors and 46% for p16 negative (p16-) tumors in one study(15). The use of p16 expression to predict DFS was superior to all clinicopathologic parameters normally used for treatment decisions and assessment of prognosis(15). Additional studies have confirmed that p16 immunohistochemistry is the best test to use for risk stratification in oropharyngeal SCC regardless of HPV status(21). An Affymetrix Human U133A GeneChip analysis of HPV-positive SCC and HPV-negative SCC reported that these tumors also had different specific gene expression profiles(22). It is unknown why p16+ tumors are more radiation responsive, but it may be due to higher proliferation rates of these poorly differentiated tumors compared to p16- tumors since radiation preferentially kills mitotically active cells. Cells are most sensitive to radiation-induced damage in the G2 and M phases of the cell cycle(23).

1.3 Study Agent(s) Background and Rationale

1.3.1 Radiation-induced Xerostomia

Xerostomia (dryness of the mouth) is the most prominent and common complication of radiotherapy for head and neck cancers (HNC), occurring in 60-90% of patients treated(24). During radiotherapy, the salivary glands may absorb enough radiation to impair or destroy their secretory function, thereby decreasing saliva production and causing xerostomia. The major salivary glands (parotid, submandibular, and sublingual) produce about 90% of salivary secretions while the remainder is produced by the minor salivary glands(24, 25). The parotid gland is extremely sensitive to radiation, and a median parotid dose of greater than 26 Gy results in permanent glandular atrophy and fibrosis(26). If both parotid glands are treated above tolerance, permanent xerostomia is likely to result. The resultant xerostomia in these patients contributes to a decrease in quality of life with adverse effects on speech, mastication, taste, swallowing, nutritional intake, and sense of well-being(24). Dryness of the oral mucosa also creates a predisposition to mucosal fissures and ulcers, and changes in the composition of the oral flora lead to dental caries and infections. The reduction in the salivary flow may also indirectly contribute to the risk of osteonecrosis of the mandible as abscessed mandibular teeth can lead to mandibular sequestration(24, 27, 28).

To relieve these symptoms, saliva substitutes are only temporarily effective and the usefulness of sialogogues, such as pilocarpine, is limited by cholinergic side effects(24). The administration of the radiation protector WR-2721 (amifostine) provides a benefit to a small proportion of head and neck cancer patients but often produces side effects including nausea and hypotension(29). On the other hand, the use of intensity modulated radiotherapy (IMRT) can sharply decrease the dose of radiation absorbed by one or part of both

parotid glands and thereby reduces xerostomia and improves quality of life(26, 30). Due to the sensitivity of the parotid glands (tolerance dose of 26 Gy median dose) and the need to treat adjacent nodal volumes to 50-70 Gy, the parotid glands are still near tolerance even with the most advanced treatment planning and delivery systems such as the Helical Tomotherapy system(31, 32). However, if the radiation dose to the electively treated cervical nodes could safely be reduced in patients with radiosensitive tumors, the dose delivered to the parotids would also be reduced and would therefore diminish the risk of xerostomia**.**

1.3.2 Intensity Modulated Radiation Therapy (IMRT)

Radiation therapy techniques for oropharyngeal SCC have undergone rapid technical advancements with the development of intensity modulated radiation therapy (IMRT) and image guidance of daily treatments. IMRT is the use of radiation beam shaping through the optimization of multi-leaf collimator positions by opening and closing leaves to change the intensity of different portions of the beam. This shaping enables the radiation dose to conform more precisely to the three-dimensional shape of the tumor. In typical LINAC-based IMRT, combinations of several (usually 7 to 9) non-opposing intensity-modulated radiation fields are used to deliver highly conformal dose distributions to target volumes while sparing adjacent non-target tissues. Thus, IMRT treatment planning requires the contouring of normal organs at risk (OARs) and target volumes on a kilovoltage CT (kVCT) image set, followed by daily treatment usually delivered with CT image guidance.

The use of IMRT for HNC has achieved near-universal acceptance, with 100% of responding US radiation oncologists reporting its use in a 2009 survey(16). When used in the treatment of head and neck cancer, IMRT has been shown to cause less biologic injury to normal adjacent structures while maintaining similar or improved locoregional tumor control rates(30, 33-35). Multiple single-institution retrospective publications have described the outcomes of OPSCC patients treated with IMRT. For example, the use of IMRT in recent studies has yielded 2 and 3-year locoregional progression-free survival rates above 90%(1, 31, 36, 37), compared to rates of about 80% with non-IMRT techniques(36). Studies with IMRT have reported comparable acute toxicities to those of conventional therapy and even reduced late toxicities, as IMRT enables significant sparing of the parotid glands, resulting in reduced xerostomia and improved quality of life(26, 30, 33, 34, 38). Recent prospective randomized controlled trials (RCT) have confirmed that the use of IMRT results in less xerostomia than conventional RT for nasopharyngeal, oropharyngeal, and hypopharyngeal carcinomas(39-41). Of these RCTs, only Nutting et al mention

survival data, and they found no differences in overall survival or locoregional control rates between IMRT and conventional RT(40).

1.3.3 Helical Tomotherapy-based IG-IMRT

The Helical Tomotherapy Technology (AccuRay, Sunnyvale,CA) is an image-guided IMRT unit based on helical CT technology and is a fully integrated treatment planning and image guided delivery system. The system has a 6 megavoltage (MV) linear accelerator, a 6.25 mm binary pneumatic multi-leaf collimator (MLC) for beam modulation, and a radiation detector allowing for fan beam megavoltage CT (MVCT) scan acquisition built onto a standard CT gantry. The inverse treatment planning system calculates the MLC position every 7 degrees of rotation or 51 times per gantry rotation. We have previously published results that show that the Helical Tomotherapy system provides improved dose homogeneity and normal structure dose compared with LINAC-based IMRT in the treatment of oropharyngeal carcinomas(32). This results in a reduced risk for complications from focal hotspots within the planning target volume and a reduced dose to the adjacent parotid glands(32). Daily MVCT images can be obtained and electronically co-registered to the planning kVCT scan, allowing for daily image guidance for highly accurate patient positioning prior to treatment. We have previously published that without image guidance, the patient isocenter vector can shift over 3mm between treatments and result in significant errors in dose delivery(42). We will deliver highly conformal IMRT to the patients in this study using image guided Helical TomoTherapy.

