PHASE II TRIAL OF INDUCTION CHEMOTHERAPY FOLLOWED BY ATTENUATED CHEMORADIOTHERAPY FOR LOCALLY ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMA ASSOCIATED WITH HUMAN PAPILLOMAVIRUS (HPV)

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Protocol CCRO022

And

Consent

February 25 2014

PHASE II TRIAL OF INDUCTION CHEMOTHERAPY FOLLOWED BY ATTENUATED CHEMORADIOTHERAPY FOR LOCALLY ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMA ASSOCIATED WITH HUMAN PAPILLOMAVIRUS (HPV)

Protocol Number:	CCRO022

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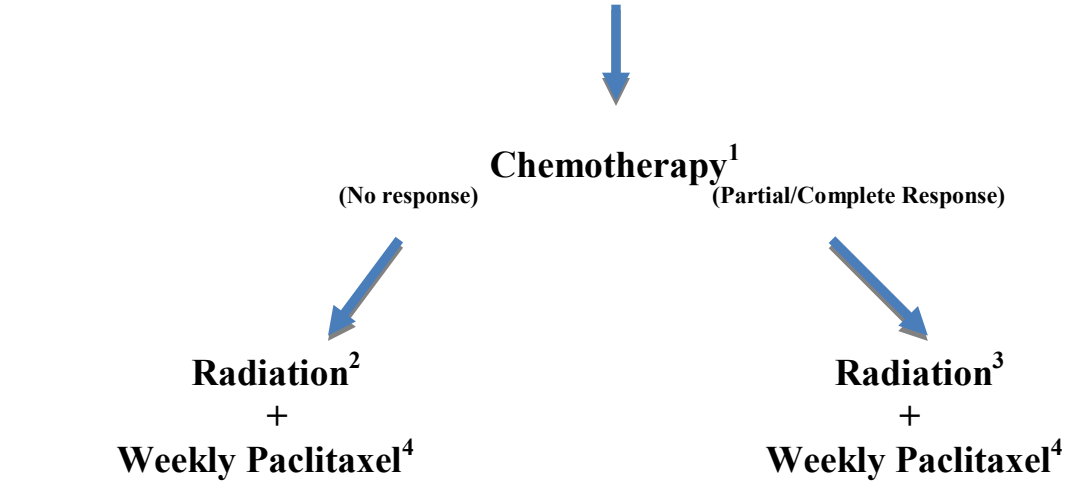
Schema



[1]Chemotherapy: Paclitaxel 175 mg/m^2 and carboplatin AUC 6 x two cycles

[2]Radiation: To begin at least 2 weeks after chemotherapy. The primary tumor and involved nodes will receive 2 Gy per fraction each day and subclinical disease sites will receive 1.6 Gy per fraction each day. The total doses will thus be 60 Gy and 48 Gy, respectively.

[3]Radiation: To begin at least 2 weeks after chemotherapy. The primary tumor and involved nodes will receive 2 Gy per fraction each day and subclinical disease sites will receive 1.6 Gy per fraction each day. The total doses will thus be 54 Gy and 43 Gy, respectively.

[4]Weekly paclitaxel: 30 mg/m^2 weekly x 5 weeks.

ELIGIBILITY CHECKLIST
(Page 1 of 2)

_____(Y) 1. Does the patient have pathologically (histologically or cytologically) proven (from primary lesion and/or lymph nodes) diagnosis of HPV-positive squamous cell carcinoma of the oropharynx, hypopharynx, larynx?

_____(Y) 2. Does the patient have clinical stage III or IV disease (T1-4, N1-3 or T3-4 any N M0)?

_____(Y) 3. Was a history/physical examination completed within 4 weeks prior to registration, including assessment of weight and weight loss in past 6 months?

_____(Y) 4. Was a Chest x-ray or Chest CT scan (or PET/CT) completed within 6 weeks prior to registration?

_____(Y) 5. Was a CT scan or MRI of the head and neck (of the primary tumor and neck nodes) and PET/CT scan completed within 6 weeks prior to registration?

_____(Y) 6. If a PET/CT was used (instead of a CT scan or MRI) was the CT component a high quality scan with contrast?

_____(Y) 7. Is the Zubrod 0-1?

_____(Y) 8. Is the patient at least 18 years of age?

_____(Y) 9. Were the following lab parameters confirmed within 4 weeks prior to study entry?

- Absolute neutrophil count (ANC) ≥ 1,800 cells/mm^3
- Platelets ≥ 100,000 cells/mm^3
- Hemoglobin ≥ 8.0 g/dl
- AST or ALT ≤ 2x the upper limit of normal
- Serum creatinine ≤ 1.5 mg/dl or institutional upper limit of normal
- Creatinine clearance (CC) ≥ 50 ml/min

____(Y/NA) 10. For women of childbearing potential, was a pregnancy test completed within 4 weeks of registration?

____(Y/NA) 11. If a male participant or a woman of child bearing potential, is the patient agreeable to practice effective birth control throughout the treatment phase of the study (until at least 60 days following the last study treatment)?

____(Y/NA) 12. Is there a history of prior invasive malignancy (other than non-melanomatous skin cancer)?

____(Y) If yes, has the patient been disease free for greater than three years?

_____(N) 13. Does the patient have simultaneous primaries or bilateral tumors?

_____(N) 14. Is the patient presenting with recurrent head and neck cancer?

_____(N) 15. Has the patient had prior systemic chemotherapy for the study cancer?

(Continued on next page)

ELIGIBILITY CHECKLIST
(Page 2 of 2)

_____(N) 16. Has the patient had prior radiotherapy to the region of study cancer that would result in overlap of radiation therapy fields?

_____(N) 17. Is the primary tumor site unknown, oral cavity, nasopharynx, sinuses, or salivary gland?

_____(N) 18. Has the patient had initial surgical treatment other than the diagnostic biopsy of the primary site or nodal sampling of neck disease?

_____(N) 19. Does the patient have any active symptoms of systemic lupus erythematosus or sceleroderma?

_____(N) 20. Does the patient have any of the severe comorbid conditions listed in Section 3.2.8 that would exclude him/her from participation?

The Eligibility Checklist must be completed in its entirety prior to registration. The completed, signed, and dated checklist used at study entry must be retained in the patient's study file.

Completed by _____ Date _____

1.0 HYPOTHESIS AND OBJECTIVES

1.1 Hypothesis

Due to the exquisite radiosensitivity of human papillomavirus (HPV)-associated squamous cell carcinoma (HNSCC) of the head and neck, patients who present with this disease may be currently "over-treated" using traditional chemoradiotherapy regimens and can effectively be treated with de-intensified strategies which result in improved tolerability and enhanced quality of life without compromising disease control or overall survival.

1.2 Objectives

To determine the progression-free survival, toxicity, local-regional control, and overall survival among patients with HPV-positive HNSCC treated by induction chemotherapy followed by attenuated chemoradiotherapy.

2.0 BACKGROUND

Head and neck cancer, mostly of squamous cell origin, ranks sixth among the most common cancers, accounting for approximately 6% of all malignancies. Each year, more than 500,000 new cases are diagnosed worldwide. For the 60% of patients presenting with locally advanced (stages III and IV) HNSCC, chemoradiotherapy has been established as a definitive treatment option through the publication of notable phase III trials (Brizel 1998; Adelstein 2003; Dennis 2004; Bourhis 2012). However, opinions regarding the proper role and timing of chemotherapy remain divided, particularly with regard to which chemotherapy drugs to use and how to optimally integrate them with radiation therapy. Moreover, attention has focused on identifying the appropriate radiation dose given that the accepted standards have remained at the same level for more than 30 years.

One of the most exciting developments in recent years is the recognition that not all HNSCC behave similarly from a biological standpoint. Prospective and retrospective data have shown that HPV-associated HNSCC, which comprises an increasing proportion of all HNSCC, represents a unique entity with distinct clinical and molecular characteristics (Braakhuis 2005, Licitra 2006; Gillison 2008; Weinberger 2006). While HPV-negative HNSCC is characterized by a multitude of genetic alterations involving deletions or methylation of tumor-suppressor genes and/or activation of tumor-promoting oncogenes, HPV-positive HNSCC is largely devoid of many of these genetic aberrations. This may be linked to the transforming potential of high-risk HPV (e.g. HPV-16), which through two viral oncoproteins, E6 and E7, inactivate two human tumor-suppressor proteins, p53 and pRb, respectively. Research is now showing that the distinct genetic profiles between HPV-positive and HPV-negative HNSCC underline not only differences related to the pathogenesis of this disease, but also differences with respect to prognosis and treatment response (Slebos 2006; Schlecht 2007; Klussman 2009). For instance, data has emerged that patients with HPV-positive HNSCC have a significantly improved prognosis, with at least half the risk of death from cancer, compared to their HPV-negative counterparts (Fakhry 2008; Kong 2008; Kumar 2008; Settle 2009; Rischin 2010; Hong 2010). Additionally, evidence is accumulating that HPV-related HNSCC is exquisitely more sensitive to the effects of radiation therapy (Lindel 2001; Lassen 2009; Ang 2010; Fischer 2010). Indeed, pre-clinical and clinical studies have demonstrated differential rates of response to irradiation between HNSCC from HPV-positive and HPV-negative settings (Spanos 2009; Gupta 2009; Williams 2009).

This recognition that HPV-positive HNSCC responds favorably to radiation therapy has prompted investigators to suggest that patients with these cancers might be “over-treated” and unnecessarily subjected to the toxicity of intensive chemoradiotherapy with excessively high radiation doses. While it has been proposed that treatment should be individualized for patients with HPV-related HNSCC, the specific recommendations on how to do so are non-existent. The proposed clinical trial, which will treat patients with HPV-positive HNSCC using radiation doses approximately 10-15% less than historically used, would be the first to individualize radiation for HNSCC based on the biological characteristics of the tumor.

2.1 Rationale for Induction Chemotherapy Followed by Concurrent Chemoradiotherapy as Definitive Treatment

With the widespread implementation of concurrent chemoradiotherapy as primary therapy for locally advanced HNSCC, the historical pattern of disease failure seems to have been altered. Single-institution phase II trials (Adelstein 2006; Brockstein 2004) of aggressive chemoradiotherapy protocols have reported that distant metastasis has emerged as the most common cause of treatment failure, even among patients who have HPV-positive HNSCC (Maxwell 2010). These data have rekindled interest in the potential use of induction chemotherapy in conjunction with definitive concurrent treatment in an effort to further improve survival by decreasing distant metastases.

Prospective trials (Machtay 2002; Kies 2010; Posner 2007; Vermorken 2007) have demonstrated encouraging outcomes using induction chemotherapy followed by concurrent chemoradiotherapy for locally advanced HNSCC. In previously untreated patients, overall response rates of 70% to 90% and complete response rates of 30% to 60% have been reproducibly reported after combination chemotherapy regimens (Salama 2008). The impressive sensitivity to chemotherapy has suggested the possibility that this treatment modality might decrease distant metastasis and improve local-regional control, organ preservation, and overall survival. Notably, induction chemotherapy is included in National Comprehensive Cancer Network guidelines for the treatment of locally advanced HNSCC and its administration before concurrent chemoradiotherapy has become increasingly accepted as a means for effective eradication of systemic micrometastases. Although many of the earlier tested regimens included 5-flourouracil as a component of the induction regimen, in recent years, taxane-based chemotherapy has emerged as a preferred strategy in the induction setting for HNSCC due to its activity and improved tolerability.

Investigators from Vanderbilt University (Cmelak 2007) reported on 44 patients with locally advanced HNSCC treated by 3 cycles of paclitaxel (175 mg/m2) and carboplatin (AUC, 6-7.5) every three weeks followed by concurrent chemoradiotherapy. The clinical response rate to induction chemotherapy was 89%, including a 51% complete response rate. The most common grade 3+ complication during induction chemotherapy was neutropenia which developed in 68% of the patients. The 2-year local control, progression-free survival, and overall survival were 82%, 77%, and 71%, respectively. As importantly, no significant difference in progression-free survival or organ-preservation was noted between concurrent regimens using cisplatin/paclitaxel or carboplatin/paclitaxel. However, due to the improved toxicity profile with the latter regimen, this was adopted as more “practical for use in the community setting.” Investigators from the University of Chicago (Vokes 2003) also reported on 69 patients treated by induction chemotherapy with 6 cycles of weekly carboplatin (AUC, 2) and paclitaxel (135 mg/m2) followed by concurrent chemoradiotherapy. The overall response rate to induction chemotherapy was 92%, with 35% of patients having a complete clinical response. The most common grade 3+ toxicity during the induction phase was neutropenia which developed in 18% of the population.

Based on encouraging single-institutional data, the Eastern Cooperative Oncology Group (ECOG) conducted a prospective phase II trial (2399) in which 111 patients with stage III/IV HNSCC received 2 cycles of induction chemotherapy every 3 weeks with carboplatin (AUC, 6) and paclitaxel (175 mg/m2) followed by concurrent paclitaxel (30 mg/m2) weekly with radiation therapy to 70 Gy (Cmelak 2007). With a median follow-up of 37 months, the 2-year rates of organ preservation and overall survival were 81% and 76%, respectively, which compared favorably to historical controls among patients treated by upfront concurrent chemoradiotherapy. The clinical response rate was 65% after induction chemotherapy (including 82% for HPV-positive tumors). Furthermore, no patient progressed during the induction phase of treatment, and its use did not preclude subsequent delivery of concurrent chemoradiotherapy. These studies have shown induction chemotherapy followed by concurrent chemoradiotherapy is a promising approach which may enhance distant control and improve treatment tolerability while maintaining high rates of local-regional control. Consequently, it is now commonly accepted that a course of induction chemotherapy with carboplatin and paclitaxel is active and well-tolerated

without compromising the ability to administer subsequent intensive chemoradiotherapy. As a result of the published data in support of this strategy, the ECOG regimen is increasingly used both as protocol and non-protocol treatment for patients with stage III/IV head and neck cancer.

Another increasingly recognized benefit of this approach is the ability of induction chemotherapy to help stratify patients to additional therapy. Since the tumor can be assessed in vivo, various investigators have shown that induction chemotherapy can serve as a predictive tool, allowing appropriate selection of the definitive management strategy. For instance, investigators from the University of Michigan recently reported a phase II trial of 66 patients with stage III/IV HNSCC in which one cycle of platinum-based induction chemotherapy was used to stratify subsequent local therapy. Responders to induction chemotherapy were subsequently selected for concurrent chemoradiotherapy and non-responders proceeded to surgery (Worden 2008). Although the limited size of the study made it difficult to draw definitive conclusions, the feasibility of this approach, particularly for patients with HPV-positive HNSCC (in which the rate of response to induction chemotherapy was 93%) was demonstrated.

2.2 Toxicity of Concurrent Chemoradiotherapy

Despite trials documenting a benefit to concurrent chemoradiotherapy in both the definitive and postoperative settings, it is important to note that this strategy (particularly with high dose cisplatin) significantly increases toxicity compared with radiation therapy alone (Trotti 2003; Bernier 2005; Garden 2008). In particular, acute mucositis and dysphagia are enhanced with the addition of concurrent chemotherapy. High dose cisplatin also causes constitutional and systemic toxicities that are well recognized and independent of the concomitant administration of radiation therapy. It is theoretically possible that these systemic toxicities might interfere with the ability of patients to tolerate and receive maximally effective dose intensity of radiation therapy in an uninterrupted fashion. For instance, the grade 3+ acute toxicity rate on RTOG 99-14, which all patients received radiation therapy with concurrent cisplatin was 79%, the most common of which were related to mucositis and esophagitis (Ang 2005). Similarly, in an analysis of late toxicity of patients treated on 3 chemoradiation trials using cisplatin for HNSCC by the RTOG, Machtay et al reported that 43% experienced grade 3+ late toxicity related to laryngeal and/or esophageal dysfunction (Machtay 2008). The toxicity of radiation therapy, in aggregate, has been shown to contribute to significant quality of life burden with respect to physical and psychosocial functioning (Langendijk 2008). These data suggests that concurrent chemoradiotherapy has eclipsed the limits of acceptable short- and long-term toxicity, and that attempts to reduce radiation dose in appropriately selected patients are warranted.

Although taxane-based chemoradiotherapy regimens appear to improve toxicity, the rates of complications are nonetheless high. Suntharalingam et al reported that the rates of acute grade 3 mucositis and dysphagia were 70% and 33%, respectively, among patients treated by concurrent carboplatin and paclitaxel at the University of Maryland (Suntharalingam 2000). Similarly, Cmelak et al reported grade 3+ acute mucositis in 47% of patients completing concurrent radiation with carboplatin and paclitaxel at Vanderbilt University (Cmelak 2007). For patients treated by radiation therapy with weekly paclixtaxel on ECOG 2399, 49% developed grade 3+ acute mucositis and 40% were G-tube dependent at end of treatment (Cmelak 2007).

2.3 Role of HPV in Predicting and Modulating HNSCC Radiation Response

Progress in the understanding of tumor biology has opened an exciting new era for research. Preclinical and correlative biomarker studies from various laboratories have so convincingly confirmed HPV status as the single most important predictor of radiation response that HPV staining is now routinely performed for prognostic purposes both in the community and in academic settings. Notably, when patients from the ECOG 2399 trial were examined by HPV status (Fakhry 20007), patients with HPV-positive tumors had significantly higher response rates after induction chemotherapy (82% versus 55%) and after chemoradiotherapy (84% vs. 57%). With a median follow-up of 39 months, patients with HPV-positive tumors had significantly improved 2-year overall survival (95% vs. 62%), progression-free survival (86% vs. 53%), and a 64% lower risk of death compared to patients with HPV-negative tumors. Similarly, recent data

published from the Radiation Therapy Oncology Group (RTOG) confirmed a dramatic difference in 3-year rates of local-regional control (86% vs. 65%) and overall survival (82% vs. 57%) between 433 patients with HPV-positive and HPV-negative phenotypes treated prospectively by chemoradiotherapy (Ang 2010). Interestingly, the risk of distant metastasis for HPV-positive and HPV-negative tumors in patients receiving upfront concurrent chemoradiotherapy was observed to be similar, affecting 10% and 13% of patients, respectively. This observation further suggests that a sequential treatment strategy utilizing induction chemotherapy prior to chemoradiotherapy for patients with HPV-positive HNSCC may be particularly applicable. Table 1 outlines published data in the form of secondary analysis from prospective trials demonstrating the improved prognosis for patients with HPV-positive HNSCC.

The mechanism of HPV-mediated radioresponse is currently unclear, and there are limited studies that have addressed this topic in the setting of head and neck cancer. The most direct explanation is that HPV infection and the subsequent degradation of the p53 and pRb proteins by the viral products E6 and E7 somehow renders the host tumor cell more susceptible to radiation-induced apoptosis. Both in vitro and in vivo studies, however, have demonstrated, quite paradoxically, that transfer of the E6/E7 genes or gene products into cells tends to increase radiation resistance, not decrease it as might be expected (Hampson 2001). Similarly, experiments designed to abrogate p53 function in head and neck cancer cells by other extrinsic means have not altered radiosensitivity, thereby suggesting that host cell characteristics, rather than the virus itself, mediates radiosensitivity (DeWeese 1997). Indeed, several recent studies have suggested that radiation therapy enhances the host immune response to viral antigens which are expressed on tumor (Rajjoub 2007; Wansom 2010).

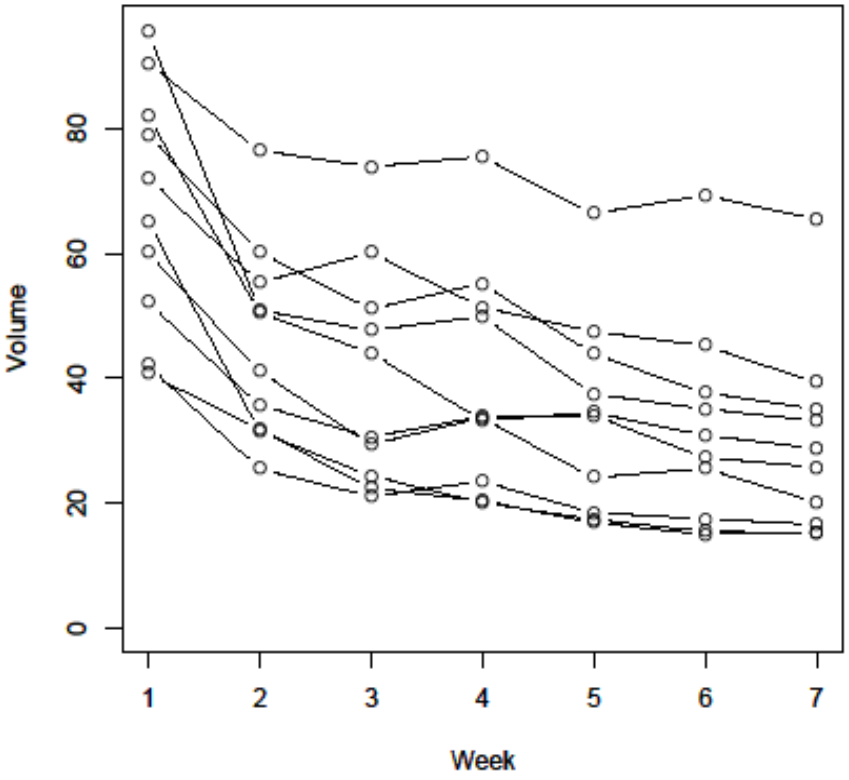
Regardless of the underlying mechanisms responsible for HPV-mediated radioresponse, preclinical work have confirmed the exquisite radiosensitivity of HPV-positive HNSCC. Gupta et al performed clonogenic survival assays of HPV-positive and HPV-negative cell-lines after exposure to various doses of radiation and showed that the former are characterized by markedly enhanced radiosensivity (Gupta 2009). Preliminary data from the University of California, Davis (Chen 2011), using a model system from axial imaging studies obtained serially during the course of radiation therapy to observe in vivo patterns of tumor response similarly showed that HPV-positive HNSCC tends to regress early during treatment, reaching a plateau by week 5-6, suggesting that radiation doses can possible be reduced (Figure 1).

Table 1: Subset Analysis of Prospective Trials Demonstrating Improved Prognosis with HPV-positive HNSCC

Author	N	Dose	Induction	Concurrent	Outcomes
Fakhry	96	70 Gy	Carbo/paclitaxel x2	Paclitaxel	86% vs 53%, 2yr PFS, p=0.02
Rischin	172	70 Gy	None	CDDP +/- Tirapazamine	87% vs 72%, 2yr PFS, p=0.01 93% vs 86%, 2yr LRC, p=0.09
Ang	323	70-72 Gy	None	Cisplatin	74% vs 43%, 3yr PFS, p<0.001
					86% vs 65%, 3yr LRC, p<0.001
Lassen	331	66-68 Gy	None	+/- Nimorazole	61% vs 35%, 5yr LRC, p<0.001
Lassen	794	66-68 Gy	None	None	78% vs 64%, 5yr PFS, p=0.001 69% vs 57%, 5yr LRC, p=0.004
Worden	66	70 Gy	Carbo/CDDP+5FU x1	Carbo/CDDP	85% vs 37%, 3yr PFS, p=0.001

Carbo: Carboplatin; CDDP: Cisplatin; 5FU, 5-fluorouracil; PFS, Progression-free survival; LRC: Local-regional control.

Figure 1: Regression in tumor volume (in cc) among 10 patients treated for HPV-positive HNSCC as determined using daily imaging (Chen 2011)



2.4 Rationale for Paclitaxel and Radiation Therapy for HNSCC

Given the toxicity of high dose cisplatin, attention has focused on the use of non-cisplatin radiosensitizers during radiation therapy as well as identifying patients at lower risk for failure who may potentially benefit from less aggressive chemoradiotherapy approaches. Paclitaxel, an inhibitor of depolymerization of microtubules, is a potent radiosensitizing agent in vitro and in vivo (Tisher 1992; Choy 1994). At our institution, it has become an important component of chemoradiotherapy for lung cancer (Lau 1997; Lau 1999) and esophageal cancer (Wang 2007). As a single agent, paclitaxel has moderate efficacy in head and neck cancer that a response rate as high as 50% has been reported (Grecula 2000). Given with radiation for head and neck cancer, promising results have also been reported for paclitaxel in multiple phase I and II trials. A summary of these trials published in the last 5 years is shown in Table 2.

Table 2: Background Phase I/II Trials Supporting Use of Paclitaxel in Concurrent Chemoradiotherapy for HNSCC

Investigators	Schedule	Dose (Gy)	Response (%)
Sunwoo, 2001	120 mg/m2/120 hr x2	70-72	70
Rosenthal,2001	10.5 mg/m2/day x7wks	70	58
Feher, 2002	45 mg/m2/wk, x8 wks	66-70	83
Bucci, 2004	40-120 mg/m2/96 hr x2	70-72	60
Wang, 2004	30 mg/m2/wk x 7 wks	68-70	NR
Pergolizzi, 2004	40 mg/m2/wk x 7 wks	66-70	NR
Amrein, 2005	60 mg/m2/wk x 6 wks	70	91
Jain, 2009	20 mg/m2/wk x 6 wks	66-70	73
Citrin, 2009	105-120 mg/m2/96 hr x2	70-72	NR

NR: Not reported.

Based on the reports of these trials, the response of HNSCC to paclitaxel and radiation is comparable to that of cisplatin and radiation. A recently published a prospective study comparing low dose paclitaxel to cisplatin for 100 patients undergoing concurrent chemoradiotherapy for HNSCC reported no statistical significant differences In outcome (Jain, 2009). The MTD of paclitaxel given concurrently with radiation therapy is estimated to be 40-50 mg/m2/week for 7 weeks. The dose-limiting toxicity for all of the above trials included mucositis and dermatitis, which were generally mild. At our institution, weekly paclitaxel, administered at 30-40 mg/m2 for 5-6 weeks with concurrent radiation, has been used to treat HNSCC for patients in whom cisplatin is contraindicated. Retrospective analysis of over 100 patients treated in such a manner have demonstrated excellent rates of local-regional control, progression-free survival, and enhanced tolerability compared to patients receiving cisplatin-based chemoradiotherapy for locally advanced HNSCC (Chen 2011).

2.5 Rationale for Attenuated Chemoradiotherapy for HPV-positive HNSCC

Given that the dose-limiting toxicity from prior chemoradiotherapy trials have been mucosal and esophageal, reducing the radiation dose in selected patients with more favorable biology (e.g. HPV-positive tumors) is an attractive option. Numerous prospective and retrospective data have demonstrated consistent dose-response relationships predicting toxicity for organs involved in salivary production, swallowing, and mucosal integrity (Eisbruch 1999; Chao 2001, Feng 2007; Narayan 2008). For xerostomia, it has been long known that the ability to keep mean parotid dose below 26 Gy will significantly reduce the incidence of hyposalivation and preserve quality of life (Deasy 2010). Normal tissue complication probability models have observed that for every 1 Gy in mean dose, the likelihood of xerostomia increases by approximately 5% at 1 year after radiation therapy (Dijkema 2008). An increasing amount of data is similarly showing that dose to anatomical structures thought to be responsible for swallowing is of critical importance in predicting acute and late toxicity from chemoradiotherapy (Eisbruch 2004). For instance, published data from the University of California Davis showed that minimizing dose to the constrictor muscles, cervical esophagus, and cricopharyngeal inlet may decrease the incidence of dysphagia, esophageal stricture, and gastrostomy-tube dependence (Chen 2009; Li 2009). Between 55 Gy and 70 Gy, a strong linear relationship was established between dose to the inferior constrictor muscles/cricopharyngeal inlet and the probability of late grade 3+ dysphagia as defined as gastrostomy-tube dependence (Figure 2). These data are consistent with published literature demonstrating that the threshold for radiation-induced long-term dysphagia likely exists at approximately 55 to 60 Gy, and dependent on dose-volume effects (Table 3). With respect to clinical mucositis, prospective data from the University of California Davis showed that limiting the maximum dose to the oral cavity to less than 40 Gy significantly reduced the incidence of acute mucositis during chemoradiotherapy (Narayan 2008). Notably none of the patients who received an oral cavity dose of less than 40 Gy developed grade 2+ mucositis compared to 50% of patients who received a dose of greater than 40 Gy (Figure 3). Additionally, it is increasingly recognized the limiting radiation dose to tissues such as the parotid gland, swallowing structures, and oral cavity translates into improved quality of life (Nguyen 2005; Langendijk 2008; Lin 2003).

The recognition that patients with HPV-related HNSCC fare exceptionally well have led some investigators to suggest that treatment can be de-intensified, particularly with respect to radiation dose. The currently utilized doses in the primary and postoperative setting are 70 Gy and 60-66 Gy, respectively. Indeed, both in vitro and in vivo studies have shown that HPV-positive HNSCC is exquisitely sensitive to the effects of radiation therapy. We hypothesize that by effectively reducing radiation to the normal structures of the head and neck, there will be a consequent reduction in side effects—particularly acute mucositis and esophagitis side effects—resulting in improved quality of life while maintaining high rates of disease control and overall survival. By potentially decreasing toxicity without lowering cure rates, de-intensification of radiation dose for HPV positive tumors has the potential to improve therapeutic ratio by decreasing toxicity while maintaining high rates of disease control.

Table 3: Dysphagia After High-Dose Radiation Therapy for HNSCC

Author	Incidence grade 3+ late	Predictive factors
Caudell	22%	Larynx, mean dose >41 Gy; V60 >24% Inferior PC V60< 12% Superior PC Middle PC
Feng	7%	
Chen	30%	Inferior PC V65 < 15% Cricopharyngeal inlet, Dmax <60 Gy
Levendag	23%	
Dirix	8%	Middle PC V50
Lawson	13%	Esophageal inlet, V60<30%
Schwartz	10%	Superior PC, V55< 80% Oral cavity, V30< 65%
Teguh	22%	Superior PC, mean dose< 60 Gy
Caglar	37%	Larynx, mean dose<48 Gy Inferior constrictor, mean dose<54 Gy
Dornfeld	33%	False vocal cords, mean dose<50 Gy

NR: Not reported; PC: Pharyngeal constrictor muscles.

Figure 2: Volume-response or dose-response relationship for the average probability of having prolonged GT dependence and (a) mean dose to the inferior constrictor muscles and (b) maximum dose to the cricopharyngeal inlet (Li 2009); GT = gastrostomy tube; IPC = inferior pharyngeal constrictors; CPI = cricopharyngeal inlet. The ♦ lines plot the mean risk; the - lines plot the estimated upper and lower limits of 95% confidence interval. The ♦ points depict the observed values.

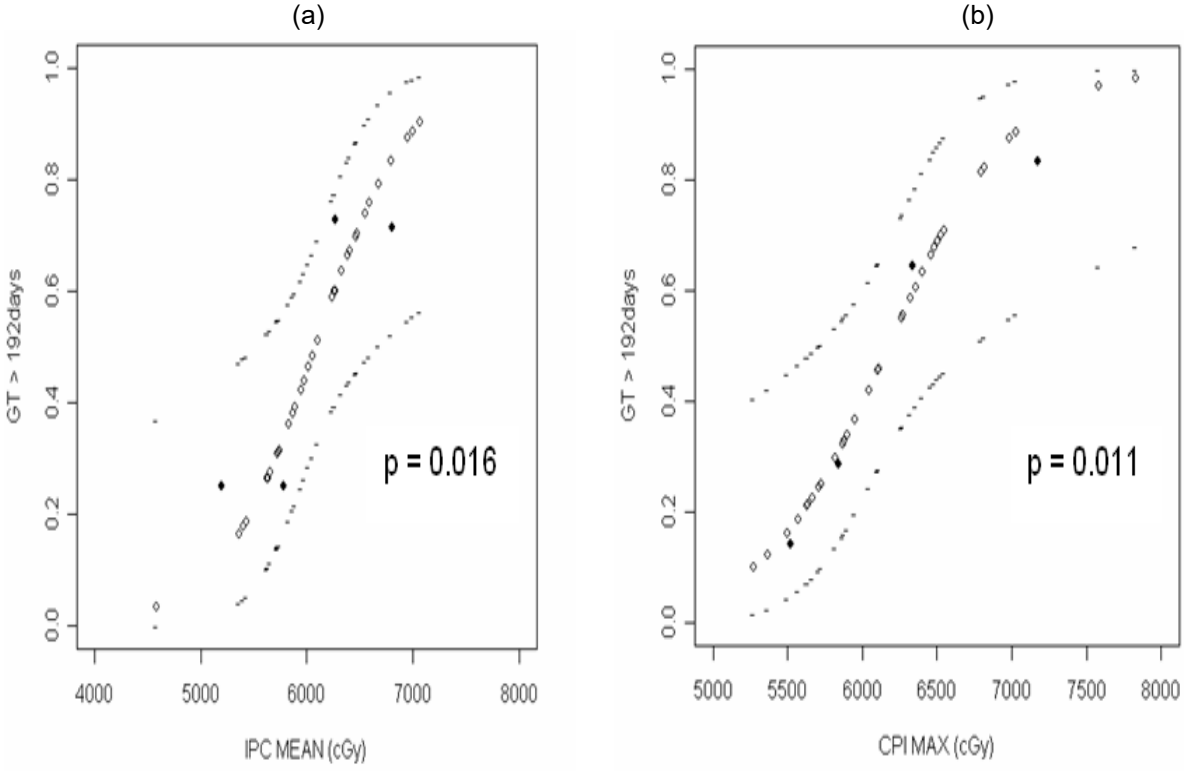
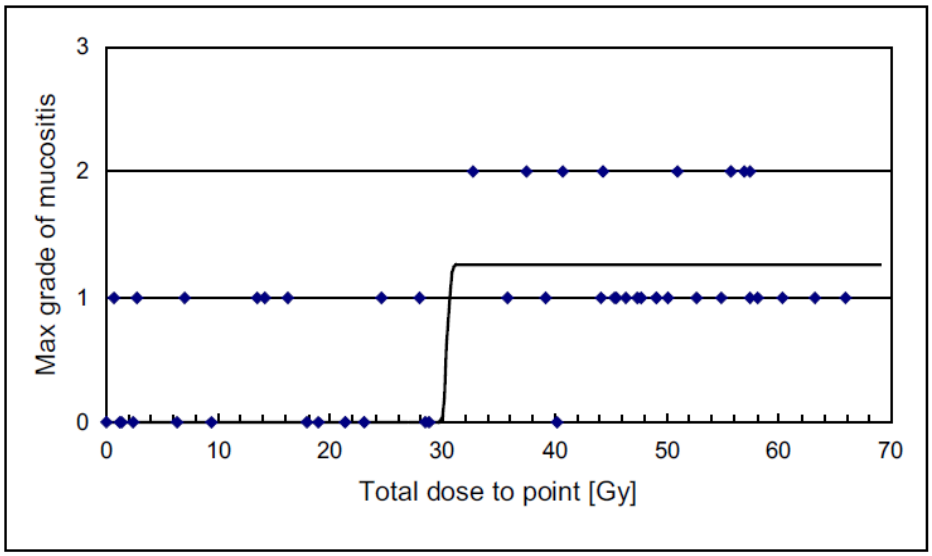


Figure 3. Dose-response relationship between maximum point dose to the oral cavity and grade of clinically significant mucositis (Narayan 2007)



2.6 Study Design

This study is the first of its kind to select patients with HPV-positive HNSCC for attenuated therapy and may have important implications for individualization of care in the future. The regimen of carboplatin and paclitaxel was selected for the induction chemotherapy phase because of its ease of administration, improved toxicity profile, high rates of dose delivery, and excellent published results showing high response rates and overall survival. We chose to use induction chemotherapy primarily as a means to select HPV-positive HNSCC patients, who may benefit from significant radiation dose de-intensification in the concurrent chemoradiotherapy phase of treatment. The rationale for this risk-adapted approach to local therapy based on HPV status is to administer effective comprehensive treatment individualized at diagnosis and after assessment of response to induction chemotherapy (for patients with HPV-positive tumors), thus avoiding unnecessary and potentially toxic treatment, and hence optimizing the therapeutic ratio.