1.3.4 Dose Reduction to the N0 Neck Lymph Nodes in p16+ Patients

Our research group performed a retrospective analysis of 112 patients at UVA with OPSCC who received IMRT, of which 72 had p16 immunohistochemical analysis of their corresponding biopsies(2). To the best of our knowledge, this study was the largest reported series of OPSCC patients definitively treated with IMRT at the date of publication and the only IMRT study reporting stratification for p16 tumor status for outcome analysis. The primary, pathologic nodal, and N0 nodal control rates at UVA for p16+, p16-, and p16 unknown patients are shown in Table 1 and Table 2 (Appendix A). This data confirms the findings of other investigators that patients with p16+ tumors have significantly better outcomes than patients with p16- tumors(15). In our study with a median follow-up of 29 months, we found that patients with P16+ tumors treated with chemoradiation (n=28) had 100% primary tumor local control, 90% sterilization of pathologic nodes based on neck dissection data, and 100% control of the N0 volumes(2).

Historically, Fletcher reported that 45-50 Gy was the necessary dose to treat the clinical N0 neck to achieve 90% chance of no nodal recurrence(43). The

N0 status was determined by physical examination only (in the pre-CT era) and was reported for radiation alone without chemotherapy. Harrison performed a meta-analysis to determine the dose response for local control of the N0 neck with radiation alone and reported that 45-50 Gy would result in a 95% chance of nodal control(44). Our data revealed 2/112 (1.8%) of patients with recurrence in the N0 cervical volumes; both had documented local recurrence of the primary, and neither was p16+. Isolated N0 nodal failure is defined as failure in an N0 volume without associated failure in the primary tumor, failure in known pathologic lymph node volume, or distant metastatic disease. Isolated N0 nodal failure in a CT or PET CT staged N0 nodal volume following 50 Gy with or without chemotherapy is rare and reported to occur in only about 2-3% of head and neck cancer patients(44-46). Our retrospective analysis found 0/112 (0%) of patients had isolated N0 lymph node failures, and p16+ patients who received chemoradiotherapy (n=28) had a 100% 3-year locoregional control rate. With such dramatic responses in p16+ patients, it is very likely that the N0 neck in this cohort is receiving more radiation than necessary. For comparison, cervical and anal cancers are also squamous cell carcinomas associated with HPV, but their N0 nodes are treated with lower radiation doses than those in head and neck cancer. In contrast to the 50 Gy delivered to the N0 neck in HNC, N0 inguinal nodes in anal cancer are often only treated to 30.6 Gy(47, 48), and N0 para-aortic nodes in cervical cancer receive 44 Gy(49). Thus, a reduction of the dose to the N0 neck in p16+ OPSCC to 39.6 Gy is consistent with doses already utilized with similar cancer histology in other anatomic sites.

1.3.5 Post-treatment Surveillance with PET-CT

Patients with head and neck cancer are often monitored after treatment with PET CT, as it has been shown to be highly sensitive in the detection of persistent and recurrent disease after treatment(50-52). Multiple studies show that an initial negative PET CT obtained 3 months after definitive radiotherapy can have a negative predictive value (NPV) as high as 100% for locoregional recurrence with an average NPV of 95%(50-52). However, sensitivity of PET is slightly lower for distant metastases(51, 52). Most authors recommend follow-up PET CT from 3 to 6 months after completion of treatment because studies have shown higher false-negative PET scans when obtained less than 3 months after treatment(50, 51, 53, 54). Thus, a negative PET scan 3 to 6 months after treatment may have a very high probability of ruling out any locoregional recurrence in patients who receive a lower dose to the N0 neck.

If a locoregional recurrence is going to occur, it is most likely to recur within 1 to 2 years, as nearly 90% of all HNC failures occur within the first 2 years after treatment(36). Yao et al (2005) found that 11/150 (7.3%) HNC

patients treated with IMRT developed locoregional recurrences in a median time of about 5 months (range of 2 to 16 months)(37). Their local recurrence-free survivals at 2 and 3 years were equivalent at 94%, and locoregional recurrence-free survivals at 2 and 3 years were also equivalent at 92%. Eisbruch et al reported a 16% rate of locoregional recurrence at a median time of 8 months (55), while Huang et al (2008) reported 10% developing locoregional recurrences at a median time of 15 months (range of 3 to 43 months)(31). Thus, any patient disease-free at 2 years has a very high likelihood of remaining disease-free. However, data is not available for the recurrence of the N0 volumes in the above studies, and they did not stratify their data according to p16 status, which provides vital prognostic significance. Our p16+ patients had 100% control of the N0 volumes at 3 years after treatment, so any isolated recurrence in the N0 volumes after dose reduction at any time in this current study would be suspicious for an inferior treatment.

However, post-treatment PET CT imaging is not the national standard of care following definitive treatment of squamous cell carcinomas of the head and neck. Post-treatment PET CT imaging will therefore be optional on this study and can be used if post treatment contrast enhanced CT or MRI scans show equivocal results and/or the patient declines a recommended neck dissection.

1.4 Rationale for Study Design

This is an unblinded, single arm study to demonstrate that reduced intensity radiation of the N0 nodes in patients (n=45) with p16+ oropharyngeal squamous cell carcinoma can provide improved tolerability compared with historic controls. The results of this study will support future studies to establish the equivalent efficacy and improved toxicity profile of this treatment in a larger population.

2 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 To estimate the N0 nodal control rate in patients with p16+ oropharyngeal squamous cell carcinoma (OPSCCA) treated with 39.6 Gy to the clinically uninvolved cervical lymphatics.