2.6.1 *Selection of the treatment arm for HPV-positive HNSCC*

The induction chemotherapy regimen was chosen based on studies from ECOG and Vanderbilt University, showing high rates of response to carboplatin and paclitaxel (Hainsworth 2002; Cmelak 2007). The radiation regimen has not been rigorously tested in a multi-institutional setting. However, investigators from the University of Chicago treated 64 patients with locally advanced HNSCC (HPV-status undetermined) to a reduced dose of 54 Gy to areas considered "high-risk" for microscopic disease after induction chemotherapy and reported that the reduction in radiation dose did not compromise survival or disease control compared to historical controls treated using higher radiation doses (Haraf 2003). More recently, retrospective data from the University of California, Davis, has shown that HPV-positive tumors have regressed in entirety as determined by clinical examination and axial imaging by 50 Gy of radiation. As such, for this trial, patients with and without a response to induction chemotherapy will receive doses of 54 and 60 Gy, respectively, which represents a 23% and 14% reduction in radiation dose, respectively, compared to the standard of 70 Gy (Chen, in press). Since weekly administration of carboplatin and paclitaxel has historically been given concurrently with radiation after induction chemotherapy, we chose to administer these agents in the same fashion for this Phase I/II trial. The regimen used by ECOG 2399 will comprise the standard induction chemotherapy strategy and will serve as the basis for exploratory comparison analyses (Cmelak 2007). Since HPV has been increasingly shown to affect cellular response to radiation, this phase I/II trial tests the hypothesis that radiation dose de-intensification for HPV-positive patients with locally advanced (stage III and IV) HNSCC will decrease toxicity while maintaining progression-free survival.

2.7 Specific Aims

2.7.1 *Primary*

2.7.1.1 To determine the progression-free survival at 2 years in patients with HPV-positive HNSCC who receive induction chemotherapy followed by dose de-intensified chemoradiotherapy

2.7.2 Secondary

2.7.2.1 To determine the overall survival and local-regional control for patients with HPV-positive HNSCC who receive induction chemotherapy and dose de-intensified chemoradiotherapy

2.7.2.2 To determine the incidence of acute grade 3+ mucosal and esophageal toxicity associated with attenuated concurrent chemoradiotherapy in patients with HPV-positive HNSCC

2.7.2.3 To determine the incidence of late toxicity in patients with HPV-positive HNSCC who receive the dose de-intensified chemoradiotherapy

2.7.2.4 To estimate the incidence of all toxicity (hematologic and non-hematologic) associated with protocol treatment for all patients on trial

2.7.2.5 To estimate the response rate of HPV-positive to induction chemotherapy using carboplatin and paclitaxel

2.7.2.6 To determine the effect of reduced radiation dose on short-term and long-term quality of life among patients treated by chemoradiotherapy.

3.0 ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

3.1.1 Pathologically (histologically or cytologically) proven (from primary lesion and/or lymph nodes) diagnosis of HPV-positive squamous cell carcinoma of the oropharynx, hypopharynx, or larynx. HPV-positivity will be defined as tumors that are p16-positive by immunohistochemistry. Numerous studies have demonstrated near 100% agreement between p16 and HPV for patients with squamous cell carcinomas. As such, the use of p16 has been accepted by large cooperative groups as an appropriate surrogate for HPV status, and testing for p16 has been routinely performed for all head and neck cancers at most centers since 2009.

3.1.2 Clinical stage III or IV disease; Note: Patients with M1 tumors are not eligible.

3.1.3 Appropriate stage for protocol entry, including no distant metastases, based upon the following minimum diagnostic workup:

3.1.3.1 History/physical examination within 4 weeks prior to registration, including assessment of weight loss in past 6 months;

3.1.3.2 Chest x-ray (or Chest CT scan or PET/CT scan) within 6 weeks prior to registration; see Section 8.0 for details of PET scans.

3.1.3.3 CT scan or MRI of the head and neck (of the primary tumor and neck nodes) and PET/CT scan within 6 weeks prior to registration; see Section 8.0 for details of PET scans.

3.1.4 Zubrod Performance Status 0-1

3.1.5 Age $\geq$ 18

3.1.6 Adequate bone marrow function, defined as follows:

3.1.6.1 Absolute neutrophil count (ANC) $\geq$ 1,800 cells/mm^3 based upon CBC/differential obtained within 4 weeks prior to registration on study;

3.1.6.2 Platelets $\geq$ 100,000 cells/mm^3 based upon CBC/differential obtained within 4 weeks prior to registration on study;

3.1.6.3 Hemoglobin (Hgb) $\geq$ 8.0 g/dl based upon CBC/differential obtained within 4 weeks prior to registration on study (Note: The use of transfusion or other intervention to achieve Hgb $\geq$ 8.0 g/dl is acceptable).

3.1.7 Adequate hepatic function, defined as follows:

3.1.7.1 AST or ALT $\leq$ 2x the upper limit of normal within 4 weeks prior to registration on study;

3.1.8 Adequate renal function, defined as follows:

3.1.8.1 Serum creatinine ≤ 1.5 mg/dl or institutional upper limit of normal within 4 weeks prior to registration

3.1.8.2 Creatinine clearance (CC) ≥ 50 ml/min within 4 weeks prior to registration determined by 24-hour collection or estimated by Cockcroft-Gault formula: CrCl male = [(140 – age) x (weight in kg)] [(Serum Cr mg/dl) x (72)] CrCl female = 0.85 x (CrCl male)

3.1.9 Pregnancy test within 4 weeks prior to registration for women of childbearing potential;

3.1.10 Women of childbearing potential and male participants must agree to use a medically effective means of birth control throughout their participation in the treatment phase of the study (until at least 60 days following the last study treatment);

3.1.11 Patient must sign study specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility

3.2.1 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years;

3.2.2 Patients with simultaneous primaries or bilateral tumors are excluded.

3.2.3 Patients who present with a cervical lymph node metastasis of unknown primary origin;

3.2.4 Prior systemic chemotherapy for the study cancer; note that prior chemotherapy for a different cancer is allowable;

3.2.5 Prior radiotherapy that would result in overlap of radiation therapy fields;

3.2.6 Primary site of tumor of oral cavity, nasopharynx, nasal cavity, paranasal sinuses, or salivary glands;

3.2.7 Recurrent head and neck cancer;

3.2.8 Severe, active co-morbidity, defined as follows:

3.2.8.1 Current uncontrolled cardiac disease; i.e., uncontrolled hypertension, unstable angina, recent myocardial infarction (within prior 6 months), uncontrolled congestive heart failure, and cardiomyopathy with decreased ejection fraction;

3.2.8.2 Congestive heart failure with left Ventricular Ejection Fraction < 20%;

3.2.8.3 Transmural myocardial infarction within the last 6 months;

3.2.8.4 Acute bacterial or fungal infection requiring intravenous antibiotics at registration;

3.2.8.5 Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration;

3.2.8.6 Active lupus erythematosus or scleroderma with ongoing physical manifestations

3.2.8.7 Any uncontrolled condition, which in the opinion of the investigator, would interfere in the safe and timely completion of study procedures;

3.2.9 Pregnant or lactating women or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

3.2.10 Prior allergic reaction to the study drug(s) involved in this protocol.

4.0 ADDITIONAL PRETREATMENT EVALUATIONS/MANAGEMENT

4.1 Additional Mandatory Pre-Treatment Evaluations/Interventions

Not applicable for this study.

4.2 Additional Recommended Pre-Treatment Evaluations/Interventions

The following pre-treatment evaluations/interventions are not required but are recommended:

4.2.1 Speech and swallow evaluation within 6 weeks prior to registration;

4.2.2 Dental evaluation and, if applicable, prophylaxis within 16 weeks prior to initiation of chemoradiotherapy (see Appendix III);

4.2.3 Serum albumin within 4 weeks prior to treatment;

4.2.4 Baseline audiogram within 12 weeks prior to registration;
4.2.5 Nutritional evaluation for prophylactic gastrostomy (PEG) tube placement;
4.2.6 Nutritional counseling to discuss optimal dietary needs during treatment

5.0 DRUG THERAPY

5.1 Rationale

This study is the first of its kind to stratify HNSCC patients for treatment based on HPV status and may have important implications for individualization of care in the future. Based on the encouraging phase II data reviewed above, patients in this trial will undergo surgery or receive induction chemotherapy prior to chemoradiotherapy. The regimen of carboplatin and paclitaxel was selected for the induction chemotherapy phase because of its track record in the treatment of HNSCC and favorable toxicity profile.

5.2 Induction Chemotherapy

Two cycles of carboplatin/paclitaxel will be planned as induction chemotherapy for all patients

5.2.1 Pre-medications for paclitaxel and carboplatin
All patients should be premedicated with dexamethasone 10 mg IV, diphenhydramine 25 mg IV, cimetidine 300 mg IV (or its equivalent) and ondansetron 8 mg IV, 60 minutes prior to paclitaxel infusion.

5.2.2 Carboplatin and paclitaxel administration
Paclitaxel 175 mg/m^2 3 hour IV infusion, Carboplatin AUC = 6, 30 minute IV infusion repeated on day 22

Note: Guidelines for Carboplatin Administration
The carboplatin dose (mg) = AUC x (CrCl + 25) where AUC = 6 depending on the dose level. The creatinine clearance will be calculated using a serum creatinine obtained within 14 days prior to dosing. Carboplatin dose will be based on GFR (glomerular filtration rate) equivalent to creatinine clearance calculated according to the Cockroft-Gault Formula:

$$\text{CrCl} = \frac{(140 - \text{age}) \times \text{actual body weight (kg)}^*}{72 \times \text{serum creatinine}^{**}}$$

*Multiply this number by 0.85 if the patient is female.
**For serum creatinine of less than 1, use 1 for calculation.

5.3 Concurrent Chemoradiotherapy with Paclitaxel

5.3.1 Weekly paclitaxel infusion with radiation: At least 2 weeks after completion of induction chemotherapy, paclitaxel will be infused at a dose of 30 mg/m2 for over one hour weekly prior to the daily radiation for 5 total cycles.
5.3.2 Pre-medications: As outlined in section 5.2.1, pre-medications will be used only for patients who have never been treated with paclitaxel or patients who experienced allergic reaction due to induction chemotherapy. Subsequent pre-medications can be deleted if a patient does not experience any allergic reaction after the first weekly paclitaxel.
5.3.3 Safety monitoring: Weekly physical examination, CBC and basic chemistry panels are required.
5.3.4 Weekly paclitaxel should not be given if radiation has been held on the day of scheduled paclitaxel administration.
5.3.5 Patients who have evidence of progressive disease after 2 cycles of induction chemotherapy will be removed from the protocol and offered therapy at the discretion of the treating physician
5.3.6 Day 1 of concurrent chemoradiotherapy must be a Monday or Tuesday

5.4 Carboplatin

5.4.1 *Formulation*: (see manufacturer prescribing information)
5.4.2 *Preparation:* (see manufacturer prescribing information)
5.4.3 *Administration:*

Carboplatin will be administered after paclitaxel as an *IV* infusion over 30 minutes. The dose will be calculated based on the patient's actual body weight at each treatment visit and the AUC (area under curve) dosing. (see Section 5.2.2)
5.4.4 *Storage:* (see manufacturer prescribing information)
5.4.5 *Adverse Events:*

- Hematologic: Myelosuppression
- Gastrointestinal: Nausea and vomiting; hepatic toxicity; electrolyte imbalance; hypomagnesemia; hypercalcemia
- Neurological: Peripheral neuropathy, ocular changes
- Other: Ototoxicity, myalgia, fatigue, allergic reaction

5.4.6 *Supply:* Carboplatin is commercially available. The use of drug(s) or combination of drugs in this protocol meet the criteria described under Title 21 CFR 312.2(b) for IND exemption.

5.5 Paclitaxel (Taxol®)
5.5.1 *Formulation*: (see manufacturer prescribing information)
5.5.2 *Preparation*: (see manufacturer prescribing information)
5.5.3 *Administration*: Paclitaxel, at the appropriate dose and dilution, will be given as a one-hour infusion. The paclitaxel is mixed in non-PVC containers and infused via polyolefin-lined nitroglycerin tubing or low absorption AVI i.v. administration with 0.22 micron in-line filter. Paclitaxel will be administered via an infusion control device (pump) using non-PVC tubing and connectors, such as the i.v. administration sets (polyethylene or polyolefin) which are used to infuse parenteral nitroglycerin. Nothing else is to be infused through the line through which paclitaxel is administered.
5.5.4 *Storage*: (see manufacturer prescribing information)
5.5.5 *Adverse Effects*: See Package Insert for complete listing.

- Hematologic: Myelosuppression
- Gastrointestinal: Nausea and vomiting, diarrhea, stomatitis, mucositis, pharyngitis, typhlitis, ischemic colitis, neutropenic enterocolitis, increased liver function tests (SGOT, SGPT, bilirubin, alkaline phosphatase*)*, hepatic failure, hepatic necrosis
- Heart: Arrhythmias, heart block, ventricular tachycardia, myocardial infarction (MI), bradycardia, atrial arrhythmia, hypotension, hypertension, lightheadedness
- Neurological: Sensory (taste), peripheral neuropathy, seizures, mood swings, hepatic encephalopathy, encephalopathy, sensation of flashing lights, blurred vision, scintillating scotoma
- Allergy: Anaphylactoid and urticarial reactions (acute), flushing, rash, pruritus
- Other: Alopecia, fatigue, arthralgia, myopathy, myalgia, infiltration (erythema, induration, tenderness, rarely ulceration), radiation recall reaction

5.5.6 *Supply*: Paclitaxel is commercially available. The use of drug(s) or combination of drugs in this protocol meet the criteria described under Title 21 CFR 312.2(b) for IND exemption.

5.6 Dose Modifications for Paclitaxel/Carboplatin- Induction Chemotherapy
Note: All dose modifications will be based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

5.6.1 Hematologic (*ANC, Platelets*)

Toxicity NCI CTCAE Grade (CTCAE v4.0)	**Paclitaxel Dose At Start of Subsequent Cycle of Therapy[a]**	**Carboplatin Dose at Start of Subsequent Cycles of Therapy[b]**
Neutropenia 1 (1500-1999/mm^3)	Maintain dose level	Maintain dose level
2 (1000-1499/mm^3)	Reduce to 150 mg/m^2	Reduce to AUC 5
3 (500-999/mm^3)	Reduce to 150 mg/m^2	Reduce to AUC 5
4 (<500-999/mm^3)	Reduce to 150 mg/m^2	Reduce to AUC 5
Neutropenic fever	Reduce to 150 mg/m^2	Reduce to AUC 5
Thrombocytopenia 1 (LLN-75,000/mm^3)	Maintain dose level	Maintain dose level
2 (50,000-74,999/mm^3)	Reduce to 150 mg/m^2	Reduce to AUC 5
3 (25,000-49,999/mm^3)	Reduce to 150 mg/m^2	Reduce to AUC 5
4 (<25,000/mm^3)	Reduce to 150 mg/m^2	Reduce to AUC 5
Other Hematological toxicities	There will be no dose modifications for changes in leucopenia or lymphopenia	

[a]For induction chemotherapy, doses will be adjusted based on the worst toxicity observed during cycle 1.
[b]To receive the second cycle of chemotherapy, all patients must meet the following minimum criteria: WNC ≥ 3000/mm^3, ANC ≥ 1500/mm^3, and Platelets ≥ 100,000/ mm^3, to be drawn within 5 days of delivery of cycle 2. Otherwise, hold the second cycle, repeat lab work weekly, and resume chemotherapy based on this table once criteria are satisfied. Failure to meet minimum criteria for 3 consecutive weeks will remove the patient from the study.

5.6.2 Hepatic - Paclitaxel
The following paclitaxel dose adjustments are based on SGOT/SGPT and bilirubin levels and (after the first cycle) should be obtained within 7 days prior to delivery of second cycle.

SGOT or SGPT		Bilirubin	Paclitaxel
Grade 0 - 1	and	Grade 0 - 2	No change
Grade 2 - 4	or	Grade 3 - 4	HOLD*

*If recovery of toxicity exceeds two weeks, discontinue carboplatin and paclitaxel. If recovery of toxicity occurs within two weeks (< Grade 2), resume treatment with paclitaxel 175 mg/m^2.

5.6.3 Neuropathy: Motor/Sensory - Carboplatin and Paclitaxel
The following dose adjustments are based on the worst toxicity grade experience of neuropathy - motor/sensory of any preceding treatment cycle.

Neuropathy - motor/sensory	Carboplatin and Paclitaxel
Grade 0 - 1	No change
Grade 2 - 3	HOLD BOTH DRUGS (until resolution to ≤ Grade 1); If within 2 weeks, resume Paclitaxel at 175 mg/m2, Carboplatin AUC = 5
Grade 4	REMOVE PATIENT FROM PACLI-TAXEL AND CARBOPLATIN TREATMENT

5.6.4 Cardiac Toxicity - Carboplatin and Paclitaxel
If a patient develops chest pain or arrhythmia during the infusion, the infusion should be stopped. Manage any arrhythmias according to standard practice. Patients who experience chest pain during paclitaxel infusion should not restart paclitaxel until a cardiac ischemic event has been ruled out. Patients will be removed from paclitaxel and carboplatin treatment in cases of symptomatic arrhythmias or AV block (except first degree) or other heart block. In case of first degree AV block, patient may continue paclitaxel infusion with continuous cardiac monitoring during the infusion, at the discretion of the treating physician.

5.6.5 Hypersensitivity Reactions - Paclitaxel
Caution: Patients who have a mild to moderate hypersensitivity reaction should be rechallenged, but careful attention to prophylaxis and bedside monitoring of vital signs is recommended.

For moderate symptoms (e.g. moderate rash, flushing, mild dyspnea, chest discomfort), stop the infusion. Give intravenous diphenhydramine 25 mg and intravenous dexamethasone 10 mg. After recovery of symptoms, resume infusion at a low rate, 20 mg/hr for 15 minutes. If no further symptoms, resume at full dose rate until infusion is complete. If symptoms recur, stop infusion. The patient should receive no additional paclitaxel for that cycle, but may be retreated after discussion with the Study Coordinator.

For severe life threatening symptoms (e.g. hypotension requiring pressor therapy,angioedema, respiratory distress requiring bronchodilator therapy, generalized urticaria), stop the infusion. Give intravenous diphenhydramine and dexamethasone as above. Add epinephrine or bronchodilators if indicated. If wheezing is present that is not responsive to administration of 0.35 cc of nebulized salbutamol solution (or equivalent), epinephrine is recommended. The patient will be taken off paclitaxel treatment.

5.6.6 Myalgia/Arthralgia
Myalgia/arthralgia will be classified as mild (grade 1*)*: muscle and joint aches; moderate (grade 2): decreased function, decreased ability to perform daily tasks, but still functioning; or severe (grade 3): unable to function, confined to bed. Treatment for myalgia and arthralgias may include nonsteroidal anti-inflammatory medication (Toradol®, ibuprofen, etc.). If there is still no relief, narcotic pain medications may be used. Grade 3 toxicity, reasonably attributable to paclitaxel, will require a dose reduction of 25% following resolution to grade ≤ 1. No further dose reduction will be permitted, and no further paclitaxel will be given.

5.6.7 For all other grade 3 or 4 non-hematological toxicity, please call the study PI.

5.7 Dose Modifications for Paclitaxel - Concurrent Therapy
Lab assessments will be repeated weekly during concurrent chemoradiotherapy and dose modification will be made according to the guidelines below at each time point. Doses that are missed during weekly schedule of concurrent radiation will not be made up but will be documented.
5.7.1 Hematologic Toxicity *(table continued on next page)*

Toxicity NCI CTCAE Grade (CTCAE v4.0)	**Paclitaxel Dose At Start of Subsequent Cycle of Therapy[a]**
Neutropenia 1 (1500-1999/mm^3)	Maintain dose level
2 (1000-1499/mm^3)	Hold therapy[b]
3 (500-999/mm^3)	Hold therapy[b]

Toxicity NCI CTCAE Grade (CTCAE v4.0)	Paclitaxel Dose At Start of Subsequent Cycle of Therapy[a]
4 (<500-999/mm^3)	Hold therapy[b]
Neutropenic fever	Hold therapy[b]
Thrombocytopenia 1 (LLN-75,000/mm^3)	Maintain dose level
2 (50,000-74,999/mm^3)	Hold therapy[b]
3 (25,000-49,999/mm^3)	Hold therapy[b]
4 (<25,000/mm^3)	Hold therapy[b]
Other Hematological toxicities	There will be no dose modifications for changes in leucopenia or lymphopenia

[a]For concurrent therapy, paclitaxel doses will not be adjusted.
[b]Repeat lab work weekly and resume chemotherapy based on this table.

Radiation therapy will be held for grade 4 hematologic toxicities described in the table above.

5.7.2 Non-Hematologic Toxicity During Concurrent Therapy

Worst Toxicity NCI CTCAE Grade (CTCAE v4.0)[a,c]	Paclitaxel Dose At Start of Subsequent Cycles of Therapy[b]
Neuropathy ≤ Grade 1	Maintain dose level
Grade 2	Hold therapy until Grade ≤ 1; restart at full dose
Grade 3	Discontinue therapy
Other grade 3-4 non-hematological toxicities	Hold treatment until ≤ Grade 2

[a]For ≤ CTCAE Grade 2 non-hematologic toxicity not described above, excluding neuropathy, maintain dose level of all study.
[b]For concurrent therapy, paclitaxel doses will not be adjusted.
[c]Radiation therapy should continue to be delivered for ≤ Grade 3 non-hematologic toxicities in or outside the radiation treatment field. Radiation therapy should be held for all Grade 4 non-hematologic toxicity in or outside the treatment field and resumed only when toxicity is ≤ Grade 2.

5.7.3 If there is a decline in Zubrod performance status to ≥ 2 for greater than 2 weeks while under treatment, radiotherapy should be held with no further chemotherapy administered. Re-evaluate patient after one week for resumption of radiotherapy.

6.0 RADIATION THERAPY

Note: Radiotherapy must be delivered with intensity modulated radiation therapy (IMRT) techniques using image-guided radiation therapy (IGRT) (see 6.2 and 6.3 for technical details)

6.1 Dose Specifications (See Section 6.4 for definition of target volumes)
6.1.1 *Definitive IMRT after Induction Chemotherapy*
6.1.1.1 For patients with a complete response (CR) or partial response (PR) after induction chemotherapy, IMRT will be delivered in 27 fractions over 5.5 weeks, with treatment daily, five days per week. The primary tumor and involved nodes (PTVHD) will receive 2 Gy per fractions and subclinical disease sites (PTVED) will receive 1.6 Gy per fraction. The total doses will thus

be 54 Gy and 43 Gy, respectively. When desired, PTVINT can receive 1.8 Gy per fractions to a total dose of 49 Gy.
6.1.1.2 For patients with stable disease (SD) or progressive disease (PD) after induction chemotherapy, IMRT will be given in 30 fractions over 6 weeks, with treatment delivered daily, five days per week. The primary tumor and involved nodes (PTVHD) will receive 2 Gy per fractions and subclinical disease sites (PTVED) will receive 1.6 Gy per fraction. The total doses will thus be 60 Gy and 48 Gy, respectively. When desired, PTVINT can receive 1.8 Gy per fractions to a total dose of 54 Gy.
6.1.1.3 The low neck or supraclavicular regions must be included in the IMRT plan using an extended-field technique. Because the doses used are below commonly accepted tolerance levels for the swallowing structures, use of an isocentric matching AP or AP/PA fields, with larynx block, matched to IMRT portals just above the arytenoids, is not allowed.
6.1.2 *Dose Prescription*
Choice of treatment plan used for each patient will be based on an analysis of the volumetric dose, including dose-volume histogram (DVH) analyses of the targets and critical normal structures. An "inverse" planning with computerized optimization should be used. The prescription dose is the isodose surface that encompasses at least 95% of the planning target volume (PTV) with no more than 20% of any PTVHD receiving ≥ 110% of the prescribed dose and no more than 1% of any PTVHD and PTVED receiving ≤ 93% of the prescribed dose. No more than 1% or 1 cc of the tissue outside the PTV should receive ≥ 110% of the prescribed dose to the PTVHD. The density corrected dose distributions shall be calculated and the dose prescription is to be based on a dose distribution corrected for heterogeneities.

6.2 Technical Factors
6.2.1 Photon beams of ≥ 4 MV are required.
6.2.2 Treatment distance must be ≥ 80 cm SAD for isocentric techniques.
6.2.3 IMRT: Megavoltage equipment capable of delivering intensity modulated beams using a step- and-shoot technique with a multi-leaf collimator or using dynamically moving leaves. Additionally, a binary multi-leaf collimator or rotational methods (e.g. Tomotherapy) can be used to modulate the beam. Other techniques, e.g. physical compensators, are acceptable as long as dose specifications and constraints are satisfied.

6.3 Immobilization, Simulation, and Localization
6.3.1 *Immobilization*
Although a thermoplastic head mask may suffice for conformal radiotherapy, the use of a head and shoulder mask is recommended for better reproducibility. The use of a thermoplastic head and shoulder mask is mandatory for IMRT. The margins used for expansion of the CTVs to PTVs are discussed in Section 6.4.4.
6.3.2 *Planning CT scan*
A treatment planning CT scan is mandatory for defining target volumes (see Section 6.4). CT scan thickness should be at most 0.3 cm as is customary for IMRT. The treatment planning CT scan should be acquired with the patient in the same position and using the same immobilization device as for treatment. All tissues receiving irradiation should be included in the CT scan. It is recommended, but not required, that a simulation CT scan (with the patient immobilized in the treatment position) be obtained both prior to and after induction chemotherapy. The pre-induction immobilization apparatus can be used if it still fits and provides sufficient support. However, weight loss, alterations in neck mobility, changes in neck contours, and primary and nodal tumor responses could render pre-induction chemotherapy immobilization devices ineffective. In this instance, new immobilization devices should be created that approximate the head, chin, shoulder, and neck position of the initial devices as closely as possible. A new mask and new planning image will be required in some cases after induction chemotherapy because of changes in body weight, neck contours, and tumor volumes.
6.3.3 *Image-Guidance*
Image guidance is required for target localization and dose verification and may be achieved using any one of more of the following:
• Orthogonal kilovoltage (KV) images, e.g. ExacTrac;

• Linear-accelerator mounted kV and MV conebeam CT images;
• Linear-accelerator mounted MV CT images (e.g., Tomotherapy);
6.3.3.1 The 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 PTVHD and adjacent spinal cord; if the supraclavicular region is a part of the target volume, the ROI should extend to the C6 level;
• If the fusion software allows the user to create an irregular ROI (e.g. ExacTrac), treatment room objects seen on in-room X-rays should be excluded from the registration;
• Both manual (e.g. based on bony anatomy) and automatic (e.g. based on mutual information) types of registration can be used; the result of the fusion must be visually checked for the alignment of the bony anatomy, such as vertebral bodies and applicable 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 margin on critical structures), 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.
6.3.3.2 *Management of Radiation Dose to the Patient from IGRT*
Available peer reviewed literature estimates the patient dose within and outside of the target region when IGRT is used to correct positioning to vary considerably. This is the case when the same imaging hardware is used with x-ray technique and with different data gathering procedures. The dose variation is even greater when different imaging equipment is used. The estimated doses are in the range of 1 mGy for 2D systems such as the BrainLab's ExacTrac system or either the Varian or Elekta kV systems used for orthogonal imaging. These doses are small compared with doses from MV portal imaging and kV or MV conebeam CT. The doses from helical MVCT scanning with a tomotherapy unit are estimated to be in range from 1 to 3 cGy for head and neck studies, similar to doses reported for kV cone-beam CT on Elekta Synergy machine. The doses for MV cone beam CT were reported to be in range from 10 cGy for a pelvis study to 6 cGy for a head and neck study. Thus, the doses for 3D imaging systems are in the range from 1 to 6 cGy for head and neck imaging and can contribute from 0.5 to 3% to the daily dose of 2.0 Gy. These doses apply each day when image guidance is used, and the numbers double and triple when extra imaging is needed to adjust positioning on a particular day. The imaging dose to the patient may become significant if repeated studies are done for patients with severe set up problems (e.g. requiring frequent corrections that are larger than the margins used to account for positional uncertainty). It is recommended that patients demonstrating severe set up problems during the first week of treatment be moved to a treatment with larger margins and taken off protocol.

6.4 Treatment Planning/Target Volumes
6.4.1 CT based treatment planning is mandatory for every patient and should be performed using the CT scan obtained after the induction chemotherapy cycle. Fusion of the pre-induction chemotherapy simulation images, when obtained, with the post-induction chemotherapy simulation CT is strongly encouraged. In these cases, the gross tumor volume (GTV) can be modified when a dramatic response would place the GTV within air or outside the patient's body such that the volume should be altered to fit within the patient's post-induction chemotherapy anatomy.
6.4.2 *Gross Tumor Volume (GTV)* represents the region judged to contain gross primary tumor or involved node(s) based on clinical and endoscopic examinations, CT scan, and, when applicable, other imaging techniques. Grossly positive lymph nodes are defined as any lymph nodes > 1 cm or nodes with a necrotic center. The pre-induction chemotherapy simulation CT scan will be used to define the GTV on the post-induction chemotherapy CT images.

6.4.3 *Clinical Target Volume (CTV)* for patients treated by induction chemotherapy is defined as the GTV plus areas considered at risk for containing microscopic disease delineated by the treating physician. CTVHD represents GTV plus a margin of generally 0.5 to 1 cm and CTVED represents GTV with a margin of about 2 cm and nodal regions to receive elective irradiation. When the tumor is infiltrative (endophytic) or when the border is ill defined, it might be desirable to deliver an intermediate dose (e.g., 49-54 Gy) to a volume (CTVINT) that is slightly larger than CTVHD. The CTV margins can be narrower when GTV is in the proximity of the spinal cord, brainstem, or critical normal tissues. (The guidelines for CT based delineation of lymph node levels can be found at the RTOG web site:http://www.rtog.org/hnatlas/main.html).
6.4.4 *Planning Target Volume (PTVHD and PTVED)* represents an additional margin around the CTV to compensate for the variability of treatment set up and internal organ motion. A minimum margin of 0.5 cm around the CTV is required in all directions to define each respective PTV if IGRT is performed on a less than daily basis. A 3 mm margin can be used in all directions as long as daily IGRT is implemented and the scans reviewed by the treating physician prior to the delivery of the subsequent fraction.

6.5 Critical Structures

6.5.1 Definition of Normal Tissues/Organs at Risk (OARs)

6.5.1.1 *Spinal Cord:* The cord begins at the cranial-cervical junction (i.e., the top of the C1 vertebral body). Superior to this is brainstem and inferior to this is cord. The inferior border of the spinal cord should be below the lowest slice level that has PTV on it. The spinal cord shall be defined based on the treatment planning CT scan. In addition, however, a Planning Risk Volume (PRV) spinal cord shall be defined. The PRVcord = cord + 5 mm in each dimension.
6.5.1.2 *Brainstem:* The inferior most portion of the brainstem is at the cranial-cervical junction where it meets the spinal cord. For the purposes of this study, the superior most portion of the brainstem is approximately at the level of the top of the posterior clinoid. The brainstem shall be defined based on the treatment planning CT scan. In addition, the PRVbrainstem = brainstem + 3 mm in each dimension.
6.5.1.3 *Lips and Oral Cavity:* These should be contoured as 2 separate structures as the goal is to keep the lip dose much lower than the oral cavity dose. The definition of lips is self-explanatory. The oral cavity will be defined as a composite structure consisting of the anterior ½ to 2/3 of the oral tongue/floor of mouth, buccal mucosa, and palate. The oral cavity OAR should not overlap any PTV.
6.5.1.4 *Parotid Glands:* Parotid glands will be defined based on the treatment planning CT scan. The objective is to limit the mean dose to at least one gland to less than 24 Gy; alternatively at least 20 cc of the combined volume of both parotid glands to <20 Gy or at least 50% of one gland to <30 Gy. Both deep and superficial lobes of the parotid glands are contoured as one structure.
6.5.1.5 *Pharynx:* This will be defined as the “uninvolved” posterior pharyngeal wall plus adjacent constrictor muscles. This extends from the superior constrictor region (the inferior pterygoid plates level) to the cricopharyngeal inlet (posterior cricoid cartilage level). This should not overlap the PTVs.
6.5.1.6 *Cervical Esophagus:* This will be defined as a tubular structure that starts at the bottom of OARpharynx and extends to the thoracic inlet.
6.5.1.7 *Glottic/Supraglottic Larynx (GSL):* This will be defined as a “triangular prism shaped” volume that begins just inferior to the hyoid bone and extends to the cricoid cartilage inferiorly and extends from the anterior commissure to include the arytenoids. This includes the infrahyoid but not suprahyoid epiglottis.
6.5.1.8 *Mandible:* This includes the entire bony structure of the mandible from TMJ through the symphysis. It is recognized that in many cases, this may overlap with CTVs and PTVs.
6.5.1.9 *Brachial plexus:* Brachial plexus contouring can be delineated as outlined by Hall 2008. It comprises of linear structures of 5 mm thickness that extend from the neural foramina of C5 through T1 to the small space between the anterior and middle scalene muscles. For CT slices where no neural foramen is present, one can contour only the space between the anterior and middle scalene muscles. If one follows the space between these muscles inferiorly; one will find the cords of the brachial plexus posterior to subclavian neurovascular bundle. They are the non-

enhanced structures posterior to the enhanced subclavian vein. These cords extent laterally along the axillary vein into the axilla.
6.5.1.10 *Cochlea:* Contour for all cases.
6.5.1.11 *Brain:* Contour the brain for all cases.
6.5.1.12 *Eyes:* Contour the globes and lens for all cases.
6.5.1.13 *Optic Nerves and Chiasm:* Contour for all cases. Care should be given to contour optic nerves through the optic canal in continuity with the chiasm.
6.5.1.14 *Unspecified Tissue Outside the Targets:* This will be defined as tissue located between the skull base and thoracic inlet that is not included in either the target volumes or the normal tissues described above.
6.5.2 Dose Constraints to Normal Structures
6.5.2.1 *Spinal Cord:* The PRVcord (as defined in Section 6.5) should not exceed 45 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm). The spinal cord PRV should not exceed 48 Gy to any volume in excess of 0.01 cc. In treatment planning, the spinal cord PRV should be given the highest priority.
6.5.2.2 *Brainstem:* The PRVcord (as defined in Section 6.5) should not exceed 48 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm) unless the skull base is included in CTVHD. When the skull base is treated, the PRVbrainstem (as defined in Section 6.5) should not exceed 52 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm). In treatment planning, the PRVbrainstem should be given the same priority as the PRVcord.
6.5.2.3 *Lips:* Reduce the dose as much as possible. The mean dose should be < 20 Gy.
6.5.2.4 *Oral Cavity:* Reduce the dose as much as possible. The mean dose should be < 30 Gy if feasible. Efforts should be made to avoid hot spots (> 60 Gy) within the oral cavity.
6.5.2.5 *Parotid Glands:* The goal is keep the mean dose to at least one parotid gland to < 24 Gy. Additional planning goals may include: 1) At least 50% of one parotid will receive < 30 Gy; and/or 2) At least 20 cc of parotid tissue (from the combination of both glands) will receive < 20 Gy.
6.5.2.6 *Pharynx:* Reduce the dose as much as possible. Some recommended (but not mandatory) treatment goals include: 1) No more than 33% of the pharynx exceeds 50 Gy; 2) Mean dose < 40 Gy; 3) No more than 10% of the pharynx exceeds 60 Gy.
6.5.2.7 *Cervical Esophagus:* Reduce the dose as much as possible. Some recommended (but not mandatory) treatment goals include: 1) No more than 30% of the esophagus exceeds 45 Gy; 2) Mean dose < 35 Gy; 3) No more than 10% of the esophagus exceeds 54 Gy.
6.5.2.8 *Glottic and Supraglottic larynx (GSL):* Reduce the dose as much as possible. It is recommended that the dose to the larynx should be kept < 40 Gy whenever feasible.
6.5.2.9 *Mandible:* Reduce the dose as much as possible. It is recognized that particularly for these cancers, portions of the mandible will overlap the CTVs and/or PTVs; however, hot spots within the mandible should be avoided. It is recommended that maximum dose within the mandible be < 64 Gy whenever possible.
6.5.2.10 *Brachial plexus:* The maximum dose to the ipsilateral brachial plexus should be kept < 60 Gy if there are no involved low neck nodes. If the low neck is involved, the maximum brachial plexus dose should be kept < 66 Gy.
6.5.2.11 *Cochlea*: It is recommended to keep the ipsilateral cochlea maximum dose < 50 Gy. It is recognized that this will not be possible when it is required to include the temporal bone in the clinical target volume.
6.5.2.12 *Brain:* It is recommended that the brain maximum dose should not exceed 60 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm) when the skull base is not included in the clinical target volume. It is recommended that the brain maximal dose should not exceed 66 Gy for all cases.
6.5.2.13 *Eyes:* The maximum dose should not exceed 30 Gy. Particular attention should be given to keep the lens maximum dose < 25 Gy.
6.5.2.14 *Optic Nerves:* The maximum dose should not exceed 54 Gy.
6.5.2.15 *Optic Chiasm:* The maximum dose should not exceed 50 Gy.
6.5.2.16 *Unspecified Tissue Outside the Targets:* <100% of the dose prescribed to the CTVHD. No more than 1% of the non-target tissue can receive greater than the dose to CTVHD.