2.2 Secondary Objectives

2.2.1 To evaluate safety and tolerability of treatment of p16+ OPSCCA treated with 39.6 Gy to the clinically uninvolved neck by overall incidence of adverse events, incidence of acute and late radiation-induced toxicities and subject-rated quality of life assessments.

2.2.2 To estimate progression-free survival and locoregional recurrence-free survival in patients with OPSCCA following treatment with 39.6 Gy to the clinically uninvolved neck.

2.2.3 To compare the dose volume histograms (DVH) of treatment plans for patients receiving 39.6 Gy to the N0 neck to the DVH of matched treatment plans with the standard 50 Gy to the N0 neck.

3 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

3.1.1 Patient must sign a study specific informed consent prior to study entry.

3.1.2 Zubrod performance status 0-2.

3.1.3 Age $\geq$ 18 years.

3.1.4 Patients must be clinically referred for radiation therapy with stage I-IVb (T1-T4, N0-N3, M0) squamous cell carcinoma of the oropharynx.

3.1.4.1 Tumor must be measurable by physical exam and or endoscopy, and PET CT. PET CT must be performed within 8 weeks of initiating treatment for cancer.

3.1.4.2 Disease must be staged using the 2010 American Joint Cancer Committee Staging System (version 7).

3.1.5 HPV (p16)-positive tumor confirmed by immunohistochemistry.

3.1.6 Patient must be able to comprehend English (or a medical interpreter for their native language must be available for all study visits)

3.1.7 Patient must be capable and reliable to participate in all study related procedures.

3.1.8 Patient must be able to lie flat on the table for IMRT and tolerate aquaplast or other immobilization/image tracking systems that reduces intra-fraction motion to 3 mm or less.

3.2 Exclusion Criteria

3.2.1 Patients may not be receiving any investigational agents.

3.2.2 Prior radiotherapy to the head and neck in the volumes to be irradiated for this malignancy.

3.2.3 Any other malignancy except non-melanomatous skin cancer or a carcinoma not of head and neck origin with the patient being disease free for $\geq$ 5 years.

3.2.4 Nutritional and general medical condition are incompatible with the proposed radiotherapy treatment

3.2.5 Any major medical psychiatric or neurologic illness, which in the investigators' opinions would interfere with either completion of therapy or with full and complete understanding of the risks and potential complications of the therapy.

3.2.6 A serious uncontrolled medical disorder that is in the opinion of the Investigator would impair the ability of the patient to receive protocol therapy.

3.2.7 Pregnant and breastfeeding women are excluded from this study.

3.2.7.1 Women of childbearing potential must have a negative pregnancy test within 14 days prior to initiation of treatment.

3.2.7.2 Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

4 TREATMENT PLAN

4.1 Registration

Patients who meet eligibility criteria must be registered in OnCore. The following minimum registration information must be entered for all patients registered:

- demographics
- date of signed informed consent
- subject number
- on-study date (date subject meets all eligibility criteria)
- disease site
- registering investigator

4.2 Intensity Modulated Radiation Therapy (IMRT) Treatment Regimen

Patients will be treated on a Helical Tomotherapy Unit (AccuRay, Sunnyvale, CA) over a period of 7 weeks. Patients will receive IMRT to two regions: Planning Target Volume 1 (PTV1), which includes the gross disease (GTV) with expansions for microscopic disease extension and 3 mm setup error expansion; and Planning Target Volume 2 (PTV2), which includes the clinically uninvolved cervical lymph nodes (N0 lymph node volumes) with a 3 mm expansion for setup error. PTV1 will receive 70 Gy/35 fractions at 2.0 Gy/fraction/day for 5 days/week. PTV2 will be treated to 39.6 Gy/22 fractions at 1.8 Gy/fraction/day for 5 days/week.

4.3 Dosing Delays/Dose Modifications

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed periodically for the development of any toxicity according to the Time and Events table (See Section 5). Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 4.0 (See Appendix A).

Treatment breaks, if necessary, ideally should not exceed 5 treatment days at a time and 10 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. Treatment breaks must be clearly indicated in the treatment record along with the reason(s) for the treatment break(s). Any treatment break(s) exceeding 2 treatment days for reasons other than toxicity/illness will be considered a protocol deviation.

4.4 Concomitant Medications/Treatments

4.4.1 Neck dissection

Patients with N2 – N3 disease may undergo neck dissections at the discretion of the head and neck surgeon after the completion of treatment if physical examination or radiologic imaging reveals persistent pathologic nodal disease.

4.4.2 . Chemotherapy

Patients with T1-T2 and N0-N1 may be treated with radiation alone without concurrent chemotherapy. Concurrent chemotherapy is strongly recommended for locoregional control in the management of advanced cancer. It is recommended that patients meeting any of the following criteria be treated with a concurrent chemoradiation regimen:

- Definitive cases with T3-T4 primary tumors and/or N2-N3 nodal disease
- Significant extracapsular spread (ECS >1 mm beyond capsule or obliteration of nodal architecture) as determined by staging imaging.

The chemotherapy regimen will be selected at the discretion of the treating physician and will be administered according to standard institutional guidelines. Suggested common concurrent regimens include:

- Cisplatin, 100mg/m^2 IV infusion on days 1, 22, and 43 of the treatment course
- Cisplatin, 30-40mg/m^2 IV infusion q week x 6-7doses during the treatment course

- All patients must receive vigorous hydration during high dose cisplatin treatment
- Treatment with cisplatin is highly emetogenic, patients must receive pre-treatment to prevent nausea and monitored for delayed nausea and vomiting
- Cetuximab 400 mg/m^2 IV loading dose 1wk before the start of radiation therapy, then 250 mg/m^2 weekly (premedicate with dexamethasone, diphenhydramine, and ranitidine)

4.5 Other Modalities or Procedures

Not applicable.

4.6 Duration of Therapy

All patients will undergo radiation treatment regimen (IMRT) which will last a planned 7 weeks.