6.5.3 Prioritization for IMRT Planning

1. Spinal cord and brainstem
2. PTVHD
3. PTVED
4. PTVID (if applicable)
5. Chiasm
6. Optic nerve
7. Brain
8. Eyes
9. Parotid gland contralateral to primary tumor site
10. Pharynx
11. GSL
12. Esophagus
13. Lips
14. Oral cavity
15. Parotid gland ipsilateral to primary tumor site
16. Mandible
17. Lens
18. Unspecified tissue outside the targets

6.6 Documentation Requirements

6.6.1 Orthogonal images that localize the isocenter are recommended on the first day of therapy.
6.6.2 A minimum of weekly volumetric IGRT is required
6.6.3 Daily IGRT imaging is strongly recommended.
6.6.4 Isodose plans and DVHs of GTV, CTVs, and critical normal structures.

6.7 Compliance Criteria

Treatment breaks must be clearly indicated in the treatment record along with the reason(s) for the treatment break(s). **Missed treatments due to holidays or logistic reasons can be compensated for by delivering additional BID treatments with a minimum inter-fraction interval of 6 hours or by treating on a Saturday or Sunday.**

Treatment breaks should be allowed only for resolution of severe acute toxicity and/or for inter-current illness and ideally, should not exceed 5 treatment days at a time and 10 treatment days in total. Any treatment break*(s)* exceeding two treatment days for reasons other than toxicity/illness will be considered a protocol deviation.

6.8 Radiation Therapy Quality Assurance Reviews

The Principal Investigator, Allen M. Chen, M.D. and the Medical Physics Co-Chair, James Purdy, Ph.D., will remotely perform RT Quality Assurance Review for the first 10 cases enrolled.

7.0 ADVERSE EVENT REPORTING

Adverse event reporting is a fundamental component of every clinical trial.

7.1 Adverse Event Monitoring

Subjects must be carefully monitored for adverse events. This monitoring includes clinical and laboratory tests. The study will utilize the NCI CTCAE 4.0 Common Terminology Criteria (CTC) for Adverse Events for toxicity and Adverse Event Reporting. A copy of the CTCAE version 4.0 can also be downloaded from the CTEP home page (http://ctep.cancer.gov/reporting/ctc.html). Adverse events will be assessed each cycle, and the highest grade according to NCI-CTCAE Version 4.0 will be recorded. Adverse events should be assessed in terms of seriousness, severity, and relationship to the study treatment.

7.2 Adverse Event Definitions

7.2.1 Adverse Events (AEs)

Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

7.2.2 Serious Adverse Events (SAEs)

Definition of an SAE: Any adverse experience occurring during any part of protocol treatment and 30 days after that results in any of the following outcomes:

- Results in death.
- Is life-threatening (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of an existing hospitalization
- Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is a medically important event. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent one of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent.

7.2.3 Intensity (Severity) of the Adverse Event

The intensity or severity of adverse events should be graded according to the NCI-CTCAE version 4.0 criteria.

7.2.4 Adverse Event Documentation

All adverse events occurring after the subject has received the first dose of investigational treatment must be fully recorded in the subject's case record form. Documentation must be supported by an entry in the subject's file. Each event should be described in detail along with start and stop dates, severity, relationship to study treatment, action taken and outcome.

7.3 Study Treatment Adverse Events

Grade 3-4 therapy-induced mucositis and/or dysphagia, which are enhanced by palcitaxel, are expected to develop in about one-half of patients. Nutritional evaluation prior to the initiation of therapy for a prophylactic gastrostomy (PEG) tube placement is highly recommended. Placement of a feeding tube should be recorded, as should use of a feeding tube during and after treatment (e.g., greater than or less than 50% of nutrition by tube). Other common radiation adverse events include: fatigue, weight loss, regional alopecia, xerostomia, hoarseness, transient ear discomfort, dysgeusia, and skin erythema and desquamation within the treatment fields. A proportion of patients may require intravenous fluid support secondary to dehydration, and this should be documented.

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), and cervical myelopathy (< 1% with restriction of spinal cord dose to ≤ 45 Gy).

Adverse events (AEs) may be spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures must be reported to Principal Investigator (or designee).

Reporting Forms:

- SAE Report Form
- Reporting to the FDA: US FDA MedWatch 3500A http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm

Each serious adverse event must be followed up until resolution or stabilization, by submission of updated reports to the principal investigator Dr. Allen Chen.

Reporting to the Institutional Review Board
Both serious and non-serious adverse events will be reported in accordance with UCD IRB Administration and UCD Cancer Center Clinical Trial Support Unit (CTSU) policies. The UC Davis IRB can be reached at (916) 703-9151.

7.4 Procedures for Reporting Drug Exposure during Pregnancy and Birth Events
If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and must permanently discontinue study treatment. All pregnancies and suspected pregnancies must be reported to Principal Investigator (or designee) immediately. The pregnancy must be followed for the final pregnancy outcome (ie, delivery, still birth, miscarriage).

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, this must be reported to Principal Investigator (or designee) immediately. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

8.0 FUNCTIONAL IMAGING: FDG-PET/CT IMAGING

A pre-treatment PET/CT scan is required for all patients on study and should be obtained prior to any treatment. A post-treatment FDG-PET/CT scan is also required 8-12 weeks after completion of treatment to assess for the possibility of residual disease. **Note**: If the CT portion of a PET/CT is done with contrast and a radiologist formally reviews and reports the findings on head and neck and thoracic regions, then there is no need to order additional diagnostic CT/MRI of the head and neck or chest x-rays or CT scan of the chest.

8.1 PET Image and Scanner Compatibility Requirements

All imaging must be conducted on a combined PET/CT scanner with full ring PET and four slice or greater multi-detector CT. The scanner should be operating in high-sensitivity 2D mode, if available. 3D mode is permissible for patients imaged on combined PET/CT scanners without a 2D mode.

8.2 Pre-FDG Injection: Patient Preparation

Height and weight will be recorded before each PET scan. Patients will observe a four to six-hour fasting period prior to FDG injection. Patients with a history of medically controlled diabetes will be counseled to check serial blood sugars prior to each scan to ensure that values average below 200 mg/dL. For these patients, a blood sugar measurement will be performed after a six-hour fast to gauge fasting tolerance. Serum glucose concentration will be measured for all patients prior to scanning and must be less than 200 mg/dL to proceed to imaging.

8.3 FDG Injection

A dose of 10-20 mCi of 18FDG will be infused intravenously. As per best clinical practice, administration of 0.5 mg of alprazolam 5-15 minutes prior to FDG injection to relax the patient and to reduce neck 18FDG muscle uptake should be considered. The patient will lie quietly for at least 30 minutes, and scanning will begin 50-70 minutes following the FDG injection.

8.4 PET Imaging

Imaging must encompass the vertex of the head down through the entire pelvis. The recommended imaging protocol incorporates two discrete phases, and is as follows: During the first phase, head and neck scanning will be performed with full neck extension. The patient will initially be imaged with a 120 KeV/300 mA, 0.5-second detector rotation time ("high mA") CT scan with intravenous contrast (100 cc contrast bolus administered at 1.5 cc/second, with a 50 second scan delay and with the scan started inferiorly, moving cranially), followed by a 120 KeV/80 mA, 0.8-second detector rotation time ("low mA") CT scan for PET attenuation correction, followed

lastly by PET scanning. Alternatively, an initial low mA CT scan may be performed for attenuation correction, followed by a high mA CT scan with intravenous contrast. Standard manufacturer recommendations for specific low and high mA CT scanning parameters can be substituted for those listed above. Two fields of view (approximately 15 cm) will be used for head and neck PET imaging. Patients then will be allowed to rest their necks for 1-2 minutes. For the second phase of imaging, the neck will be shifted into neutral position, and the remainder of the body will be surveyed per routine local institutional protocol with arms raised above the head to allow for optimal thoracic and upper abdominal imaging. At least four to five PET fields of view will be used for this phase. Images will be reconstructed via the filtering algorithm provided by the scanner manufacturer.

8.5 Assessment at 8-12 Weeks Post-Treatment

A post-treatment FDG-PET/CT scan is required 8-12 weeks after completion of treatment for all patients. The post-treatment PET/CT scan should be done on the same scanner, as specified above. It is anticipated that most patients with stage N2-3 disease at presentation and all with residual adenopathy will undergo neck dissection. Surgery should take place within 4 weeks of post-treatment FDG-PET/CT imaging. Bilateral neck dissection, if necessary, can take place in two stages. See Section 8.1 for details of surgery.

8.6 Maximum Standardized Uptake Value (SUVmax)

SUV normalized by specific injected dose and patient weight will be calculated using vendor-provided software. Maximum standardized uptake value (SUVmax) will be defined as (tissue activity) (μ Ci/ml)/(injected dose (mCi)/(patient weight [kg]) within the voxel having the highest activity within a given region of interest (ROI). This will be determined for ROIs within the primary tumor and within the involved cervical node with highest FDG uptake. It is strongly recommended that an experienced head and neck radiologist assist with delineation of tumor volumes. Detection of primary and nodal disease by FDG-PET/CT will not be classified according to an FDG SUV threshold. Instead, malignancy will be qualitatively determined by FDG uptake greater than surrounding normal soft tissue within a CT-delineated anatomic (primary disease or nodal) abnormality. FDG-PET ROIs delineation will be generated on the PET/CT scanner workstation. Each ROI must encompass the entire FDG-avid lesion of interest, with boundaries guided by CT delineation. Maximum standardized uptake values (SUVmax) for primary tumor and nodal disease will be recorded for these manually generated ROIs.

8.7 Functional Imaging Adverse Events

There is a negligible risk of exposure to radiation from PET imaging. Less likely adverse events include potential bruising or bleeding and/or infection at the site of the injection of the tracer. Serious allergic reactions to the tracer are rare.

9.0 SURGICAL THERAPY

9.1 Salvage Neck Dissection after Chemoradiotherapy

It is required that all patients be assessed 8-12 weeks post-treatment with CT scan or MRI. A post-treatment PET/CT scan is also required (see Section 8.5). **Note**: If the CT portion of a PET/CT is done with contrast and a radiologist formally reviews and reports the findings on head and neck and thoracic regions, then there is no need to order additional diagnostic CT/MRI of the head and neck or chest x-rays or CT scan of the chest.

If the primary site is cleared of residual disease yet residual disease at the cervical nodal basin is suggested by imaging/clinical evaluation, then selective neck dissection will be performed unless a cytologic sampling 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) in order to permit resolution of HPV-associated lymphadenopathy, which is commonly cystic and has 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 will be determined by the treating surgeon. The status of the primary tumor should be assessed thoroughly at the beginning of the surgical procedure before undertaking nodal dissection. Presence of persistent disease at the primary site, confirmed by frozen section, will be considered a failure of protocol treatment. In the case of negative PET in patients who did not achieve clinical or CT/MRI-based radiological nodal CR, follow-up PET scans are recommended every 3-4 months for 24 months, then every 6 months for years 3-5, as well as careful recording of the clinical dimensions of the residual abnormality.

For Patients Undergoing a Neck Dissection
Cervical lymphadenectomy will encompass the original levels of lymph node involvement, which should be removed *en bloc*. Preservation of the accessory nerve, jugular vein, and sternomastoid muscle is encouraged if consistent with complete removal of all residual nodal disease; however, the extent of the neck dissection will be at the discretion of the surgeon. A selective neck dissection should be performed when feasible. At no time will synchronous bilateral radical neck dissections be performed. If bilateral radical neck dissections are necessary the neck procedure must be staged at an interval of 6 weeks between lymphadenectomies.

The neck dissection specimens must be divided and oriented into discrete anatomic levels in the operating room by the supervising surgeon, and submitted for pathologic review in separate containers. Discrete groups of nodes that are matted or spaced too closely to be resolved as separate nodes under the microscope or by FDG-PET/CT (< 0.5 cm intervening distance) will be categorized as “nodal clusters.” These clusters will be considered equivalent to solitary nodes to allow for simpler and more accurate categorization of all sampled tissue. An attending pathologist should oversee evaluation of all neck dissection specimens.

9.2 Surgical Removal (Salvage) of the Primary Tumor
Directed biopsies at the site of the index lesions will not be performed in the absence of suspicion for relapse. Criteria for biopsy after chemoradiation include a persistent mucosal abnormality or imaging studies that are suspicious for persistent or recurrent disease at 8-9 weeks after completion of therapy. Options for salvage therapy will depend upon the clinical situation and are at the discretion of the treating physicians. Surgical removal (salvage resection) of the primary tumor will be performed, if possible, when biopsy-proven cancer remains more than three months after completion of therapy. The nature of the surgical resection will be dictated by the extent of tumor at the initial evaluation. The operation will be conducted using accepted criteria for primary surgical treatment of the cancer.

Tissues for pathologic evaluation of margins should be taken from the patient (rather than the surgical specimen itself). However, the specimen itself should be marked at sites corresponding to the evaluated margins in order to assess sampling error in obtaining clear margins. If gross tumor remains or when no effort to remove tumor has been made, the patient will be considered to have "gross residual disease." In the absence of residual disease, if the cancer extends to within 5 mm of a surgical margin, the patient would be considered to have "close" margins.

Questions about salvage surgery should be directed to the Co-Principal Investigator, Dr. Gregory Farwell.

10.0 OTHER THERAPY

10.1 Permitted Supportive Therapy
All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site’s source documents as concomitant medication. The use of amifostine and pilocarpine is not allowed in light of the overlapping adverse event profile with paclitaxel and possible impact on the endpoints.

11.0 TISSUE/BLOOD/SPECIMEN SUBMISSION

NOTE: Patients must be offered the opportunity to participate in the correlative components of the study, such as tissue/blood/specimen submission.

11.1 Specimen Collection for Tissue Banking and Translational Research (Highly Recommended)

The overall objective of collecting specimens for translational research is to prospectively establish a repository of both risk factor profiles and biospecimens from patients to facilitate future hypothesis generated research. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions. Please contact the translational research co-principal investigator, Dr. Andrew Vaughan for additional questions.

11.1.1 *Tumor Tissue*

Tissue for banking will be taken from the tumor tissue block for central review. The Radiation Oncology laboratories at the University of California Davis will acquire and maintains high quality specimens from this trial. Paraffin-embedded tissue blocks are preserved through careful block storage and processing per standard institutional protocols. These tissue specimens will be used by investigators for future translational research studies.

11.1.2 *Serum, Plasma, and Whole Blood Collection*

Plasma, serum and whole blood will be collected pre-treatment as well as various periods during treatment (see 12.0). In addition, plasma and serum will be collected at the 3- and 6-month follow-up visits. If a site misses the pre-treatment collection time point, they may collect the whole blood specimen at any time during treatment or after follow-up. Recent data has suggested that plasma HPV DNA is released from HPV-positive tumors, and that circulating HPV DNA may be detectable and ultimately used to identify patients at high risk for progression (Cao 2012).

Two blood specimens will be collected from each patient prior to initiating protocol treatment (2 x 10 ml, 1 purple top tube, 1 red top tube). Subsequent blood specimens (1 x 10 ml, purple top tube) should be collected weekly during radiation therapy and 3- and 6- months.

Prior to therapy, and weekly during radiation, one blood specimen should be collected in a 10 ml purple-top (EDTA) tube, inverted several times, and placed on wet ice until centrifugation. The tube should be centrifuged as soon as possible at approximately 1,000-1,500 rpm for 10 minutes. Plasma should be removed and placed in 1 ml aliquots in labeled cryotubes. Buffy coat cells should be separately removed and placed in labeled cryotubes. **All specimens must be labeled with protocol number, patient registration number, and date of specimen collection.** All tubes are then to be frozen (snap frozen with liquid nitrogen if possible) and stored at -70°C.

Prior to initiating protocol therapy, a second blood specimen should be collected in a 10 ml red-top tube, allowed to clot at room temperature for 30 minutes, and placed on wet ice until centrifugation. The tube should be centrifuged at 3000 rpm for 10 minutes. Serum should be removed and placed in 1 ml aliquots in labeled cryotubes. **All specimens must be labeled with protocol number, patient registration number, and date of specimen collection.** All tubes are then to be frozen (snap frozen with liquid nitrogen if possible) and stored at -70°C.

11.2 Confidentiality/Storage

11.2.1 Upon receipt, the specimen is labeled with the protocol number, the patient's registration number, and date of specimen collection. Encoded databases will only include the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were collected. No clinical information is kept in the database.

11.2.2 Specimens for tissue banking will be stored for an indefinite period of time. Specimens for central review will be retained until the study is terminated. Specimens for the translational research component of this protocol will be retained until the study is terminated, unless the

patient has consented to storage for future studies. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

Shipping Instructions: All archival paraffin block or slide specimens should be sent at ambient temperature. Frozen specimens should be shipped on dry ice. These should be shipped by overnight courier Monday through Wednesday only, to the following address:

Andrew Vaughan, Ph.D.
Department of Radiation Oncology
UC Davis Comprehensive Cancer Center
4501 X Street, Sacramento, CA 95817
Office Phone: 916-734-8726
Laboratory Phone: 916-213-1810
Fax: 916-703-5069

The Federal Guidelines for Shipment are as follows (these periodically change, please check for the most current guidelines):
1. The specimen must be wrapped in an absorbable material
2. The specimen must then be placed in an AIRTIGHT container (resealable bag)
3. Pack the resealable bag and specimen in a styrofoam shipping container
4. Pack the styrofoam shipping container in a cardboard box
5. The cardboard box should be labeled “UN3373 Biological Substance, Category B” “BIOHAZARD”

12.0 PATIENT ASSESSMENTS

12.1.1 Study Parameters- Patients treated by Induction Chemotherapy followed by Concurrent Chemoradiotherapy

Assessments		During Treatment		Follow Up		
	Pre-study entry	After each cycle ICT	Weekly during CRT	4 wks after CRT	8 wks after CRT	12 weeks after CRT
Evaluations						
History/physical	X	X	X	X	X	X
Zubrod, weight	X	X	X	X	X	X
Protocol-specific AE evaluation	X	X	X	X	X	X
Dental evaluation	Y					
Audiogram	Y					
Nutrition evaluation	Y					
Imaging						
Chest x-ray or chest CT	X					
CT/MRI of primary site	X					X
PET/CT	X				P	
Labs						
CBC, Diff, platelets	X	X	X	X		
Mg, Ca, Na, K, Phos	X	X	X	X		
Creatinine, BUN	X	X	X	X		
LFTs	X					
Serum albumin	Y					
Pregnancy test	Z					
QOL assessments						
FACT-H&N	X			X		X
UW-Qol	X			X		X
Tissue/Blood, for research if patient consents	X		X			X

X) Required
Y) Not required, but highly recommended
Z) For women of childbearing potential, within 4 weeks prior to registration
P) Required; Can be obtained 8-12 weeks after completion of chemoradiotherapy

After 12 weeks from the completion of protocol treatment, all patients will return for follow-up at 6, 9 and 12 months. For year 2, all patients will be seen every 3 months then every 6 months for years 3-5. Additional imaging after 12 weeks will be optional and may be performed at the discretion of the treating physician.

12.2 Evaluation during and post-treatment

12.2.1 *Protocol-Specific Adverse Event Evaluation*
In an effort to improve the capture and consistency of adverse event (AE) reporting, essential adverse events commonly associated with head and neck treatment are to be assessed at baseline, during treatment, and at follow up using **CTCAE version 4.0**. Additional AE terms and grading criteria can be accessed online at http://ctep.cancer.gov/reporting/ctc.html

12.3. Criteria for Evaluation and Endpoint Definitions

12.3.1 *Measurable Disease*: Unidimensionally measurable, with clearly defined margins on photograph, x-ray or scan. At least one diameter must be > 1 cm. Bone lesions are not included.

12.3.2 *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. At baseline and in follow-up, only the short axis will be measured and followed..
12.3.3 *Objective Status to be Recorded at Each Evaluation***:** When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total representative of all involved organs should be identified as *target lesions* and will be recorded and measured at basline. 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.
12.3.3.1 *Complete Response (CR):* Complete disappearance of all measurable disease and target lesions In the absence of any new lesions.
12.3.3.2 *Partial Response (PR***):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
12.3.3.3 *Stable Disease***:** Neither sufficient shrinkage to quality for PR nor sufficient increase to quality for progression, taking as reference the smallest sum diameters while on study.
12.3.3.4 *Progression:* At least a 20% increase in the sum of 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 lesion is also considered progression).
12.3.5 *Determination of Response after Induction Chemotherapy*
Evaluation of response to induction chemotherapy will be performed via physical examination (including direct endoscopic evaluation). Repeat biopsies are not recommended. Palpation of the neck to determine response of lymphadenopathy is also required. In cases where the treating physician is uncertain whether clinical complete response has occurred, a CT scan may be used, but this not required. A patient will be considered to have complete response to induction chemotherapy if there is no visible or palpable tumor.
12.3.5 *Tumor Clearance after Completion of Protocol Treatment*
A patient will be considered to have complete response if there is no measurable or palpable tumor either on clinical or radiographic (CT scan or MRI) examination. The PET portion of a PET/CT scan is investigational and therefore should not be used in determining a patient's response to treatment for purposes of evaluating efficacy endpoints, such as progression-free survival. If the CT portion of a PET/CT is done with contrast and a radiologist formally reviews and reports the findings on head and neck and thoracic regions, then there is no need to order additional diagnostic CT/MRI of the head and neck or chest x-rays or CT scan of the chest. The primary tumor and regional nodes will be evaluated and reported separately.
12.3.6 *Local or Regional Relapse*
Relapse is defined as reappearance of tumor after complete response. Relapse should be confirmed by biopsy.
12.3.7 *Local or Regional Progression*
Progression is defined as an estimated increase in the size of the tumor (product of the perpendicular diameters of the two largest dimensions) of greater than 20%, taking as reference the smallest value of all previous measurements or appearance of new areas of malignant disease. In addition to the relative increase of 20, the sum must also demonstrate an absolute increase of at least 5 mm.
12.3.8 *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.
12.3.9 *Progression-free Survival*
This endpoint will be defined from date of registration to date of first documentation of progression and/or distant metastasis, or death due to any cause. Patients last known to be alive without report of progression will be censored at date of last contact.

12.3.10 *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.

12.3.11 *Discontinuation of Protocol Treatment*
Protocol treatment may be discontinued for any of the following reasons:

- Progression of disease;
- Unacceptable adverse events [at the discretion of the treating physician(s)];
- Patient refusal.

If protocol treatment is discontinued, follow up and data collection will continue as specified.
12.3.12 *Discontinuation of Follow-Up Assessments*
Follow-up assessments may be discontinued for either of the following reasons:

- Patient refusal;
- Patient's withdrawal of consent; Data for these patients will not be used for analysis.

Otherwise, patients will be followed at least every 3 months during the first year after completion of protocol treatment; at least every 6 months during the second and third year after completion of protocol treatment; and yearly thereafter

12.4 Quality of Life Assessments
12.4.1 *Functional Assessment of Cancer Therapy-Head & Neck (FACT-H&N)* is a multidimensional, QOL instrument specifically designed and valid for use with HNSCC patients that the patient can complete in 5-10 minutes. The site research nurse or clinical research associate (CRA) is encouraged to be sensitive to each patient's demeanor. If patients appear particularly uncomfortable answering a question, they will be informed that they can skip that question. Similarly, interviewers will give patients a short break if the patient appears fatigued or otherwise in need of a few minutes break.
12.4.2 *The UWQol (UWQol) instrument* is a questionnaire that the patient can complete in approximately 5 minutes. self-administered scale consisting of 15 questions assessing nine domains including pain, physical appearance, activity, recreation, employment, chewing, swallowing, speech, shoulder function, and overall QOL. The site research nurse or CRA should encourage the patient not to skip questions on the UWQol or take breaks during the completion of this questionnaire, as this will invalidate assessment.

13.0 STATISTICAL CONSIDERATIONS

This is a one-arm phase II trial designed to assess treatment efficacy in terms of 2-year progression free survival. A two-stage Simon design (Simon, 1989) was adopted, which will permit early stopping of the trial if there is strong evidence that the study regimen is inactive or is effective enough to warrant further investigation in a phase III trial.

13.1 Primary Endpoint
The primary endpoint of the study is 2-year progression-free survival, and failure is defined as disease progression or death. The primary objective of the study is to determine the treatment efficacy evaluated using the 2-year progression-free survival rate. The 2-year progression-free survival rate is the proportion of efficacy-evaluable patients progression-free 2 years from registration. This will be defined based on the total number of efficacy-evaluable patients on study without documentation of disease progression from registration divided by the total number of efficacy-evaluable patients enrolled. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for 2-year progression-free survival.

13.2 Patient Accrual and Study Duration
We plan to enroll 50 patients into the study. Based on accrual history in this disease, we anticipate accruing approximately 20 eligible patients per year (about 2 patients per month). We will follow up all patients closely and do not expect any patients to drop out of the trial except for death, so censoring due to other reasons would be unlikely. We expect to complete the accrual in 2.5 years and will follow up the last enrolled patient for additional 2 years to allow all patients to become evaluable for the primary endpoint. We expect to carry out the interim analysis approximately at 3 years when the initial stage of accrual is met and these patients become

evaluable for the primary endpoint. Since the proposed dose de-intensified regimen is expected to have relatively low toxicity, we will not stop enrolling patients during this period unless high incidence of adverse events occurs. The final analysis will start toward the end of year 5.

13.3 Primary Objective and Study Design

13.3.1 Study Design

The primary objective of the study is to determine the treatment efficacy evaluated using the 2-year progression-free survival rate and to decide whether induction chemotherapy followed by dose de-intensified chemoradiotherapy is worth further investigation in a phase III trial. A two-stage Simon design (Simon 1989) was adopted to study the 2-year progression-free survival rate in patients with HPV-positive HNSCC who receive this regimen. We will consider a 2-year progression-free survival rate of 72% or lower as ineffective for the proposed dose de-intensified therapy in this population, and a 2-year progression-free survival rate of 86% or higher would warrant further subsequent studies. The following two-stage Simon design (Simon 1989) was employed using 50 patients to test the null hypothesis that the true 2-year progression-free survival rate is at most 72%.

Stage 1: Consider the first 25 enrolled patients in the study. If 19 or fewer of the first 25 evaluable patients enrolled are progression-free at 2 years, then the study will be terminated and the regimen would be considered inactive in this patient population. If 22 or more of the first 25 evaluable patients enrolled are progression-free at 2 years, then the trial will be stopped and accept the alternative hypothesis that the true 2-year progression-free survival rate is 86% or higher. Otherwise, the trial would continue to the second stage.

Stage 2: Consider the additional 25 patients in the study. If 40 or fewer of the first 50 evaluable patients enrolled are progression-free at 2 years, then we accept that the dose de-intensified therapy is ineffective in this population and not worth further investigation. If 41 or more patients are progression-free at 2 years, then we will further study the regimen in a phase III trial.

13.3.2 Power Consideration

With 50 patients, given the true 2-year progression-free survival rate is 72%, the probability of ending the trial during stage 1 is 79.3%; given the true 2-year progression-free survival rate is 86%, the probability of ending the trial in Stage 1 is 66%. The overall significance level is about 9% and the power is 81%. Assuming the significance level is at most 10%, if the true 2-year progression-free survival rates are78%, 81%, 85% and 87%, the probabilities of declaring that this regimen warrants further studies (i.e. statistical power) are 32%, 52%, 78%, 0.61, and 0.89, respectively.

13.3.3 Other Considerations

Adverse events, duration of response, overall survival, and the pace of accrual as well as other scientific discoveries or changes in standard of care will be taken into account in any decision to terminate this study earlier than designed.

13.4 Analysis Plan

13.4.1 Primary Endpoint

All patients meeting the eligibility criteria who have signed a consent form and begun treatment will be considered evaluable for estimation of the 2-year progression-free survival rate. Those who die within 2 years will be considered to have had disease progression unless documented evidence clearly indicates no progression has occurred. In the event that such evidence is obtained, or in the case of major treatment violation, the patients' response data will be considered censored at the date the patient is withdrawn from treatment. However, based on our previous experience, we expect such cases are unlikely and we will be able to evaluate all patients for their 2-year progression-free survival. The true 2-year progression-free survival rate will be estimated by the proportion of efficacy-evaluable patients on study without documentation

of disease progression or death 2 years from registration. A 95% confidence interval (CI) for the true progression-free survival rate will be constructed using the Duffy-Santner approach (Duffy 1987). However, Kaplan-Meier methodology (Kaplan 1958) will be used to estimate the final 2-year progression-free survival rate and its 95% CI in case there are censored patients.

13.4.2 Secondary Endpoints

- Overall survival
- Local-regional control
- Mucosal and esophageal toxicity (Rates of ≥ grade 3, clinical exam)
- Other toxicity (Rates of ≥ grade 3)
- Protocol treatment delivery
- Death during or within 30 days of discontinuation of protocol treatment
- Quality of life as assessed by FACT-H&N and UWQol

Overall survival will be defined as the time from registration to death. Time to event distributions will be estimated using the Kaplan-Meier method (Kaplan 1958). The 2-year rates of local-regional control will be calculated along with 95% CI for HPV-positive patients receiving the dose de-intensified therapy. We will also compare it with the rate from historical controls (93%, Rischin 2010) using a one-sided Z-test. Rates and 95% CIs of grade 3+ mucosal and esophageal toxicity, late toxicity, other toxicities, protocol treatment delivery (PTD) and death during or within 30 days of discontinuation of protocol treatment will be calculated for the patients receiving the dose de-intensified therapy. Measures of quality of life as assessed by FACT-H&N and UWQol will be obtained. Continuous variables will be summarized using the mean (s.d.) or median (range). Frequency tables will be used to summarize categorical variables. The distribution of time-to-event endpoints will be estimated using the method of Kaplan and Meier (Kaplan 1958).

We will also obtain descriptive statistics for quality of life measurements, using mean and standard deviation for continuous measures and frequency tables for categorical measures.

13.4.3 Over Accrual

If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process; however, they will be included in final point estimates and confidence intervals as they were accrued in the final stage.

13.4.4 Monitoring

The principal investigator and the study statistician will review the study periodically (at least semi-annually) to identify accrual, adverse events, and any endpoint problems that might be developing. This study will also be monitored by the UC Davis Data and Safety Monitoring Board (DSMB) at least annually, or more frequently as warranted.

This protocol is also subject to the UC Davis Cancer Center's (UCDCC) Data and Safety Monitoring Plan. The UCDCC is committed to pursuing high-quality patient-oriented clinical research and has established mechanisms to ensure both scientific rigor and patient safety in the conduct of clinical research studies. The UCDCC relies on a multi-tiered committee system that reviews and monitors all cancer clinical trials and ensures the safety of its participants, in compliance with institutional and federal requirements on adverse event (AE) reporting, verification of data accuracy, and adherence to protocol eligibility requirements, treatment guidelines, and related matters. The Scientific Review Committee (SRC) assumes overall oversight of cancer studies, with assistance and input from two independent, but interacting, committees: the Quality Assurance Committee and the Data and Safety Monitoring Committee. A multi-level review system strengthens the ability of the UCDCC to fulfill its mission in conducting high quality clinical cancer research.

As per University of California Davis Cancer Center (UCDCC) Clinical Trials Support Unit (CTSU) SOP AM 506: Protocol Specific Meetings, the principal investigator (PI), clinical research coordinator, and the clinical research nurse meet at least monthly for ongoing study information,

to discuss patient data and adverse events and to determine if dose escalation is warranted, when applicable.

According to the UCDCC Data and Safety Monitoring Plan, any new serious adverse events related to the drugs being used on this trial are reviewed monthly by the UCDCC Data and Safety Monitoring Committee and any applicable changes to the study are recommended to the PI, if necessary.

The UCDCC SRC determines if a UCDCC Data and Safety Monitoring Board (DSMB) is required. If required, the Data and Safety Monitoring Committee will appoint a DSMB. The DSMB is responsible for reviewing study accrual logs, adverse event information and dose escalation meeting minutes (where applicable) to ensure subject safety and compliance with protocol defined guidelines.

13.4.5 Adverse Events Stopping Rule

If 20 or more of the first 25 patients (80% of all patients after 25 are accrued) experience grade 3+ toxicity for esophageal toxicity or mucosal toxicity that are probably, possibly, or definitely related to study treatment, accrual to the study will be suspended to allow for investigation. After consideration by the study team and the primary data safety monitoring board, a decision will be made as to whether accrual can be resumed. In addition, all adverse event patterns will be monitored by an independent UC Davis DSMB on a limited review basis.

14.0 Data Review and Management

14.1 Patient Registration

Once signed, informed consent has been obtained and all pretreatment evaluations have been performed, patients will be entered on study according to UCD Clinical Trials Support Unit (CTSU) policy. To register a patient, the research nurse or data manager must complete the Eligibility Checklist and the Patient Registration Form. A patient accession number will then be assigned. Study therapy may not be initiated until the patient is registered. In accordance with UCD CTSU policy an original signed and dated participant Informed Consent document will reside in a secured location within the UCD Radiation Oncology Department. Copies of the signed and dated Informed Consent document will be provided to the study participant and UCD Health System Information Management for inclusion in the participant's UCD Health System Medical Record.

14.2 Data Collection

All data will be collected using the UCD Database System (eVELOS) forms. All data forms will be completed, submitted and processed in accordance with UCD CTSU policies. See Appendix VI.

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APPENDIX I

ZUBROD PERFORMANCE SCALE

0 Fully active, able to carry on all pre-disease activities without restriction (Karnofsky 90-100).

1 Restricted in physically strenuous activity but ambulatory and able to carry 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 self-care. Totally confined to bed or (Karnofsky 10-20).

5 Death (Karnofsky 0).

APPENDIX II
AJCC STAGING SYSTEM, 6th Edition
HEAD & NECK

STAGING-PRIMARY TUMOR (T)
TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
Tis: Carcinoma in situ

PHARYNX
Oropharynx
T1: Tumor 2 cm or less in greatest dimension
T2: Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3: Tumor more than 4 cm in greatest dimension
T4a: Tumor invades the larynx, deep/extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible.
T4b: Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery.

Hypopharynx
T1: Tumor limited to one subsite of hypopharynx and 2 cm or less in greatest dimension.
T2: Tumor invades more than one subsite of hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest diameter without fixation of hemilarynx.
T3: Tumor measures more than 4 cm in greatest dimension or with fixation of hemilarynx.
T4a: Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophagus or central compartment soft tissue.
T4b: Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures.

LARYNX
Supraglottis
T1: Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2: Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx.
T3: Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic tissues, paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex).
T4a :Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g.,trachea, soft tissues of the neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus).
T4b: Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures.

APPENDIX II (Continued)
AJCC STAGING SYSTEM, 6th Edition
HEAD & NECK

Glottis
T1: Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility
T1a: Tumor limited to one vocal cord
T1b: Tumor involves both vocal cords
T2: Tumor extends to supraglottis and/or subglottis, or with impaired vocal cord mobility
T3: Tumor limited to the larynx with vocal cord fixation, and/or invades paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex).
T4a: Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g.,trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus).
T4b: Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures.

Subglottis
T1: Tumor limited to the subglottis
T2: Tumor extends to vocal cord(s) with normal or impaired mobility
T3: Tumor limited to larynx with vocal cord fixation
T4a: Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus).
T4b: Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures.

REGIONAL LYMPH NODES (N) Excluding Nasopharynx
NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Metastasis in a single ipsilateral node, 3 cm or less in greatest dimension.
N2: Metastasis in a single ipsilateral node, more than 3 cm, but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none greater than 6 cm in greatest dimension, or bilateral or contralateral nodes, none more than 6 cm in greatest dimension.
N2a: Metastasis in a single ipsilateral node more than 3 cm, but not more than 6 cm in greatest dimension.
N2b: Metastasis in multiple ipsilateral nodes, none more than 6 cm in greatest dimension.
N2c: Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension.
N3: Metastases in a lymph node, more than 6 cm in greatest dimension.