4.7 Duration of Follow Up

Patients will be followed for three years after completion of the treatment or withdrawal from the study, or until death (whichever occurs first). All patients, regardless of the duration of therapy, will be asked to complete QOL questionnaires every 3 months for the first year (starting at 6 months post-IMRT), and every 6 months for the second and third years.

4.8 Pregnancy

Women of childbearing potential (WOCBP) includes any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal [defined as amenorrhea ≥ 12 consecutive months; or women on hormone replacement therapy (HRT) with documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL]. Even women who are using oral, implanted or injectable contraceptive hormones or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy or practicing abstinence or where partner is sterile (e.g., vasectomy), should be considered to be of child bearing potential.

WOCBP must have a negative serum pregnancy test within 14 days prior to initiation of treatment.

Prior to study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. **In addition, all WOCBP should be instructed to**

contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

4.9 Removal of Patients from Protocol Therapy

Patients enrolled in this study will receive 7 weeks of IMRT and then be followed for up to 3 years. Patients may discontinue from the study at any time and for any of the following reasons:

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

The reason for study removal and the date the patient is removed will be documented in the Case Report Form. Patients discontinued or withdrawn from protocol therapy will continue to be treated per standard of care.

If a patient discontinues or is withdrawn from the study for the above listed reasons, then all data collected prior to discontinuation/ withdrawal will be included in the final analysis.

5 EVALUATIONS AND ASSESSMENTS

5.1 Time and Events Table

Table 1: Treatment Assessments

	Pre-study[1]	**Treatment (weeks 1-7)**		**Post IMRT**
Assessment	once	daily	weekly	once[2]
Informed Consent	X			
Inclusion/exclusion	X			
History	X		X	X
Physical Exam[3]	X		X	X
p16 immunohistochemistry	X[4]			
PET CT scan	X[5]			
Contrast enhanced CT (or MR)	X[5]			X
Serum pregnancy	X[6]			
Vital Signs (BP, HR, temp)	X		X	X
Weight	X			
Zubrod Performance Status	X		X	X
Toxicity Assessments		X		X[7]
IMRT		X		
Disease status				X[8]
QOL questionnaires	X			

Table 2: Follow-Up Assessments

	Months[9] following last IMRT									
	3	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**30**	**36**
Contrast enhanced CT (or MR) or PET CT	X[10]			X				X		X
QOL questionnaires[11]	X	X	X	X	X	X	X	X	X	X
History	X	X	X	X	X	X	X	X	X	X
Physical Exam[12]	X	X	X	X	X	X	X	X	X	X
Vital Signs (BP, HR, temp)	X	X	X	X	X	X	X	X	X	X
Zubrod Performance Status	X	X	X	X	X	X	X	X	X	X
Toxicity Assessments[7]	X	X	X	X	X	X	X	X	X	X
Disease status[8]	X	X	X	X	X	X	X	X	X	X

[1] Must be performed within 28 days of initiation of study treatment, unless a different timeframe is specified
[2] Assessments should be conducted between 4-6 weeks following the last IMRT treatment
[3] Includes height and body surface area (BSA); height is collected at pre-study visit only
[4] p16 expression for eligibility must be detected by immunohistochemistry and in situ hybridization (HPV)
[5] Must be performed within 8 weeks of start of treatment for cancer
[6] WOCBP must have a negative serum pregnancy test at least 14 days prior to initiation of cancer treatment
[7] Acute AEs will be collected up to 90 days following the last IMRT; late radiation toxicities will be collected from 3 months up to 3 years following the last IMRT
[8] Disease status should be assessed at each follow-up, using RECIST criteria
[9] Assessments should be performed ± 2 weeks from date
[10] The imaging assessments at 3 months post-IMRT are optional.
[11] May be completed by mail if patient is not scheduled for or misses a clinic visit
[12] Follow-up physical exams may include a flexible fiberoptic nasolaryngoscopy

5.2 Pre-Study Assessments

Patients must sign an informed consent prior to undergoing any protocol specific assessments. All pre-treatment evaluations must be performed within 14 days prior to Day 1 of IMRT, except the imaging assessments which must be performed within 8 weeks of start of treatment for cancer. Patients entered on study should be asked to complete the quality of life (QOL) questionnaires prior to the Day 1 visit in order to obtain an accurate baseline assessment. Instructions on how to complete these questionnaires are provided on the forms.

The following radiologic studies must be performed to provide accurate tumor staging and baseline assessments (within 8 weeks of start of treatment):

1. PET CT
2. Contrast enhanced CT (can be planning CT) or MRI

5.3 Treatment Assessments

All patients will undergo a 7 week radiation treatment regimen. The sections below outline the assessments to be performed at each visit. Assessments denoted by an asterisk (*) should be performed prior to initiation of any radiation treatments at that visit.

Daily: The following assessments should be performed daily (5 days/week) during the 7 week treatment interval:

- IMRT

Weekly: The following assessments should be performed once per week during the 7 week treatment interval:

- History and abbreviated physical exam (including performance status)*
- Vital signs (HR, BP and temp)*
- Collection of adverse events*

Post IMRT: At 5 ± 1 week following the last IMRT treatment, the following assessments should be performed:

- History and abbreviated physical exam (including performance status)*
- Vital signs (HR, BP and temp)*
- Contrast enhanced CT (or MR) to assess for disease status and nodal control
- Evaluation for acute radiation toxicity (see Appendix B)
- Evaluation by the head and neck surgeon for neck dissection of persistent pathologic nodal disease.

5.4 Post-Treatment/Follow-up Assessments

The below follow-up evaluations should be performed at the intervals specified in Table 2 following the last IMRT:

- Contrast enhanced CT (or MR) or PET CT should be performed every 12 months to assess for disease progression
- The following should be performed each time a patient is seen in clinic, per standard care (approximately every 3 months for 2 years, every 6 months in year 3). If a clinic visit is missed, then these assessments should be performed at the next visit:
    - History and Physical (including performance status)
    - Vital signs
    - Performance Status
    - Disease status
    - Acute and late toxicity assessments
- QOL questionnaires should be performed at clinic visits. If no clinic visit is scheduled it can be completed by mail and reviewed with the patient at the next clinic visit.
- Acute toxicity assessments should be performed to collect signs of radiation toxicity which occur up to 90 days following the last IMRT with grading per version 4 CTCAE.
- Late radiation toxicity (effects that occur after 90 days following completion of IMRT) will be evaluated at the time points shown in Table 2: Follow-up Assessments (every 3 months until 24 months after completion of IMRT and then every 6 months from 24-36 months after completion of IMRT). Late Toxicity will be scored per version 4 CTCAE.