DISTANT METASTASIS (M)
MX: Distant metastasis cannot be assessed
M0: No distant metastasis
M1: Distant metastasis

APPENDIX II (Continued)
AJCC STAGING SYSTEM, 6th Edition
HEAD & NECK

STAGE GROUPING Excluding Nasopharynx

Stage 0	T*is*, N0, M0
Stage I	T1, N0, M0
Stage II	T2, N0, M0
Stage III	T3, N0, M0 T1-3, N1, M0
Stage IVA	T4a, N0-2, M0 Any T, N2, M0
Stage IVB	T4b, Any N, MO Any T, N3, M0
Stage IVC	Any T, Any N, M1

APPENDIX III
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 in excess of 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 post-irradiation surgery or other traumas. Conservative management should be tried first, though in more aggressive lesions a more radical approach may ultimately be necessary.

APPENDIX IV
University of Washington Quality of Life Questionnaire
Version 4

This questionnaire asks about your health and quality of life **over the past seven days**.
Please answer all of the questions by ticking one box for each question.

1. **Pain**. (Tick one box: ☑)

   I have no pain.
   There is mild pain not needing medication.
   I have moderate pain - requires regular medication (e.g. paracetamol).
   I have severe pain controlled only by prescription medicine (e.g. morphine)
   I have severe pain, not controlled by medication.

2. **Appearance**. (Tick one box: ☑)

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

3. **Activity**. (Tick one box: ☑)

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

4. **Recreation**. (Tick one box: ☑)

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

5. **Swallowing**. (Tick one box: ☑)

   I can swallow as well as ever.
   I cannot swallow certain solid foods.
   I can only swallow liquid food.
   I cannot swallow because it "goes down the wrong way" and chokes me.

6. **Chewing**. (Tick one box: ☑)

   I can chew as well as ever.
   I can eat soft solids but cannot chew some foods.
   I cannot even chew soft solids.

7. **Speech**. (Tick one box: ☑)

My speech is the same as always.
I have difficulty saying some words but I can be understood over the phone.
Only my family and friends can understand me.
I cannot be understood.

8. **Shoulder**. (Tick one box: ☑)

I have no problem with my shoulder.
My shoulder is stiff but it has not affected my activity or strength.
Pain or weakness in my shoulder has caused me to change my work / hobbies.
I cannot work or do my hobbies due to problems with my shoulder.

9. **Taste**. (Tick one box: ☑)

I can taste food normally.
I can taste most foods normally.
I can taste some foods.
I cannot taste any foods.

10. **Saliva**. (Tick one box: ☑)

My saliva is of normal consistency.
I have less saliva than normal, but it is enough.
I have too little saliva.
I have no saliva.

11. **Mood**. (Tick one box: ☑)

My mood is excellent and unaffected by my cancer.
My mood is generally good and only occasionally affected by my cancer.
I am neither in a good mood nor depressed about my cancer.
I am somewhat depressed about my cancer.
I am extremely depressed about my cancer.

12. **Anxiety**. (Tick one box: ☑)

I am not anxious about my cancer.
I am a little anxious about my cancer.
I am anxious about my cancer.
I am very anxious about my cancer.

Which issues have been the most important to you during the past 7 days?
Tick ☑ **up to 3 boxes.**

Pain	Swallowing	Taste
Appearance	Chewing	Saliva
Activity	Speech	Mood
Recreation	Shoulder	Anxiety

GENERAL QUESTIONS

Compared to the month before you developed cancer, how would you rate your health-related quality of life? (Tick one box: ☑)

Much better
Somewhat better
About the same
Somewhat worse
Much worse

In general, would you say your **health-related quality of life** during the past 7 days has been: (Tick one box: ☑)

Outstanding
Very good
Good
Fair
Poor
Very poor

Overall quality of life includes not only physical and mental health, but also many other factors, such as family, friends, spirituality, or personal leisure activities that are important to your enjoyment of life. Considering everything in your life that contributes to your personal well-being, rate your **overall quality of life** during the past 7 days. (Tick one box: ☑)

Outstanding
Very good
Good
Fair
Poor
Very poor

Please describe any other issues (medical or nonmedical) that are important to your quality of life and have not been adequately addressed by our questions (you may attach additional sheets if needed).

APPENDIX V

FACT-H&N (Version 4)

Below is a list of statements that other people with your illness have said are impmtant. Please circle or mark one number per line to indicate your response as it applies to the past 7 davs.

	PHYSICAL WELL-BEING	ot at all	A littl bit	Som what	Quit a bit	Vry much
GP1	I have a Jack of energy	0		2	3	4
GP2	I have nausea	0		2	3	4
GP1	Because of my physical condition, I have trouble meeting the needs of my family	0		2	3	4
GP4	I have pain	0		2	3	4
GP5	I am bothered by side effects of treannent	0		2	3	4
GP6	I feel ill	0		2	3	4
GP7	I am forced to spend time in bed	0		2	3	4

	SOCIAL/FAMILY WELL-BEING	i\"ot at all	A littl bit	Som what	Quit a bit	vry much
GSI	I feel close to my friends	0		2	3	4
GS2	I get emotional support from my family	0		2	3	4
GSI	I get support from my friends	0		2	3	4
GS4	My family has accepted my illness	0		2	3	4
GSI	I am satisfied with family con11nunication about my illness	0		2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0		2	3	4
QJ	*Regardless ofyour current ll!l·el of sexual acfil·iv, please ai/Sll'er tile following question. ifyou prefer nor to ailSlJ"er it, please mark rliis box* D *and go ro the nexi seciion.*					
GS7	I am satisfied with my sex life	0		2	3	4

FACT-H&N (Version 4)

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

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0		2	3	4
GE1	I am satisfied with how I am coping with my illness	0		2	3	4
GE1	I am losing hope in the fight against my illness	0		2	3	4
GE4	I feel nervous	0		2	3	4
GE1	I worry about dying	0		2	3	4
GE6	I worry that my condition will get worse	0		2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0		2	3	4
GF3	My work (include work at home) is fulfilling	0		2	3	4
Gf1	I am able to enjoy life	0		2	3	4
Gf4	I have accepted my illness	0		2	3	4
Gf1	I am sleeping well	0		2	3	4
Gf6	I am enjoying the things I usually do for fun	0		2	3	4
GF1	I am content with the quality of my life right now	0		2	3	4

FACT-H&N (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the nast 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
H&N1	I am able to eat the foods that I like	0		2	.›	4
H&N2	My mouth is d1y	0		2	.›	4
H&NJ	I have trouble breathing	0		2	.›	4
H&N4	My voice has its usual quality and strength	0		2	3	4
H&N1	I am able to eat as much food as I want	0		2	3	4
H&N6	I am unhappy with how my face and neck look	0		2	3	4
H&N7	I can swallow naturally and easily	0		2	3	4
H&NS	I smoke cigarettes or other tobacco products	0		2	.›	4
H&N9	I drink alcohol (e.g. beer, wine, etc.)	0		2	.›	4
H&N 10	I am able to communicate with others	0		2	.›	4
H&N 11	I can eat solid foods	0		2	.›	4
H&N 12	I have pain in my mouth, throat or neck	0		2	3	4

APPENDIX VI Data Submission Schedule

- SUBMIT WITHIN 24 HOURS OF REGISTRATION:
  Patient Registration Form

- SUBMIT WITHIN 14 DAYS OF REGISTRATION:
  In-House Pre-Study Evaluation Form (IH-102)

- SUBMIT WITHIN 7 DAYS OF SCREENING FAILURE:
  Patient Screen Failure Form

- SUBMIT WITH 14 DAYS OF CYCLE COMPLETION:
  Adverse Event-Drug Relationship Form

- SUBMIT WITHIN 14 DAYS OF END OF EACH TREATMENT CYCLE:
  In-House Treatment Cycle Form (IH-201)

- SUBMIT WITHIN 14 DAYS OF EACH RESPONSE ASSESSMENT:
  Tumor Measurement Log

- SUBMIT WITHIN 14 DAYS OF OFF TREATMENT:
  Off Treatment/In Follow-up/Off Study/Expiration Form (IH-301)

- SUBMIT WITHIN 14 DAYS OF KNOWLEDGE OF DEATH IF PATIENT IS STILL ON STUDY OR 30–DAYS IF OFF STUDY:
  Off Treatment/In Follow-up/Off Study/Expiration Form (IH-301)

- SUBMIT WITHIN 2 DAYS OF KNOWLEDGE OF PROTOCOL DEVIATION:
  Clinical Trials Support Unit: Notice of Protocol Deviation

- SUBMIT WITHIN 14 DAYS OF EACH REQUIRED FOLLOW-UP ENCOUNTER:
  Follow-Up Form (IH-302)

- ALL SERIOUS ADVERSE EVENTS MUST BE REPORTED AS OUTLINED IN THE PROTOCOL

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS
Medical Research Studies

The rights below are the rights of every person who is asked to be in a medical research study. As an experimental subject, you have the following rights:

1) To be told what the study is trying to determine.

2) To be told what will happen to you and whether any of the procedures, drugs, or devices is different from what would be used in standard practice.

3) To be told about the frequent and/or important risks, side effects, or discomforts of the things that will happen to you for research purposes.

4) To be told if you can expect any benefit from participating and, if so, what the benefit might be.

5) To be told the other choices you have and how they may be better or worse than being in the study.

6) To be allowed to ask any questions concerning the study, both before agreeing to be involved and during the course of the study.

7) To be told what sort of medical treatment is available if any complications arise.

8) To refuse to participate or to change your mind about participating after the study is started. This decision will not affect your right to receive the care you would receive if you were not in the study.

9) To receive a copy of the signed and dated consent form.

10) To be free of pressure when considering whether you wish to agree to be in the study.

If you have other questions, please ask the researcher or research assistant. In addition, you may contact the Institutional Review Board, which is concerned with protecting volunteers in research projects. You may reach the IRB office by calling (916) 703-9151, from 8:00 a.m. to 5:00 p.m., Monday through Friday, or by writing to the Institutional Review Board, CTSC Bldg., Suite 1400, Rm. 1429, 2921 Stockton Blvd., Sacramento, California 95817.

_____ _____

Signature of Subject or Legal Representative | Date

APPROVED by the Institutional Review Board at the University of California, Davis	
Protocol	Approved
359512	03-07-2014

UNIVERSITY OF CALIFORNIA, DAVIS
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Principal Investigator: Megan Daly (Radiation Oncology)
Co-Principal Investigator: Karen Kelly, MD (Hematology Oncology)

STUDY TITLE: CCRO022: Phase II Trial Of Induction Chemotherapy Followed By Attenuated Chemoradiotherapy For Locally Advanced Head And Neck Squamous Cell Carcinoma Associated With Human Papillomavirus (HPV) [Protocol version: 02.25.14]

INTRODUCTION

This is a research study. Research studies only include subjects who choose to participate. Your study doctor will explain the clinical trial to you. As a study participant you have the right to know about the procedures that will be used in this research study so that you can make the decision whether or not to participate. The information presented here is to make you better informed so that you may give or withhold your consent to participate in this research study. Please take your time to make your decision and discuss it with your family, friends, or with your personal physician. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have advanced head and neck cancer. We hope to learn more about a less aggressive regimen of radiation therapy for your type of cancer. You must be 18 years of age or older. In order to participate in this study, it will be necessary to give your written consent.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to determine whether your human papillomavirus (HPV)-positive head and neck cancer can be treated with a less aggressive regimen of radiation therapy and chemotherapy (paclitaxel) after initially receiving two cycles of chemotherapy (carboplatin/paclitaxel). If you agree to enroll on this study, you will be receiving a lower dose radiation therapy in the chemoradiotherapy phase of treatment than is typically used for head and neck cancer. The purpose of this study is to see if using this less aggressive regimen improves the tolerability of treatment and results in cure rates as high as standard treatment.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

We plan to enroll up to 50 people at UC Davis Cancer Center.

BEFORE YOU BEGIN THE STUDY

If you choose to take part in this study and sign this informed consent form, you will complete “pre-study screening tests” to determine if you meet the study requirements. Some of these exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. The pre-study screening tests are listed below and on the next page.

Pre-study Screening Tests:

- Physical examination by several doctors (including a radiation oncologist and a medical oncologist (a chemotherapy doctor))
- Evaluation of your weight and ability to carry out daily activities
- Chest x-ray or CT (Computed Tomography) scan of your chest. A CT scan uses special x-ray equipment to make detailed pictures of body tissues and organs.
- CT scan or an MRI (Magnetic Resonance Imaging) of your head and neck. MRI uses a strong magnetic field to look at one part of your body)

BEFORE YOU BEGIN THE STUDY (continued)
Pre-study Screening Tests: (continued)

- Combination of PET (Positron Emission Tomography)/CT scan of your body. A PET scan is a computerized image that looks at the activity of tumor cells in your entire body and that requires injection of a special marker into your vein, such as sugar (glucose) combined with a low-dose radioactive substance (a tracer). A camera records the tracer's signal as it travels through your body.
- Routine blood tests (about 2-3 teaspoons of blood will be taken from your vein)
- Quality of Life questionnaire
- For women able to have children, a pregnancy blood test (about 1-2 teaspoons of blood will be required)
- If your study doctor recommends:
  - Dental evaluation before receiving radiation
  - Hearing test
  - Evaluation of your diet and ability to chew and swallow to see if a feeding tube is needed

WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?

If you decide to participate in this study, you will receive 2 cycles of chemotherapy (paclitaxel and carboplatin) given three weeks apart. Before each dose of chemotherapy, you will be given some medicine through your vein to prevent an allergic reaction. Then you will be given chemotherapy through your vein for approximately two hours. You will not receive radiation therapy on the day you receive the initial chemotherapy.

Your blood pressure and overall physical condition will be closely monitored while you receive chemotherapy and for at least one hour afterwards. If you have a severe allergic reaction to the initial chemotherapy or any later doses, the study doctor will treat you for the reaction, and you may not receive further chemotherapy on this study. You and the study doctor can discuss other treatments that you can receive off study.

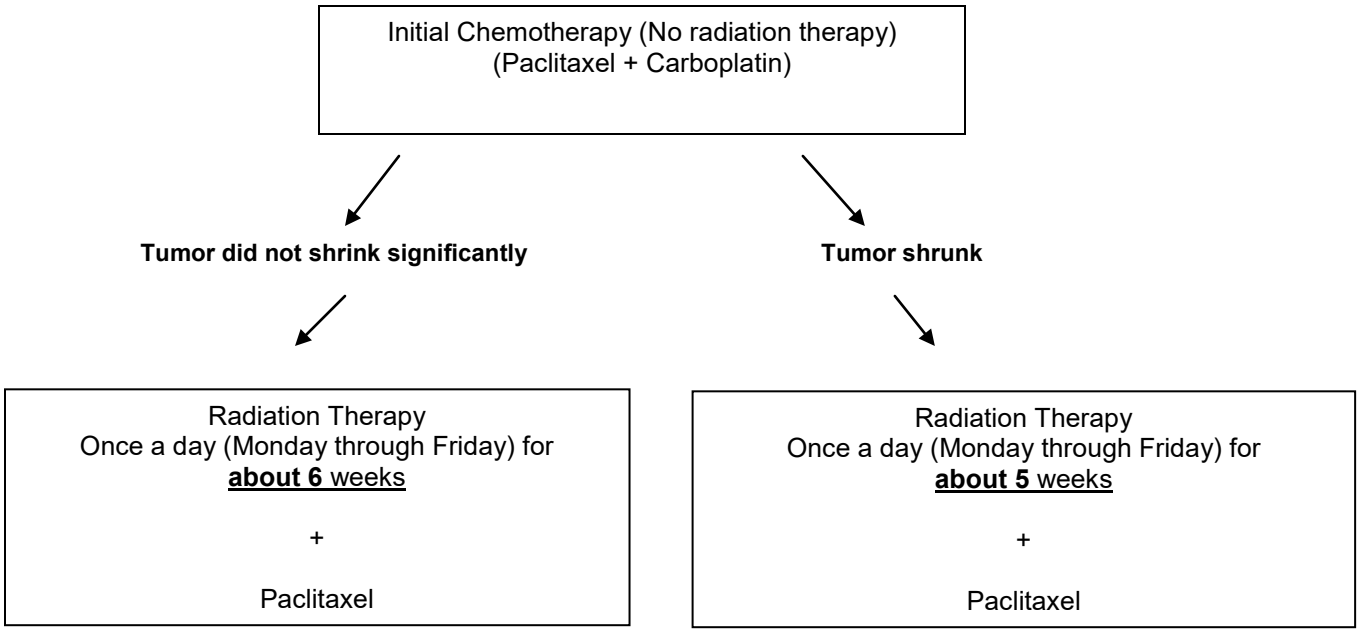
If you tolerate the initial dose of chemotherapy well, approximately two weeks later, you will begin receiving radiation therapy combined with chemotherapy. All patients will receive daily radiation therapy, Monday through Friday. Each radiation treatment will take about 20 minutes. Your study doctor will discuss with you how exactly your radiation therapy will be given. After completing the initial chemotherapy and prior to the beginning of radiation therapy, a physical examination (including endoscopy which is an examination of the throat and voice box with a mirror and/or flexible lighted tube inserted through your mouth) will be performed. This information will be used to determine how long you will receive radiation therapy.

- If the tumor was felt to have shrunk significantly after initial chemotherapy, you will receive radiation therapy once a day, Monday through Friday, for about 5 weeks.
- If the tumor response was felt to be less significant after initial chemotherapy, you will receive radiation therapy once a day, Monday through Friday, for about 6 weeks.

All patients also will receive chemotherapy (paclitaxel), through the vein, weekly during treatment. This will take 60 minutes. Some patients may stay overnight in the hospital after each chemotherapy treatment to receive medicines to replace body fluids.

* Another way to find out what will happen to you during the study is to read the chart on the next page. Start reading at the top and read down the list, following the arrows.

WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY? (continued)



Evaluation of Treatment:
Eight to twelve weeks after completion of all treatment, patients will have a CT scan or MRI of the head and neck and an additional PET/CT to evaluate the effect of treatment on their cancer.