In addition, if a patient has an unresolved adverse event at the end of study treatment, the event should be followed every 4-6 weeks until it has resolved, returned to baseline or is deemed irreversible, whichever is longer.

6 EVALUATION CRITERIA

6.1 Parameters of Response: RECIST for Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (Version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

6.1.1 Eligibility for response assessment

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

6.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area will not be considered measurable unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

6.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination

unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans), but NOT lung.

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET CT At present, the low dose or attenuation correction CT portion of a combined PET CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET CT can be used for RECIST measurements and can be used interchangeably with conventional CT in

accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy The utilization of endoscopic techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not

confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

6.1.4 Response Criteria

6.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

6.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

6.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 weeks confirmation**

CR	Non-CR/Non-PD	No	PR	
CR	Not Evaluated	No	PR	
PR	Non-CR/Non-PD/Not Evaluated	No	PR	
SD	Non-CR/Non-PD/Not Evaluated	No	SD	documented at least once ≥4weeks from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Not all evaluated	No	Not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

6.1.4.4 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the

smallest measurements recorded since the treatment started, including the baseline measurements.

6.2 Other Measures of Effect

6.2.1 N0 nodal control

The N0 nodal volumes will be defined prior to initiation of the radiation treatment regimen by PET scan and contrast enhanced CT and MR scans performed as part of the pre-study assessments. N0 control will be assessed by weekly physical exams performed during treatment and CT scan of the neck performed at 4- 6 weeks and annually post-treatment. Patients with observed involvement of any of the N0 nodes at any post-treatment interval will be considered to have an N0 failure.

6.2.2 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from start of treatment to time of recurrence/progression or death from any cause, whichever occurs first. Progression will be measured as defined by the RECIST criteria (Section 6.1). Patients who do not experience an event (recurrence/progression or death) will be censored at date of last contact.

6.2.3 Locoregional recurrence-free survival

Locoregional recurrence-free survival, or locoregional control, is defined as the duration of time from start of treatment to time of recurrence in either the primary tumor or the nodal regions. Patients who do not experience an event will be censored at date of last contact.

6.2.4 Dose Volume Histograms

Dose volume histograms will be used to evaluate the difference in radiation dose to critical structures with the decreased dose regimen compared to what the organs would have received if the PTV2 received 50 Gy. DVHs will be prepared from the mean, max, minimum doses to structures, as well as volumes of particular structures receiving certain doses for comparison.

6.2.5 Quality of Life Questionnaires

All patients entered on study will complete the quality of life (QOL) questionnaires at the pre-study assessment and every 3 months for the first year (starting at 6 months post-IMRT), every 6 months for the second and third years. These can be completed in person during a routine scheduled clinic visit or by mail. The QOL questionnaires to be completed are:

1. MD Anderson Symptom Inventory – Head & Neck (MDASI-HN)

2. MD Anderson Dysphagia Inventory (MDADI)
3. Voice Handicap Index-10 (VH-10)

For the MDASI-HN and VH-10, the patient provides a numerical response to each question. For the MDADI, the patient provides one of the following answers to each statement: strongly agree, agree, no opinion, disagree, strongly disagree. The responses provided on each questionnaire at each interval will be tabulated and summarized and post-treatment responses compared to pre-treatment values.

6.3 Toxicity and Safety

Patients will be evaluated for toxicity and safety weekly during radiation treatments (Section 5.1). Adverse events and other symptoms will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. See Section 8 for more details.

The following additional endpoints for toxicity will also be assessed at the toxicity assessments:

1. Grade of acute radiation dermatitis and late subcutaneous fibrosis (stratified by neck dissection or no neck dissection) in the N0 volumes
2. Late radiation toxicity (events that persist or occur after 90 days of completion of IMRT)
3. Neck dissection complication rate (wound breakdown)
4. Grade of xerostomia
5. Grade of dysphagia
6. Acute and late grade 3 or higher adverse event
7. Rate of PEG dependence at 6 months post-IMRT

7 STATISTICAL CONSIDERATIONS

This is a single institution, single arm phase II trial to estimate the efficacy and safety of reduced intensity modulated radiation therapy (39.6 Gy to the clinically uninvolved cervical lymph nodes in the neck) in patients with p16+ oropharyngeal squamous cell carcinoma. Specifically, the study is designed to estimate N0 nodal control and locoregional control rates, to estimate 3-year progression-free survival, and to define the safety profile of the treatment regimen to determine if the data support further research.

7.1 Study Design/Endpoints

Estimation and safety monitoring for N0 nodal control, locoregional control and 3-year progression-free survival guided sample size determination and monitoring

rules. Data from sixty p16+ OP-SCCA patients treated with standard IMRT at UVA from 2002-2011 with adequate follow-up were used to define 'historical' outcomes. The primary endpoint is N0 nodal control rate. In order to consider the treatment regimen worthy of further study the data need to support a N0 control rate no worse than that observed from the historical data. Similar conditions need to be observed for the secondary endpoints of locoregional control rate and 3-year disease-free survival.

N0 nodal control rate is defined as the percent of eligible patients who experience N0 recurrence within the minimum follow-up period of 3 years. Locoregional control rate is defined as the percent of eligible patients who experience local and/or regional failure within the minimum follow-up period of 3 years. The N0 neck represents lymph node regions of the neck that were not clinically or radiographically determined to be pathologically involved with metastatic disease to regional lymph nodes at initial presentation. N0 recurrence = failure in the N0 neck region. Isolated N0 recurrence = failure in the N0 neck region without failure elsewhere. Local (primary) recurrence = failure at the initial site of disease. Regional (nodal) recurrence = failure in lymph nodes in the neck (includes N0 recurrence). Distant recurrence = metastatic failure. Progression-free survival (PFS) is defined in section 6.2.2.

Safety is determined by frequency and severity of adverse events (AEs) related to treatment, and are classified and graded according to CTCAE version 4. AEs related to swallowing function during and after treatment will be assessed. Other endpoints of interest include locoregional recurrence-free survival, dose to regional organs at risk (OARs compared to if the N0 volumes received 50 Gy), and QOL as measured by subject-reported functional outcome questionnaires that will quantify patient-reported speech and swallowing function [MD Anderson Symptom Inventory – Head & Neck (MDASI-HN), MDADI (MD Anderson Dysphagia Index) and VHI-10 (Voice Handicap Index)].

7.2 Sample Size and Accrual

We know of no detailed published data for the primary and secondary endpoints for the study specific $p16^{+}/HPV^{+}$ OP-SCCA patient population of interest. However, the 'historical' data from sixty patients (updated since publication) treated at UVA provides us with a reliable source to guide sample size determination and monitoring guidelines. For those sixty patients, N0 recurrence occurred in 1/60=1.7% and locoregional failure occurred in 6/60=10% with the upper limit of a one-sided 95% CI being 7.7% and 19%, respectively. Three-year PFS from start of radiation treatment is 80% (95% CI (67, 88%)). For sample determination, these estimates will be used to define the null and alternative 3-

year PFS rates. Specifically, we would like to be able to differentiate between a null 3-year PFS rate of 80% versus the alternative of 67%. Assuming uniform accrual of 15 eligible patients a year for 3 years, a minimum follow-up time of 3 years, PFS is exponentially distributed, a one-sided 10% level test then accrual of 45 eligible patients provides approximately 89% power at the alternative. If the exponential assumption is not supported by the data then accrual of 45 eligible patients results in 80% power to test for a decrease of 14% in 3-year PFS with a one-sided 10% exact binomial level test.

A sequential probability ratio test (SPRT) based upon a binomial test of proportions for N0 control rates will be used. Only the upper boundary will be used for monitoring to protect against excessive failures. The stopping boundary are for a SPRT contrasting a 2% versus 8% N0 control rate, with nominal type I and II errors of 10% and 10%, respectively. The slope of the parallel lines for monitoring is 0.043 and the intercepts are 1.516 and 1.516.

Stopping guideline for N0 Failure	
Number of participants	Boundary
2-9	≥ 2
10-33	≥ 3
34-45	≥ 4

For estimation of locoregional control, a sample size of 45 eligible patients produces a two-sided 90% confidence interval with a width equal to 0.17 when the sample proportion is assumed at the observed historical rate of 10%.

7.3 Analyses

Point estimates and confidence interval will be calculated for all dichotomous endpoints (N0 control rate, locoregional control rate, AE specific rates). The Kaplan-Meier product-limit method will be used to estimate PFS and locoregional recurrence-freesurvival. Confidence intervals will be estimated for all efficacy endpoints. Under the assumption of exponential PFS we will estimate the exponential parameter (λ) and test whether the data support the alternative hypothesis that that λ=0.1335 versus the null hypothesis that λ=0.0744. Repeated measure models will be used to describe the change over time in QOL as measured by questionnaire. Data from the treatment planning software which produces graphs on mean, max, minimum doses to structures, as well as volumes of particular structures receiving certain doses will be used to compare the dose volume histograms (DVH) of treatment plans for patients receiving 39.6 Gy to the N0 neck to the DVH of matched treatment plans with the standard 50 Gy to the

N0 neck (i.e., to quantify the difference in radiation dose to critical structures in the neck with the decreased dose regimen compared to standard practice).

7.4 Reporting and Exclusions

All patients will be evaluable for toxicity and adverse events from the time of protocol intervention (start of treatment).

Evaluation of efficacy – All patients included in the study should be assessed for efficacy endpoints, even if there are major protocol treatment deviations or if they are ineligible. All of the patients who met the eligibility criteria will be included in the main analysis of the efficacy.

8 ADVERSE EVENTS AND REPORTING

Adverse events will be collected from the initiation of the radiation treatment until at least 30 days following completion of study treatment (i.e. end of seven week regimen or date of discontinuation). All adverse events should be reviewed by the treating physician to determine if expedited reporting is required. The following sections provide definitions for adverse event characteristics and reporting requirements.

8.1 Definitions

8.1.1 Adverse Event

An adverse event is any undesirable medical experience occurring to a subject who has been given an investigational product, whether or not related to the study drug(s). Medical conditions present before starting the investigational drug/intervention will be considered adverse events only if they worsen after starting study treatment. The following are adverse events:

- All unfavorable, harmful or pathological changes in the general condition of a patient.
- Subjective or objective symptoms (spontaneously offered by the patient and/or observed by the Investigator or the study nurse).
- All intercurrent events or exacerbation of pre-existing diseases which occurred after the administration of the study drug.
- All clinically significant changes in laboratory abnormalities.
- Any undesirable and unintended effect of research occurring in human subjects as a result of the collection of identifiable private information under the research.

AEs should be followed to resolution or stabilization, and reported as SAEs if they become serious (see below, definition of SAE). This also applies to patients experiencing AEs that cause interruption or discontinuation of investigational product, or those experiencing AEs that are present at the end of their participation in the study. Such patients should receive post-treatment follow-up as appropriate. AEs will be collected at least for 30 days post last day of radiation treatment in all cases including early study termination. If an ongoing AE changes in its severity or in its perceived relationship to study drug, a new AE entry for the event should be completed.