Tests and Procedures:
If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures during the study. They are part of regular cancer care.

- Physical examination by your several doctors
- Evaluation of your weight and ability to carry out daily activities
- Blood tests after each cycle of initial chemotherapy and then every week during radiation therapy about 2-3 teaspoons of blood will be taken from your vein
- Evaluation of any side effects you may be having

WHEN I AM FINISHED WITH THE TREATMENT

You will need the following tests and procedures. These are done to see how you and your cancer was affected by the treatment you received.

At 4 weeks after treatment:

- Physical examination
- Evaluation of your weight and ability to carry out daily activities
- Blood tests (about 2-3 teaspoons of blood will be taken from your vein)
- Evaluation of any side effects you may be having
- Completion of 2 quality of life questionnaires (requiring about 5-10 minutes to fill out)

WHEN I AM FINISHED WITH THE TREATMENT (continued)

At 8-12 weeks after treatment:

- Physical examination
- CT scan or MRI of the head and neck
- PET/CT scan of the body
- Completion of 2 quality of life questionnaires (requiring about 5-10 minutes to fill out)

At 6, 9, and 12 months from the start of treatment:

- Physical examination
- Evaluation of your weight and your ability to carry out your daily activities
- Evaluation of any side effects you may be having
- Blood tests (about 2-3 teaspoons of blood will be taken from your vein)

Every 3 months for year 2, every 6 months for years 3-5:

- Physical examination
- Blood tests (about 2-3 teaspoons of blood will be taken from your vein)

HOW LONG WILL I BE IN THE STUDY?

You will be asked to participate for as long as your cancer is not growing and you are not having any unmanageable side effects. After you are finished with treatment, the study doctor will ask you to visit the office for routine follow-up exams, beginning 4 weeks after completion of treatment and then at 8-12 weeks after completion of treatment. As part of long-term follow-up, you will be seen at 6, 9, and 12 months from the start of treatment. For year 2, you will be seen every 3 months then every 6 months for years 3-5.

CAN I STOP BEING IN THE STUDY?

Yes. You can decide to stop at any time. Tell your study doctor if you are thinking about stopping or decide to stop. Your doctor will tell you how to stop safely. It is important to tell the study doctor if you are thinking about stopping so any risks from the treatment can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

Your study doctor may stop you from taking part in this study at any time if he or she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

WHAT SIDE EFFECTS OR RISKS CAN I EXPECT FROM BEING IN THE STUDY?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, researchers don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop radiation and chemotherapy, if you receive chemotherapy. In some cases, side effects can be serious, long lasting, or may never go away. As in any treatment with side effects, there also is a risk of death. You should talk to your study doctor about any side effects that you have while taking part in the study.

Combining chemotherapy with radiation to the head and neck can increase the effectiveness of radiation therapy on your cancer, but also can increase the side effects of radiation on normal tissue in treatment area. In addition, receiving a combination of chemotherapy with radiation can result in the side effects described below being more likely or more severe.

WHAT SIDE EFFECTS OR RISKS CAN I EXPECT FROM BEING IN THE STUDY? (continued)

Risks Associated with Radiation to the Head and Neck:

Likely:

- Sores in the mouth and/or throat which can make it difficult to chew and or swallow foods
- Mouth dryness or changes in taste and/or smell that may be permanent
- Thick saliva
- Hoarseness
- Tanning or redness of the skin in the head and neck area being treated with radiation
- Ear pain and/or pressure
- Fatigue
- Weight loss
- Permanent hair loss in the area treated with radiation

Less Likely, But Serious:

- Decrease in function of the thyroid gland that may require you to take thyroid replacement medicine to prevent you from feeling tired or sleepy
- Serious damage to the spinal cord, nerves in the neck, throat, jawbone, voice box, skin, or other parts of the head and neck that may require a major operation to correct and, rarely, can even be life threatening
- Pain or scarring around nerves in the shoulder that could cause numbness and/or weakness
- Breathing problems
- Difficulty with swallowing and eating for which you might need a long term feeding tube;
- Inhaling food and/or liquids into the lungs – which could also result in pneumonia.
- Serious ear infections and/or hearing loss
- Damage to the spinal cord leading to permanent weakness and/or symptoms like a “stroke”
- Permanent hair loss (of the face/chin/neck)
- Loss of teeth, or cavities in the teeth, and/or hypersensitivity of teeth

Risks Associated with PET/CT scans:

A PET/CT scan involves exposure to a low dose of radiation from an injection of a radioactive substance (a tracer). The risk from this level of radiation exposure is about 60% of the allowable annual dose for radiation workers (such as an x-ray technician) and is small when compared with other everyday risks. Ask the study doctor if you would like more information about exposure.

Less Likely:

- Discomfort from lying still on an enclosed scanning table
- Bruising or bleeding or infection at the site of the injection of the tracer

Rare but Serious:

- An allergic reaction to the radioactive substance

Risks Associated with Carboplatin:

Likely:

- Decrease in blood counts, which can lead to a risk of infection and/or bleeding
- Anemia (decrease in red blood cells)
- Loss of appetite and/or taste; metallic taste in your mouth
- Nausea and/or vomiting
- Fatigue
- Generalized loss of strength
- Hearing loss, ringing in the ears
- Loss of muscle or nerve function that may cause weakness or numbness in your hands/feet
- Loss of appetite and weight loss
- Low magnesium in the blood, which could result in muscle cramps and/or weakness
- Low calcium in the blood

WHAT SIDE EFFECTS OR RISKS CAN I EXPECT FROM BEING IN THE STUDY? (continued)
Risks Associated with Carboplatin: (continued)

Likely: (continued)

- Kidney damage

Less Likely:

- Allergic reactions (sweating, difficulty breathing, rapid heartbeat)
- Muscle cramps or spasm
- Facial swelling
- Loss of taste
- Loss of coordination
- Involuntary movement
- Restlessness
- Loss of hair, which is temporary
- Blood clots
- Low blood pressure

Less Likely, But Serious:

- Seizures
- A severe allergic reaction, which could be life threatening
- Decrease in the kidneys' ability to handle the body's waste, which may be permanent
- Calcium or potassium levels so low that it may affect heart function
- Decrease in liver function
- Another cancer called acute leukemia
- A condition called hemolytic uremic syndrome that involves decreased red blood cells and platelets, fever, and kidney failure

Possible allergic reactions to Carboplatin:
Carboplatin also may cause allergic reactions such as hives, itching, and/or skin rash. Some patients have had allergic reactions with the first dose of carboplatin, but some patients have had reactions with later doses. The allergic reactions also can be severe, involving shortness of breath, wheezing, difficulty swallowing, lightheadedness, very low blood pressure, and rarely, heart attack and/or death. If you have a severe reaction, your doctor will treat you for the reaction, and you will not receive further treatment on this study. If you have a delayed severe reaction after receiving carboplatin, you must immediately tell your doctor.

Risks Associated with Paclitaxel:

Likely:

- Weakness
- Headache
- Fever
- Dry skin
- Low calcium in the blood
- Low magnesium in the blood, which could result in muscle cramps and/or weakness

Less Likely:

- Inflammation under fingernails and/or toenails, which can last for several months
- Mouth sores
- Nausea and/or vomiting
- Diarrhea
- Constipation
- Upset stomach
- Reduced appetite, which could lead to weight loss
- Stomach pain

WHAT SIDE EFFECTS OR RISKS CAN I EXPECT FROM BEING IN THE STUDY? (continued)
Risks Associated with Paclitaxel (continued):

Less Likely: (continued):

- Chills
- Dehydration
- Trouble sleeping
- Tiredness and/or sluggishness
- Feeling depressed
- Muscle aches
- Joint or back pain
- Build-up of fluid in ankles, feet, and/or legs
- Shortness of breath
- Hair loss
- Inflammation of the lining of the eye

Less Likely, But Serious:

- Reduced blood counts, which could lead to an increased risk of infection, weakness, and/or in bleeding and bruising easily; this lowering of blood counts can lead to need for treatment with antibiotics, transfusions, or hospitalization if severe.
- Calcium or potassium levels so low that it may affect heart function
- Blood clots within a blood vessel in the lungs, legs, pelvis, or other places
- Kidney failure, which could lead to being hospitalized, or rarely, to death

Rare:

- Changes in blood tests that check how your liver is working

Rare, But Serious:

- Scarring of lung tissue, which could be life threatening or lead to death
- Heart attack
- Blood clots outside of the lungs, legs, and pelvis

Risks Associated with Paclitaxel and Radiation Therapy:

The combination of paclitaxel with chemotherapy and radiation therapy could increase the likelihood and/or severity of the side effects of chemotherapy and radiation therapy. The combination also could increase the risk of heart damage, including heart attack, abnormal heart rhythms, and/or heart failure, which could lead to death.

Additional Risks:

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs and scans in this study can affect an unborn baby. Women who are able to have children will have a pregnancy test before beginning treatment. Women should not breastfeed a baby while on this study and for at least 60 days after the last study treatment. It is important you understand that you need to use birth control while on this study and for at least 60 days after the last study treatment. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. There is a risk of not being able to have children in the future due to the chemotherapy. If you think that you may want to have children in the future, discuss this with the study doctor.

Venipuncture/Intravenous (IV) Needle Insertion: Routine laboratory tests and the research blood draws, which may result in bruising, infection and minor pain or discomfort comparable to a needle prick.

WHAT SIDE EFFECTS OR RISKS CAN I EXPECT FROM BEING IN THE STUDY? (continued)

Radiological Risks: This study involves a radiation exposure that is higher than most other diagnostic tests using ionizing radiation. The exposure to radiation from this procedure might result in a slight increase in cancer risk in normal healthy individuals. However, since you already have cancer, a risk estimate cannot be accurately determined. The amount of radiation for this research study is low compared to the radiation dose from the treatment of your cancer.

Privacy Risks: There may also be risks to your privacy. The researchers will store study records and other information about you in a secure location and will grant access only to those with a need to know. However, just like with other personal information kept by your health care providers, your banks, and others, even these safeguards cannot guarantee absolute protection of the data. If private information gets into the wrong hands, it can cause harm. Although rare, there are reported cases of breaches that have resulted in discrimination in insurance or employment.

For more information about risks and side effects, ask your study doctor.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

You may not benefit from taking part in this research. The information we get from this study may help us to learn more about this study treatment, and this may help future cancer patients.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?

Your alternative is not to take part in this study. If you choose not to take part in this study, your future care will not be affected. Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Participating in a different study, if available
- Getting no treatment
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems, and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?

We will do our best to make sure that your personal information will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law.

If information from the study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your research records for research, quality assurance, and data analysis include:

- The investigators involved in the conduct of this study and their designees
- The UC Davis Institutional Review Board (IRB)

A description of this clinical trial will be available on http://www.ClinicalTrials.gov. This Web site will not include information that can identify you. At most, the Web site will include a summary of study results. You can search this Web site at any time.

You will be asked to sign a separate form to give your permission for us to access protected health information (e.g., your medical record).

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE? (continued)
Your Social Security number may be accessed and used for the purposes of registration and follow-up for this study. This is for research purposes only and is separate from your medical care outside of this research study. The policies and guidelines of UC Davis will be followed to secure and use your Social Security number. If you do not want your Social Security number accessed and used for research purposes, your care will not be affected, and you will still be able to take part in this research study.

Please write your initials next to "Yes" or "No", depending on your decision to let us access and use your Social Security number for research purposes.

Yes _____ (Initials) No _____ (Initials)

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

It is important that you promptly tell the Researcher if you believe that you have been injured because of taking part in this study. If you are injured as a result of being in this study, the University of California will provide necessary medical treatment. The costs of the treatment may be covered by University or the study sponsor or may be billed to your insurance company just like other medical costs. The University and the study sponsor do not normally provide any other form of compensation for injury. You do not lose any legal rights by signing this form.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

There will be no charge to you or your insurance company for processing the research blood draws or research studies on your tumor biopsy tissue and blood. They will be paid for by the study. However, if the specimens are obtained during a standard diagnostic procedure, that procedure will be charged to you or you insurance company in the usual way.

Paclitaxel and Carboplatin are commercially available and will be billed to you and/or your insurance company.

You or your insurance carrier will be responsible for the associated costs of administering paclitaxel and carboplatin including infusion room charges, all routine laboratory tests, x-rays, scans, clinic visits or hospital stays.

Whenever possible, pre-authorization will be obtained. If the costs are not covered, these costs will be discussed prior to proceeding with the study.

The UC Davis Pharmacy, Investigational Drug Service (IDS) will provide drug charge information to patients when requested. The IDS can be reached at (916) 703-4093.

WILL I BE COMPENSATED FOR BEING IN THIS STUDY?

You will not be compensated for your participation in this study.

Samples taken during this study may be used for research and development purposes not related to your treatment or condition. You will not have any property rights or ownership interest in products or data which may be derived from your samples.

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or willingness to continue in the study.

DOES THE RESEARCHER HAVE A FINANCIAL INTEREST IN THIS RESEARCH STUDY?

The Principal Investigator does not have any personal or financial interest in this study.

ADDITIONAL STUDIES

Please note: This section of the informed consent form is about additional research that is being done with people who are taking part in the main study. You may take part in this additional research if you want to. You can still be a part of the main study even if you say 'no' to taking part in this additional research. You can say "yes" or "no" to each of the following studies. Below, please mark your choice for each study.

Quality of Life Study

We want to know your view of how your life has been affected by cancer and its treatment. This "quality of life" study looks at how you are feeling physically and emotionally during your cancer treatment. It also looks at how you are able to carry out your day-to-day activities.

This information will help doctors better understand how patients feel during treatments and what effects the medicines are having. In the future, this information may help patients and doctors as they decide which medicines to use to treat cancer.

You will be asked to complete 2 questionnaires at the following times: before starting treatment, 4 weeks- and 12 weeks after treatment. It takes about 5 to 10 minutes to fill out each questionnaire.

If any questions make you feel uncomfortable, you may skip those questions and not give an answer.

If you decide to take part in this study, you will be asked to fill out the 2 questionnaires. You may change your mind about completing the questionnaires at any time. Just like in the main study, we will do our best to make sure that your personal information will be kept private.

Please write your initials next to your answer
I choose to take part in the Quality of Life Study. I agree to fill out the Quality of Life Questionnaires.

YES _____ (Initials) **NO _____ (Initials)**

WILL SPECIMENS (tissue, blood, urine or other body materials) TAKEN FROM ME BE USED FOR FUTURE RESEARCH PURPOSES?

You have had a biopsy to see if you have cancer. Your doctor removed some body tissue to do some tests. The results of these tests were given to you by your doctor and are being used to plan your care.

We would like to keep some of the tissue that is left for future research purposes. In addition to the tumor tissue, we would like to collect your blood before treatment, weekly during radiation therapy, and at 3 months after the completion of treatment.

Your specimen(s) will only be used for research purposes. If you agree, these specimen(s) will be kept and used to learn more about your disease as well as other diseases.

The research that may be done with your specimen(s) will not benefit you directly nor have an effect on your care. It might help people who have your disease and other diseases in the future. Any reports about the research, done with your specimen(s), will not be shared with you or your doctor and the reports will not be put in your health record.

WILL SPECIMENS (tissue, blood, urine or other body materials) TAKEN FROM ME BE USED FOR FUTURE RESEARCH PURPOSES? (continued)

Your name, address, phone number and any other identifying information will be taken off anything associated with your specimen before it is given to the researcher. This would make it very difficult for any research results to be linked to you or your family. To help protect your privacy, people outside the research process will not have access to results about any one person.

The benefits of research using specimens include learning more about what causes diseases, how to prevent them, how to treat them, and how to cure them. There are very few risks to you. The greatest risk is the release of information from your health records which may be necessary for us to obtain along with your specimens. We will protect your records so that your name, address, and phone number will be kept private.

Please read each question below and think about your choice. After reading each question, initial next to "YES" or "NO". If you have any questions, please discuss this with the researcher.

1. My tissue/blood may be kept for use in future research: YES_____ NO_____
2. Someone may contact me in the future to ask me to use my specimens in future research: YES_____ NO_____

For further information on the use of specimens for future research purposes and your rights as a research participant, please visit: http://research.ucdavis.edu/IRBAdmin/Participants.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

If you have any questions, please ask us. If you have questions regarding the research treatments or if you think you may have been injured as a result of your participation, please contact the doctor supervising your treatment or Megan Daly, MD, the principal investigator, by calling (916) 734-8252 or by writing to them at the Radiation Oncology clinic, UC Davis Cancer Center, 4501 X Street, Sacramento, CA 95817. If you are unable to the reach the Principal Investigator of this study, please contact the clinical research coordinator (CRC) responsible for your care. The CRC's contact information will be provided to you. The CRC will assist you in contacting another investigator for this study. In addition, there is a 24-hour emergency telephone number for the hospital, which is able to contact the Radiation Oncologist on callMegan Daly, MD, or one of their associates at any time of the day or night. That number is (916) 734-2011.

Contact information for each site (including the 24-hour emergency number) is summarized below:

UC Davis Medical Center/UC Davis Cancer Center

Megan Daly, M.D.	(916) 734-8252
24-hour emergency phone number:	(916) 734-2011 **(ask for the radiation oncologist on call)**

For questions about your rights while taking part in this study call the IRB Administration at (916) 703-9151 or write to IRB Administration, CTSC Building, Suite 1400, Room 1429, 2921 Stockton Blvd., Sacramento, CA 95817. The IRB Administration will inform the Institutional Review Board which is a group of people who review the research to protect your rights. The IRB Administration has also developed a web site designed to make you familiar with your rights. The web site discusses your basic rights as a research participant, an explanation of the informed consent process, the basic requirement that written consent be in a language understandable to you, and suggested sample questions to ask the research investigator regarding your participation in the study. This web site can be accessed at: www.research.ucdavis.edu/IRBAdmin.

Initials of Participant

WHERE CAN I GET MORE INFORMATION?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

VOLUNTARY CONSENT:

My signature below will indicate that I have decided to participate in this study as a research subject. I have read and understand the information above. I understand that I will be given a signed and dated copy of this consent form and the Bill of Rights.

_____ _____
Signature of Subject Print Name of Subject

_____
Date

_____ _____
Signature of Person Obtaining Consent Print Name of Person Obtaining Consent

_____
Date

APPROVED by the Institutional Review Board at the University of California, Davis	
Protocol	Approved
359512	03-07-2014