8.1.2 Expectedness

The expectedness of the adverse event will be determined by the Investigator based on current literature and the Investigator's experience. Below is a listing of the adverse events, and maximum grade of event, expected in this study:

Adverse Events with Possible Relationship to Study Treatment			**Maximum Grade**
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			1
	Anemia		2
Lymphopenia			2
Lymph Node Pain			1
	Lymph Node Pain		2
CARDIAC DISORDERS			
	Tachycardia (any type)		2
EAR AND LABYRINTH DISORDERS			
Ear Pain			1
	Ear Pain		2
		Ear Pain	3
Hearing Impaired			1
	Hearing Impaired		2
		Hearing Impaired	3
Middle Ear Inflammation			2
Tinnitus			1
	Tinnitus		2
		Tinnitus	3
	Vertigo		1
		Vertigo	2
ENDOCRINE DISORDERS			
Hypothyriodism			1
	Hypothyriodism		2
EYE DISORDERS			
	Cataract		1
	Conjunctivitis		1
		Retinopathy	2
	Watering Eyes		1
GASTROINTESTINAL DISORDERS			
Dental Caries			2

	Dental Caries		3
Dry Mouth			2
	Dry Mouth		3
Dysphagia			3
		Dysphagia	4
Esophageal Stenosis			1
	Esophageal Stenosis		3
		Esophageal Stenosis	4
Gingival Pain			2
Lip Pain			1
	Lip Pain		2
Mucositis Oral			3
Nausea			2
	Nausea		3
Oral Pain			3
	Peridontal Disease		3
Salivary Duct Inflammation			2
	Salivary Duct Inflammation		3
	Toothache		2
Vomiting			1
	Vomiting		3
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Edema Face			1
	Edema Face		2
		Edema Face	3
Fatigue			3
Irritability			2
	Irritabiity		3
Neck Edema			1
	Neck Edema		2
		Neck Edema	3
Pain Generalized			2
INFECTIIONS AND INFESTATIONS			
Mucosal Infection			2
	Mucosal Infection		3
	Otitis Media		2
	Sinusitis		2
	Soft Tissue Infection		2
	Tooth Infection		2
	Tracheitis		2
	Upper Respiratory Infection		2
		Upper Respiratory Infection	3
INJURY, POISING AND PROCEDURAL			
Dermatitis Radiation			2
	Dermatitis Radiation		3
	Injury to Carotid Artery		3
		Injury to Carotid Artery	4
INVESTIGATIONS			
Creatinine Increased			1
	Creatinine Increased		2
Lymphocyte Count Decreased			2
	Lymphocyte Count Decreased		3
	Platelet Count Decreased		1

		Platelet Count Decreased	2
Weight loss			1
	Weight Loss		2
		Weight Loss	3
White Blood Cell Decreased			1
	White Blood Cell Decreased		2
		White Blood Cell Decreased	3
METABOLISM AND NUTRITION DISORDERS			
Anorexia			3
		Anorexia	4
Dehydration			1
	Dehydration		2
		Dehydration	3
	Hyperkalemia		1
		Hyperkalemia	2
	Hypercalcemia		1
		Hypercalcemia	2
	Hypomagnesemia		1
		Hypomagnesemia	2
	Hyponatremia		1
		Hyponatremia	2
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
Generalized muscle weakness			1
		Head Soft Tissue Necrosis	3
Neck Pain			2
	Neck Pain		3
	Osteonecrosis of Jaw		2
		Osteoradionecrosis ofJaw	3
Trismus			1
	Trismus		2
		Trismus	3
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED			
	Treatment-related Second Malignancy		3
		Treatment-related Second Malignancy	4
Tumor Pain			2
	Tumor Pain		3
NERVOUS SYSTEM DISORDERS			
	Brachial Plexopathy		1
		Brachial Plexopathy	2
		Central Nervous System Necrosis	3
Dysguesia			2
Lethargy			1
	Lethargy		2
	Myelitis		1
		Myelitis	2
		Stroke	3
		Syncope	3
PSYCHIATRIC DISORDERS			
Agitation			1
	Agitation		2
Anxiety			2

	Anxiety		3
Depression			1
	Depression		2
		Depression	3
Insomnia			2
	Insomnia		3
Libido decreased			1
	Libido decreased		2
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
Aspiration			2
	Aspiration		3
		Aspiration	4
Cough			2
	Cough		3
	Dyspnea		2
Hoarseness			1
	Hoarseness		2
Laryngeal Edema			1
	Laryngeal Edema		2
		Laryngeal Edema	4
Laryngeal Mucositis			3
Nasal Congestion			1
	Nasal Congestion		2
		Nasal Congestion	3
Pharyngeal Mucositis			3
		Pharyngeal Necrosis	4
Pharyngolaryngeal Pain			2
	Pharyngolaryngeal Pain		3
		Stridor	3
Tracheal Mucositis			1
	Tracheal Mucositis		2
		Tracheal Mucositis	3
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Alopecia			1
Pain of Skin			2
	Pain of Skin		3
Skin Atrophy			1
	Skin Hyperpigmentation		2
Skin Induration			1
	Skin Induration		2
		Skin Induration	3
Telangiectasia			1
VASCULAR DISORDERS			
Hypotension			1
	Hypotension		2
		Hypotension	3
Lymphedema			1
	Lymphedema		2
		Lymphedema	3

8.1.3 Severity

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

To assess severity of adverse events not included in the CTCAE version 4.0, use **Table 3** below.

Table 3. Adverse Event Severity Grading Scale for Adverse Events Not Specifically Listed in the NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[1]
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL[2]
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to AE

[1]Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[2]Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

8.1.4 Attribution Assessment

The Principal Investigator will evaluate all AEs and assess their toxicity and attribution, if any, to study drug. The following criteria will define the attribution:

Definite: The AE is clearly relation to the investigational agent.
Probable: The AE is likely related to the investigational agent.
Possible: The AE may be related to the investigational agent.
Unlikely: The AE is doubtfully related to the investigational agent.
Unrelated: The AE is NOT related to the investigational agent.

8.1.5 Serious Adverse Event

A serious adverse event or experience (SAE) or serious adverse drug reaction (ADR) is any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

- Death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);

- Requires inpatient hospitalization or prolongation of existing hospitalization;*
- Results in congenital anomaly/birth defect;
- Results in a persistent or significant disability/incapacity;
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. For reporting purposes, also consider the occurrences of pregnancy as an event which must be reported as an important medical event.

*Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.

8.2 Expedited Adverse Event Reporting Requirements

8.2.1 UVA Cancer Center DSMC Reporting Requirements

All adverse events will be recorded on appropriate case report forms. In addition, all adverse events must be recorded into the University of Virginia Cancer Center OnCore database within the time frame specified below:

Table 4: Medium Risk Studies
Reporting requirements for AEs that occur within 30 days of the last day of radiation treatment

	Grade 1	Grade 2		Grade 3				Grade 4 & 5	
				Expected		Unexpected			
	Expected and unexpected	Expected	Unexpected	Without hospitalization	With hospitalization	Without hospitalization	With hospitalization	Expected	Unexpected
Unrelated Unlikely	Not required	Not required	Not required	ONCORE 30 days	ONCORE 15 days	ONCORE 30 days	ONCORE 15 days	ONCORE 15 days	ONCORE 15 days
Possible Probable Definite	ONCORE 30 days	ONCORE 30 days	ONCORE 15 days	ONCORE 30 days	ONCORE 15 days	ONCORE 15 days	ONCORE 15 days	ONCORE 15 days	ONCORE (24-hrs)* 7 days

*Enter into Oncore within 24 hours if unexpected and definitely related to protocol specified treatment
Hospitalization defined as an inpatient hospital stay or prolongation of a hospital stay equal to or greater than 24 hours

8.2.2 UVA IRB Reporting Requirements

The Principal Investigator (PI) or designee is responsible for reporting AEs and unanticipated problems to the UVA HSR-IRB according to the following guidelines.

Table 5

Type of Event	**To whom will**	Time Frame for	How reported?

	it be reported:	Reporting	
Any internal event resulting in death that is deemed DEFINITELY related to (caused by) study participation *An internal event is one that occurs in a subject enrolled in a UVa protocol*	IRB-HSR	Within 24 hours	IRB Online and phone call www.irb.virginia.edu/
Internal, Serious, Unexpected adverse event *See Oncore reporting requirement*	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event. *Timeline includes submission of signed hardcopy of AE form.*	IRB Online www.irb.virginia.edu/
Unanticipated Problems that are not adverse events or protocol violations This would include a Data Breach.	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Unanticipated Problem report form. *http://www.virginia.edu/vprgs/irb/HSR_docs/Forms/Reporting_Requirements-Unanticipated_Problems.doc)*
Protocol Violations (*The IRB-HSR only requires that MAJOR violation be reported, unless otherwise required by your sponsor, if applicable.)* Or Enrollment Exceptions	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Protocol Violation and Enrollment Exception Reporting Form *http://www.virginia.edu/vprgs/irb/hsr_forms.html* *Go to 3rd bullet from the bottom.*
Data Breach	The UVa Corporate Compliance and Privacy Office, a ITC: if breach involves electronic data- UVa Police if breach includes such things as stolen computers.	As soon as possible and no later than 24 hours from the time the incident is identified. As soon as possible and no later than 24 hours from the time the incident is identified. IMMEDIATELY.	UVa Corporate Compliance and Privacy Office- Phone 924-9741 **ITC:** Information Security Incident Reporting procedure, http://www.itc.virginia.edu/security/reporting.html Phone- (434) 924-7166

Table 6

INDEPENDENT DSMB/DSMC			
DSMB/DSMC Reports	IRB	15 calendar days of the study team receiving the report	Copy of DSMB/ DSMC report

9 DATA SAFETY MONITORING PLAN

The Principle Investigator will provide continuous monitoring of patient safety in this trial with periodic reporting to the UVA Cancer Center Data Safety Monitoring Committee (DSMC).

9.1 UVA Cancer Center Data Safety Monitoring Committee

The University of Virginia Cancer Center Data and Safety Monitoring Committee (DSMC) will provide oversight of the conduct of this study. The CC DSMC will report to the UVA Protocol Review Committee (PRC).

The DSMC will review the following:

- All adverse events
- Audit results
- Application of study designed stopping/decision rules
- Whether the study accrual pattern warrants continuation/action
- Protocol violations

The CC DSMC will meet every month for aggregate review of AE data. Tracking reports of the meetings are available to the PI for review. Issues of immediate concern by the DSMC are brought to the attention of the PI (and if appropriate to the PRC and IRB) and a formal response from the PI is requested. Per the Cancer Center NIH approved institutional plan this study will be audited approximately every 12 months.

10 STUDY MANAGEMENT

10.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

10.2 Registration Procedures

All patients must be registered with the OnCore database at the University of Virginia Cancer Center before enrollment to study.

10.3 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

10.3.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB-HSR approval/favorable opinion.

For any such emergency modification implemented, a UVA IRB modification form must be completed by study Personnel within five (5) business days of making the change.

10.3.2 Single Patient Exceptions

Any request to enroll a single patient who does not meet all the eligibility criteria of this study requires the approval of the Principal Investigator and the IRB.

10.3.3 Other Protocol Deviations/Violations

All other planned deviations from the protocol must have prior approval by the Principal Investigator and the IRB.

Protocol Deviations: A protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

Study personnel will record the deviation, and report to the IRB and DSMC as described in Sections 8.2.2 and 9.1, respectively.

Protocol Violations: An unplanned protocol variance is considered a violation if the variance:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

Violations should be reported by study personnel to the IRB within one (1) week of the investigator becoming aware of the event.

10.4 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring

logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

10.5 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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12 APPENDICES

APPENDIX A: Performance Scale

ZUBROD PERFORMANCE SCALE

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

APPENDIX B: Toxicity Criteria

Acute and Toxicity

Version 4.0 will be used to define acute toxicity in this trial. An electronic copy of the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4 can be obtained from the World Wide Web CTEP site. The web address is: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm
