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SITE: Head and Neck

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STAGE (If applicable): III - IV

MODALITY: Neoadjuvant Chemotherapy, Surgery/Chemoradiation

TYPE: Phase II

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Multimodality Management of Head and Neck Cancer: A Phase II Trial of Induction Chemotherapy, Organ Preservation Surgery, and Concurrent Chemoradiotherapy

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SCHEMA

Neoadjuvant Chemotherapy

1) Docetaxel 60 mg/m^2 i.v. over one hour, followed by
2) Cisplatin 25 mg/m^2 i.v. over 24 hours. Repeat q day x 4 for a total of 100mg/m2.
3) Leucovorin 500 mg/m2 over 24 hours. Repeat qday for 4 days.
4) 5-fluorouracil 700 mg/m2 over 24 hours. Repeat q day for a total of 4 days.
5) Tumor biopsy before chemotherapy and after day 1 of treatment.

Day 28 Repeat chemotherapy

Day 55 Clinical Evaluation of Response

Day 56 Repeat chemotherapy

Concurrent Chemoradiotherapy

Gemcitabine 25mg/m^2 intravenously over 30 minutes

Cisplatin 25mg/m^2 intravenously over 60 minutes. Hydrate with 500 ccs D5NS with 10 Meq KCL/liter and 8 Meq MgSO4. Give 500cc of same IV after cisplatin after. Premedications at the discretion of the treating physician.

Chemotherapy to be given on day 1 of each week of radiation.

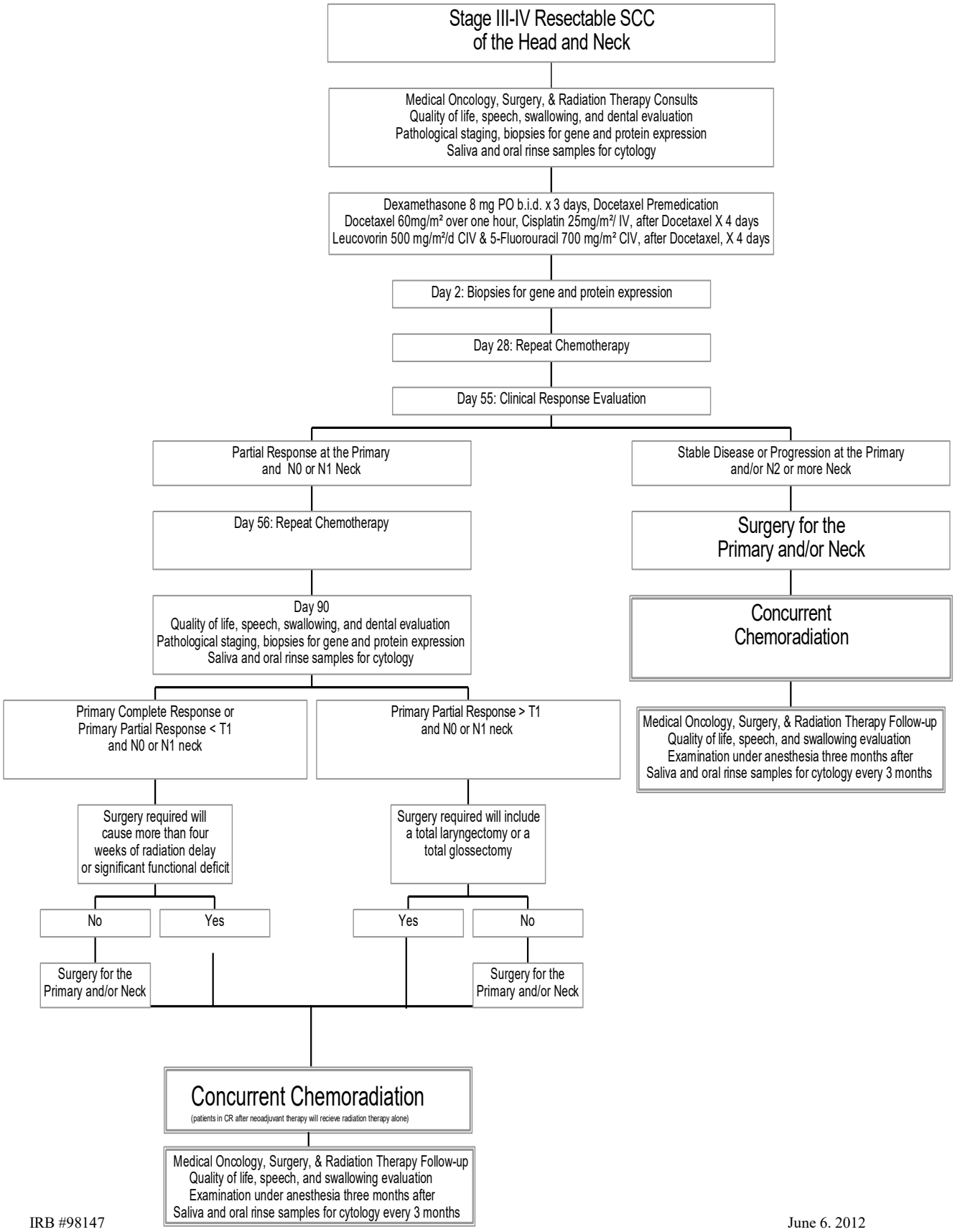
Stage III-IV Resectable SCC of the Head and Neck
Medical Oncology, Surgery, & Radiation Therapy Consults
Quality of life, speech, swallowing, and dental evaluation
Pathological staging, biopsies for gene and protein expression
Saliva and oral rinse samples for cytology
Dexamethasone 8 mg PO b.i.d. x 3 days, Docetaxel Premedication
Docetaxel 60mg/m² over one hour, Cisplatin 25mg/m²/ IV, after Docetaxel X 4 days
Leucovorin 500 mg/m²/d CIV & 5-Fluorouracil 700 mg/m² CIV, after Docetaxel, X 4 days
Day 2: Biopsies for gene and protein expression
Day 28: Repeat Chemotherapy
Day 55: Clinical Response Evaluation
Partial Response at the Primary and N0 or N1 Neck
Stable Disease or Progression at the Primary and/or N2 or more Neck
Day 56: Repeat Chemotherapy
Surgery for the Primary and/or Neck
Day 90
Quality of life, speech, swallowing, and dental evaluation
Pathological staging, biopsies for gene and protein expression
Saliva and oral rinse samples for cytology
Concurrent Chemoradiation
Primary Complete Response or Primary Partial Response < T1 and N0 or N1 neck
Primary Partial Response > T1 and N0 or N1 neck
Medical Oncology, Surgery, & Radiation Therapy Follow-up
Quality of life, speech, and swallowing evaluation
Examination under anesthesia three months after
Saliva and oral rinse samples for cytology every 3 months
Surgery required will cause more than four weeks of radiation delay or significant functional deficit
Surgery required will include a total laryngectomy or a total glossectomy
No
Yes
Yes
No
Surgery for the Primary and/or Neck
Surgery for the Primary and/or Neck
Concurrent Chemoradiation
(patients in CR after neoadjuvant therapy will recieve radiation therapy alone)
Medical Oncology, Surgery, & Radiation Therapy Follow-up
Quality of life, speech, and swallowing evaluation
Examination under anesthesia three months after
Saliva and oral rinse samples for cytology every 3 months

TABLE OF CONTENTS

6/13/01

1.0 OBJECTIVES

1.1 Primary Objectives

1.1.1 To assess the complete and overall response rate of neoadjuvant docetaxel/cisplatin/5-fluorouracil/leucovorin in previously untreated patients with local-regionally advanced head and neck cancer.

1.1.2 To evaluate the feasibility of a multimodality treatment approach with the goal of reducing long-term sequelae.

1.1.3 To evaluate prospectively the impact of neoadjuvant chemotherapy, concurrent chemoradiotherapy, and organ preservation surgery on overall survival, time to progression, and pattern of disease recurrence in patients with locally advanced head and neck cancer.

1.1.4 To evaluate prospectively biochemical correlates of response and prognosis. Markers will include, among potentially others, thymidylate synthetase, ribonucleotide reductase, and ERCC1 which will be measured by quantitative PCR. P53 will be evaluated by immunohistochemistry. The HPV status and apoptosis (TUNEL assay) will also be assessed.

1.2 Secondary Objectives

1.2.1 To evaluate treatment-associated morbidity with the use of a quality of life assessment tool.

1.2.2 To compare the results of diagnostic salivary cytology with those of histopathology at initial diagnosis as well as follow-up in head and neck cancer patients.

1.2.3 To evaluate the tolerability of combined chemoradiation using gemcitabine and cisplatin after definitive surgery for SCC of the Head and Neck.

2.0 BACKGROUND

2.1 Neoadjuvant Chemotherapy

2.1.1 Introduction

Worldwide, carcinoma of the head and neck is a relatively common malignancy: in developing countries alone, an estimated 300,000 new cases of oral cancer occurred in 1985 [1]. The comparable figure for the United States in 1996 is greater than 29,000 cases of oral cancer and additional 11,600 cases of laryngeal cancer [2]. The great majority of patients have squamous cell carcinoma.

Most patients present with local or regionally advanced disease (stage III or IV), fewer than 30 percent of such patients are cured with standard surgery and radiation therapy [3].

The clinical evaluation of the addition of chemotherapy to surgery and radiation therapy has been ongoing for nearly two decades. In patients with local-regionally advanced head and neck cancer, the strategy of neoadjuvant chemotherapy has been the most studied. The goals of primary chemotherapy include enhancement of survival and organ-function preservation.

The promising rates of complete response have been reported for the combination of cisplatin and infusional fluorouracil [3],[4]. Rapid tumor response occurs in 70-90% of patients after 2 to 3 cycles of this combination. Although consistently high response rates are observed, no randomized trial to date has demonstrated improved survival [3], [5], [6]. Three randomized trials of [7],[8],[9] and two randomized trials testing adjuvant chemotherapy [10],[11] have demonstrated reduced rates of distant metastases; however, a favorable impact on local-regional disease control has yet to be demonstrated in a randomized trial. The potential for induction chemotherapy to allow for larynx preservation for patients with locally advanced squamous cell carcinoma of the larynx [7] or pyriform sinus [8] has been demonstrated.

2.1.2 Docetaxel

The clinical investigation of new active agents appears essential if improved outcome is to be achieved for advanced head and neck cancer patients. The taxoid family includes a group of compounds that share the taxane skeleton. These include paclitaxel and docetaxel, agents that share a unique mechanism of action as promoters of microtubule assembly and inhibitors of microtubule disassembly. Both paclitaxel [12] and docetaxel [13],[14] have demonstrated consistent significant activity in a variety of cancers. In vitro studies of paclitaxel in concentrations as low as 0.001 μg/ml resulted in cytotoxic activity in a squamous cell cancer of the tongue cell line [15]. Braakhuis and colleagues observed significant growth inhibition in the two tested human tumor xenografts derived from head and neck squamous cell carcinoma when docetaxel was administered intravenously at a dose of 20 mg/kg [16]. Both head and neck tumor xenograft lines were less sensitive to treatment with cisplatin, suggesting absence of cross-resistance between the two drugs.

To date, three clinical trials evaluating docetaxel in patients with head and neck cancer have been reported. Catimel and colleagues reported the results of a multicenter trial of docetaxel in patients with recurrent or advanced disease [17]. An overall response rate of 32% was observed, with two CRs

and 10 PRs in 37 assessable patients. Dreyfuss et al. reported a major response rate of 42% (four CRs and nine PRs in 29 assessable patients) in patients with advanced or metastatic squamous cell cancer of the head and neck [18]. Premedication with dexamethasone, cimetidine, and diphenhydramine was associated with a reduced incidence of edema, hypersensitivity reactions, and dermatologic toxicities. A preliminary report of a phase II study of docetaxel in patients with metastatic or unresectable squamous cell carcinoma of the head and neck was reported by Couteau and colleagues [19]. Patients with a single site of local relapse in a previously irradiated field were ineligible. Three PRs (one in a patient with a previously untreated hypopharynx cancer) were recorded in the 11 patients evaluable for response.

The studies above may be compared to the 40% response rate reported by Forastiere et al [20] in patients with recurrent disease after surgery or radiotherapy or previously untreated, advanced, incurable or distant metastatic disease treated with high-dose paclitaxel, 250 mg/m² by 24-hour continuous IV infusion every 3 weeks with granulocyte colony-stimulating factor (G-CSF). The same dose and schedule of paclitaxel was investigated in 23 previously treated and untreated patients with squamous cell cancer of the oral cavity, oropharynx, hypopharynx, or larynx [21]. Two complete (12%) and four partial responses (24%) were recorded in 17 evaluable patients.

2.1.3 Taxane/cisplatin combination chemotherapy

The Eastern Cooperative Oncology Group has completed a randomized comparison of high- versus low-dose paclitaxel in combination with cisplatin. The high-dose arm uses paclitaxel 200 mg/m² by 24-hour infusion plus cisplatin 75 mg/m² plus G-CSF. The low dose arm consists of paclitaxel 135 mg/m² by the same infusion schedule plus cisplatin 75 mg/m² without G-CSF. The study completed accrual in June 1995 and is still undergoing analysis. As of March 1, 1995, there did not appear to be any difference in response rate, toxicity, or survival. A direct comparison of the low dose arm with the combination of cisplatin and 5-FU is planned.

The Early Clinical Trials Group of the European Organization for Research and Treatment of Cancer reported the results of a multicenter phase II study of the combination of docetaxel and cisplatin in patients with locally advanced, recurrent, or metastatic squamous cell carcinoma of the head and neck [22]. The feasibility and potential efficacy of this chemotherapy combination had previously been demonstrated in a phase I study [23]. One cycle of treatment consisted of docetaxel, 100mg/m², as an intravenous (IV) infusion over 1 hour, followed after 3 hours by cisplatin, 75 mg/m², as an IV infusion over 3 hours; cycles were repeated every 3 weeks. Twelve patients had received prior radiation therapy and four had recurrent disease after

neoadjuvant chemotherapy. All patients received a five-day course of methylprednisolone beginning one day prior to the day of infusion. Dose reduction and chemotherapy delay were required in three and 12 chemotherapy cycles, respectively. Major toxicities included neutropenia (grade 3-4 in 72% of 57 cycles), asthenia (grade 3-4 in 12% of administered cycles), sensory neurotoxicity (grade 1-2 in 23% of cycles with no grade 3-4 neurotoxicity noted), and dermatologic toxicity (grade 3-4 in 2%). The incidence of edema was 9% (all grade 1-2) and febrile neutropenia occurred in 3% of chemotherapy cycles. Two CRs and 12 PRs were observed yielding an overall major response rate of 78%, indicating high activity in this patient population.

2.1.4 Docetaxol combinations with other chemotherapeutic agents

Docetaxol has also been combined with other chemotherapeutic agents. 5-fluorouacil has been combined with docetaxol with synergistic results in preclinical studies [24]. Phase I studies have shown the feasibility of combining 60mg/m^2 of docetaxol with 300mg/m^2 if 5-FU as a continuous infusion over 5 days [25]. Primary toxicities were neutropenia and mucositis.

Docetaxol has also been combined with cisplatin, 5-fluorouracil, and leucovorin. A recently published report notes that this is a feasible combination with high response rates [26]. The treatment consisted of docetaxol 60mg/m^2 given over one hour, followed by continuous infusions of cisplatin (125 mg/m^2 over 5 day), 5-FU (700 mg/m^2/24 hr x 4 day), and leucovorin (500mg/m^2/24 hr x 5 day). This treatment was supported with G-CSF and prophylactic antibiotics. Significant toxicities included neutropenia, mucositis, diarrhea and salt-wasting nephropathy. Response rates were a 61% clinical complete response with a 39% clinical partial response for a 100% total response rate. At the primary site, 91% of patients had a pathologic complete response.

Although this regimen was felt to be feasible, toxicity was significant, and may not be tolerable in patients with less than optimal performance status. In light of this, a modification of this protocol has been piloted [27]. This involves the same drugs in the same doses as the regimen described above. However, the daily dose of cisplatin is changed to 31.25 mg/m^2/day and 5-fluorouracil and leucovorin are started together at the same time as cisplatin. The rationale for the change has been to shorten the time of delivery and thereby allow earlier institution of G-CSF. Preliminary results show response rates similar to those reported by the original regimen. However, patients continued to require a significant level of support with 14% of the cycles requiring hospitalizations for post chemotherapy support.

2.1.5 Neoadjuvant chemotherapy protocol

Based on the above background, we propose to test a combination of docetaxel, cisplatin, 5-fluororuacil and leucovorin in the neoadjuvant setting in patients with local-regionally advanced squamous cell carcinoma of the head and neck. In an attempt to improve tolerability, the cisplatin dose will be fixed at 25 mg/m^2 per day x four days, combined with docetaxol at 60 mg/m^2, and a continuous infusion of 5-fluorouracil (700 mg/m^2 per day x 4) and leucovorin (500 mg/m^2 per day x 4).

2.1.6 P53 and chemotherapeutic agent sensitivity

2.1.6.1 General Background

Approximately one half of human tumors have deleted or mutated p53 [28]. Individuals with heterozygous p53 germline mutations such as in the Li-Fraumeni syndrome show an increased susceptibility to the development of multiple malignancies including breast cancer, brain tumors, leukemias, and sarcomas [29], [30],[31]. P53 protein is a regulator of cell cycle control, via direct control of the G_1 + G_2 checkpoints. After DNA damage p53 levels increase and mediate multiple cellular responses including cell cycle arrest via the transcriptional induction of the CDK inhibitor p21 [32], DNA damage repair mediated via the transcriptional induction of Gadd45 [33], and activation of a p53 dependent apoptotic pathway [34], [35]. In addition to p53 genetic alterations, viral oncogenes such as the human papilloma virus (HPV) E6 protein can cause direct degradation of the p53 protein via a ubiquitin dependent pathway [36], [37]. MDM2, a cellular oncogene has also been shown to down regulate p53 in several types of cancers (Momand et al. 1998). It is unclear what effect the loss of p53 function has on the efficacy of chemotherapeutic agents in-vivo. Loss of p53 function by mutation is associated with chemotherapy resistance and short overall survival in hematologic malignancies [38], and to decreased chemotherapy and radiation sensitivity in lymphoma cell lines [39],[40]. These findings are supported by cell culture studies of mouse embryonic fibroblasts (MEF) derived from p53 (-/-) knock-out mice, showing resistance to chemotherapy and [41], as well as in vivo studies in nude mice with transplanted fibrosarcomas derived from adenovirus early region (E1A) and ras oncogene transformed fibroblasts [42]. The correlation between p53 mutations and increased chemotherapy resistance has been reported in colorectal cancer

[43], in non-small cell lung cancer [44], in ovarian primary tumors [45], and in breast cancer [46].

Interestingly in some situations, p53 mutations may also lead to enhanced chemosensitivity, as was reported in ovarian cancer cell lines [47]. Increased sensitivity to chemotherapeutic agents has also been shown in cultured human foreskin fibroblasts (HFF) transformed with a retrovirus vector containing the HPV 16 gene for E6 to abolish p53 protein function. In this study, HFF transfected with the HPV 16/E6 vector were 6-9 times more sensitive to cisplatin when compared to the controls, and 8-12 times more sensitive to paclitaxel [48]. When levels of p53 and p21 were measured by Western blotting, HFF transfected with a control vector showed increased levels of p53 and p21 following exposure to 1 μg/ml of cisplatin for 6 hours, whereas HFF transfected with a vector containing the HPV 16/E6 gene showed almost non detectable levels of p53 and p21 even after the exposure to 25 μg/ml of cisplatin for one hour. These studies suggest that the mechanism of p53 function abrogation, and the response of its downstream effectors are critical in understanding p53-dependent chemosensitivity.

Analysis of pre-chemotherapy and in post-chemotherapy tumor and normal tissue biopsies following the first cycle of chemotherapy will help to establish the function of the p53 axis in response to chemotherapy. Among the most critical functions of p53 after DNA damage are the induction of cell cycle arrest (mediated through p21) and initiation of the apoptotic pathway. This study should allow a better understanding of the mechanism of p53-dependent chemosensitivity in patients with SCC of the head and neck treated with a platinum-taxane containing regimen, and may provide insight into the possible p53 downstream pathways that determine this sensitivity.

2.1.6.2 P53 expression and Head and Neck Cancer response to therapy

In a study of 22 patients with squamous cell carcinomas of the head and heck (SCCHN), histocultures were established from surgical specimens [49]. Following 24 hr continuous exposure of the cells to paclitaxel, response was measured by DNA synthesis inhibition and apoptosis. DNA synthesis inhibition measured by bromodeoxyuridine (BrdUrd) DNA incorporation was not complete, and apoptosis measured by TUNEL assay

and by nucleosomal DNA fragmentation in agarose gels was present in all tumors. P53 and Bcl-2 protein expression were determined by immunohistochemistry and did not correlate with paclitaxel-induced inhibition of DNA synthesis or apoptosis. These data suggest that paclitaxel-induced apoptosis may occur via a p53-independent pathway as observed in other cell lines [47]. However, since immunohistochemistry is not always a reliable method to determine p53 mutations, these data do not rule out the possibility that paclitaxel-induced apoptosis is mediated through a p53-dependent mechanism. Furthermore, clonal selection of the most resistant cells might have occurred during the establishment of the histocultures, making these data difficult to apply to the clinical setting.

In another study, 73 patients with unresectable SCCHN were treated with cisplatin (CDDP) 80 mg/m^2 or with carboplatinum (CBDCA) 375 mg/m^2 with concomitant radiation. P53 and Bcl-2 expression were determined by immunohistochemistry. One third of the tumors showed a strong diffuse staining for bcl-2 protein; this expression was not associated with any specific clinico-pathological feature nor with any other biological marker studied. P53 immunostaining was present in 56% of the tumors, and the increase of p53 expression correlated with a decrease in disease free survival by multivariate analysis[50]. The p53 expression did not correlate with Bcl-2 expression, and these proteins were not independent predictors of chemoradiation response. Although p53 expression did not reach statistical significance in this study as a predictor of chemoradiation response, the odds ratio for p53 (-) vs. p53(+) tumors was 0.61 (C.I. 0.22-1.67), suggesting that p53(-) (perhaps with a wild type p53 gene) tumors were more sensitive to the treatment. Analysis of p53 in tumor samples immediately following treatment, might clarify the role of p53 in this setting.

2.1.6.3 Apoptosis and chemotherapy response.

Resistance to apoptosis is a new mechanism for multiple drug resistance [51]. The most traditional pathways for drug resistance are: **(**1**)** elevation of P-glycoprotein, encoded by the *mdr-1* gene that acts at the level of the plasma membrane pumping the drug out of the cell; **(2)** increased gluthathione redox detoxification and p450 hepatic activity decreasing the amount of drug-induced DNA damage; **(3)** modification of the drug target as in the amplification of the dihydrofolate reductase gene following exposure to methotrexate, and

mutations in topoisomerase 2, a target for multiple drugs; and **(4)** increased repair rates of drug-induced DNA damage [52],[53]

Apoptotic response is regulated by the *bcl-2* gene family, with the expression of Bcl-2 acting as a negative apoptosis regulator, and Bax expression sensitizing cells to programmed cell death [51], [54]. The role of the *bcl-x* gene with its two alternative splice forms with opposing functions, *bcl-*x_L (promotes survival) and *bcl-*x_S (promotes cell death), is not fully understood [55], but their differential expression seem to be important in the apoptosis regulation of hematopoietic cells progenitors and the central nervous system. Based on the experimental evidence available to date, Reed et al. proposes that Bax promotes apoptosis through the formation of Bax-Bax homodimers, and this activity is inhibited when Bax heterodimerize with Bcl-2 homologues (Bcl-2, Bcl-$_{XL}$, Mcl-1) that have anti-death activity [53]. Other apoptosis promoters such as Bcl-$_{XS}$ and Bad promote cell death through the binding and sequestration to Bcl-2 homologues, thus preventing them from heterodimerizing with Bax [53].

Following cell exposure to chemotherapy or radiation, there is an increase in p53 that mediates a decrease in Bcl-2 and an increase in Bax expression, promoting the homodimerization of Bax and the activation of programmed cell death. This p53 mediated apoptosis is independent of cell cycle regulation [56], and can also be activated through a p53 independent pathway [57]. The study of the Bcl-2/Bax expression in leukemic cells obtained from 24 patients with chronic lymphocytic leukemia (CLL) was a predictor of apoptosis following the in-vitro treatment with glucocorticoids (methylprednisolone), or with chemotherapy (fludarabine and mitoxantrone) [58]. In these patients both the apoptosis-resistant and sensitive cells showed a down-regulation of Bcl-2 expression following treatment, but Bax down-regulation occurred only in the apoptosis resistant cells. A similar study, in samples obtained from 21 patients with B-cell CLL treated in-vitro with a purine analogue (fludarabine) or a camptothecin analogue (9-amino-209s0-camptothecin), showed that none of the samples with low Bcl-2/Bax ratios were drug-sensitive, and that B-CLL cells with intermediate or high ratios were drug-resistant, independently of p53 mutations [59]. In an in-vitro study of testicular tumors and bladder cancer, etoposide-induced apoptosis was also dependent on the Bcl-2/Bax ratio [60]. Etoposide-induced apoptosis in testicular tumor cell lines was 40% with high

levels of Bax and low levels of Bcl-2 expression, while treatment-induced apoptosis in bladder cancer cell lines was 9% with high levels of Bcl-2 and low levels of Bax expression. This evidence suggests that the Bcl-2/Bax ratio measurement, rather than the levels of functional p53 may be a better predictor of the apoptotic response to chemotherapy-induced damage.

2.1.6.4 Intratumoral levels of mRNAs

Intratumoral levels of mjRNA for the enzymes targeted by several different chemotherapeutic agents have correlated with clinical outcome in a variety of tumors (61,62). These results are important because they suggest that pre-treatment mRNA levels of critical target enzymes may predict responsiveness to treatment. It would be useful to distinguish patients with a high chance of benefiting from those that may be better served by an alternate therapy.

It is proposed in this study to use relative quantitation PCR to determine mRNA levels of the M2 subunit of ribonucleotide reductase (RR), ERCC1, and thymidylate synthase (TS) and potentially others . These enzymes are involved in the activity of 5-fluorouracil and gemcitabine. Gemcitabine (63) is an inhibitor of RR. Gemcitabine requires phosphorylation by DCK as part of its activation (63). TS, which is inhibited by 5-fluorouracil, is involved in the formation of thymidylate from dUMP and as such influences DNA precursor pools and potentially DNA repair. It is postulated that measurement of the expression of the genes coding for these enzymes may allow prediction of response to treatment and also possible prognostic information. As tumor is usually accessible in head and neck cancer, it is expected that a high percentage of patients entered on this trial can be safely biopsied.

2.2 Concurrent Chemotherapy and Radiotherapy

2.2.1 Introduction

The rationale and clinical experience with concurrent administration of chemotherapy and radiation therapy in patients with solid tumors has been reviewed [64],[65],[66]. Although the terms, "enhancement," "sensitization," or "potentiation" are commonly used to describe the potential for increased antitumor activity within the radiation field as a direct result of the interaction of chemotherapy with radiation, other types of interaction have been[67]" The use of thymidine analogs, fluoropyrimidines,

hydroxyurea, as well as newer agents such as gemcitabine and fludarabine as radiosensitizer has been recently reviewed [68], [69], [70], [71].

The investigation of the combined use of chemotherapy and radiation therapy in head and neck cancer patients has been long pursued with the goals of increasing overall survival and organ-function preservation as endpoints [5], [72]. Because 40-60% of advanced head and neck cancer patients die of persistent or recurrent local-regional disease (while 20-30% of deaths are due to distant metastases), it is clear that improvement in local-regional control will be necessary in order to improve survival [5], [73].

Trials of concurrent chemotherapy and radiation therapy in head and cancer have been performed primarily in those patients with unresectable disease. Randomized trials have demonstrated improvement in disease-free survival with the addition of bleomycin [5], [74]; [75] or mitomycin-C [76]. Improved overall survival has been noted when 5-FU is used with concomitant radiotherapy [77]. Until recently, however, radiation as a single agent has remained standard therapy because the acute toxicity of combined modality therapy (predominantly mucositis) is invariably greater and the differences in survival have been small.

Cisplatin has major single agent activity in this disease and may also act as a radiosensitizer [77], [65]. Myelosuppression is modest, making it possible to use in full-dose during radiation therapy without compromise of either modality. The possible mechanisms of cisplatin radiosensitization include inhibition of repair of sublethal or potentially lethal radiation-induced DNA damage, selective radiosensitization of hypoxic cells, and direct results of cisplatin at the time of irradiation. The latter "preradiation enhancement" is postulated to involve the intracellular formation of free radicals or altered binding of platinum complexes to DNA during radiation [78], [79].

Single agent cisplatin and radiation therapy has been evaluated in several trials. The Eastern Cooperative Oncology Group performed a pilot study evaluating weekly cisplatin 10-30 mg/m² during radiation therapy, 1.8 Gy/day for 5 days/week to a total of 68-76 Gy [80]. A cisplatin dose of 20 mg/m²/week was identified for further evaluation. A randomized trial in 371 patients with unresectable disease compared radiation therapy alone to radiation therapy plus cisplatin 20 mg/m²/week [81]. The overall response rate was significantly greater for patients receiving cisplatin, 73% vs. 59%, p=.007, but there was no difference in complete response rate (34% vs. 30%) or survival. The doses used can be considered suboptimal, as the maximum total cisplatin dose was only 160 mg/m²/patient.

An alternative dose and schedule of cisplatin administration, 100 mg/m² every 3 weeks for three doses during concurrent radiotherapy, was investigated by the Radiation Therapy Oncology Group (RTOG) [82].

Eighteen and 82% of patients, had stage III and IV disease, respectively. The clinical complete response rate in 124 patients was 71%. The most common severe (grade 3) toxicity was stomatitis occurring in 28% of patients. Leukopenia was severe in 11% and moderate in 36% (resulting in dose reduction), but chemotherapy-related toxicity did not interfere with delivery of radiotherapy. Eighty-six percent of patients received at least 64.5 Gy. The administration of three doses of cisplatin was possible in only 61% of patients: severe toxicities and patient refusal were the principal reasons for non-compliance. The estimated 4-year survival rate excluding nasopharyngeal primaries was 28%, compared with 12% (all patients) and 22% (performance status greater than or equal to 90%) from the RTOG data base. The 4-year local-regional control rate was 34%, compared with 18% (all patients) and 29% (performance status greater than or equal to 90%).

Patients with advanced but clinically resectable disease may be most likely to attain benefit (improved local-regional control) from combined modality treatment strategies [83]. A feasibility study of cisplatin and postoperative radiotherapy in 51 patients was conducted by the RTOG [84]. Treatment consisted of cisplatin 100 mg/m² every 3 weeks for three doses with 60 Gy radiotherapy. Seventy-one percent of patients had Stage IV disease and 53% had positive margins. Ninety percent of patients received within 10% of the intended radiotherapy dose and 61% received all three doses of chemotherapy. Acute radiotherapy related toxicity was graded severe in 27% of patients and was predominantly mucocutaneous. Chemotherapy-related toxicity was graded severe in 33% of patients and was mainly leukopenia. The 12-month actuarial survival rate was 74.9% (61.8-88.0%) and the local-regional failure rate was 11.7% (2.0-21.5) in a preliminary analysis. A significant improvement in local-regional control was evident when compared with a group of matched resected patients treated with post-operative radiotherapy alone. Again, the need to investigate measures to reduce the incidence of therapy-related toxicity (mucositis and leukopenia) is evident.

Bachaud et al conducted a randomized trial of postoperative cisplatin and radiotherapy compared with radiotherapy alone in a group of "high risk" patients with histologic evidence of lymph node metastases with extra-capsular spread [85]. Eighty-eight patients were randomized to receive radiotherapy alone or with cisplatin 50 mg/week for a total of 7 to 9 cycles. The incidence of severe mucositis, nausea and vomiting, and neutropenia was greater in the patients treated with cisplatin, but interruptions in radiation therapy were required in only three patients. Fifty-nine percent of patients received all scheduled chemotherapy. Local-regional failure was lower in the cisplatin-treated group, 21% vs. 41% ($p<.05$). Both 2-year disease specific survival and disease-free survival were significantly greater in the combined modality group, 75% vs. 44% ($p<.05$) and 65% vs. 41% ($p<.01$), compared with the radiotherapy alone group.

This positive trial is of interest because of the high risk group under study; the report of the Head and Neck Intergroup Study by Laramore and colleagues also suggested the potential benefit of adjuvant chemotherapy (cisplatin and 5-FU) may be limited to specific high risk subsets [11]. In the study by Bachaud et al and in each of the other cited studies, only about 60% of patients were able to receive the entire intended treatment. A recently completed randomized trial (Intergroup 0099) in patients with nasopharyngeal cancer and two ongoing randomized trials (Intergroup 0126 for patients with unresectable locally advanced head and neck cancer excluding nasopharynx, paranasal sinus, and parotid gland primaries and RTOG 91-11 for patients with laryngeal cancer) will add substantially to the smaller studies of concurrent cisplatin and radiation therapy reviewed above.

Intergroup 0099 randomized patients with Stages III and IV nasopharyngeal cancer to radiation therapy with or without chemotherapy [86]. Chemotherapy consisted of cisplatin 100 mg/m² on days 1, 22, and 43 during radiation therapy, followed by cisplatin 80 mg/m² with 5-FU 1000 mg/m²/d on days 1-4 every 3 weeks for three courses after completion of radiation. In October 1995, during the first planned interim analysis, highly statistically significant differences in favor of the combined modality group were found leading to early closure of the trial. Nausea, vomiting and myelosuppression occurred more often in the combined therapy group. Local toxicities were similar in both treatment groups. Median progression-free survival and 2 year overall survival were both superior in the combined treatment group: 52 months vs. 13 months and 80% vs. 55%, respectively. The concurrent chemotherapy and radiotherapy arm has been accepted as a new standard of care in patients with advanced nasopharyngeal cancer; however, this study does not allow conclusions to be drawn regarding the relative contributions of the concurrent and adjuvant therapies to the overall study results.

Ongoing randomized trials evaluating concurrent cisplatin chemotherapy and radiation therapy include INT 0126 and RTOG 91-11 [73]. The Intergroup study is a three-arm trial for patients with unresectable Stage III and IV squamous cell carcinoma of the head and neck. The control arm is standard radiotherapy, 2 Gy/day, 5 days/week for 7 weeks, total dose 70 Gy. The second arm tests cisplatin 100 mg/m² every 3 weeks for three doses with concurrent radiation therapy; this is the regimen piloted by RTOG [82]. The third arm utilizes a regimen piloted by Adelstein et al: split course radiation therapy, 30 Gy, is given with 2 cycles of cisplatin and 5-FU, followed by resection of residual disease and split course radiation therapy, 20 Gy, with 2 additional cycles of cisplatin and 5-FU [87].

RTOG 91-11 is a larynx preservation study in patients with Stage III and IV resectable squamous cell carcinoma of the glottis and supraglottis. The first treatment arm tests 2 cycles of induction cisplatin and 5-FU followed by

definitive radiotherapy in responding patients; non-responders undergo resection followed by the same radiotherapy. This arm is identical to that published by the Department of Veterans Affairs Laryngeal Study Group [7]. The second arm consists of concurrent cisplatin, 100 mg/m² every three weeks for three doses, with radiotherapy. The third arm evaluates radiotherapy alone. This study differs from the Department of Veterans Administration Trial in two ways: T4 patients are excluded and an elective neck dissection will be performed on all patients with multiple neck nodes or any single lymph node 3 cm or greater. These study modifications should allow the three treatments to be tested in a prognostically more favorable group of patients than previously studied in randomized trials of combined modality therapy.

The recently completed Intergroup Trial demonstrating improved survival with combined cisplatin and radiotherapy compared with radiotherapy alone has resulted in a new standard of care for patients with advanced nasopharyngeal cancer. The two randomized trials in progress involving other head and neck primary sites build on the results of pilot studies and small randomized trials that suggest better local-regional control and survival with combined modality therapy.

2.2.2 Gemcitabine as a radiation sensitizer

Gemcitabine, which inhibits ribonucleotide reductase and causes chain termination of DNA, is an excellent radiation sensitizer [71]. It has been used clinically in a phase I trial of head and neck patients where severe mucositis has been dose limiting [88]. Currently doses in the range of 100 – 150 mg/ m2 are being tested [89]. It is possible that given the strong radiosensitizing attributes of gemcitabine that a combination of a modest dose of gemcitabine in combination with another active agent, may provide enhanced radiation sensitization with manageable toxicity. Cisplatin would be an agent that would be a candidate for this approach. It has demonstrated radiosensitizing effects as noted in section 2.2.1. It also has possible synergistic effects in combination with gemcitabine as suggested by preclinical studies [90].

2.2.3 Proposed chemoradiation

Based on the information presented, it is proposed to study the combination of gemcitabine 25mg/m^2 and cisplatin 25mg/m^2 on day 1 of each week of radiation. Patients will be followed for tolerance, and for duration of local control. There will be no planned dose escalations. Treatment will be held if radiation is held due to excessive mucositis or other radiation related toxicity. Treatment will also be held for hematologic toxicity. If > 3 patients are unable to adequately complete therapy, this part of treatment will be

placed on hold and be reevaluated (see section 8.7). If this occurs, protocol treatment will continue, but patients will receive radiation alone.

2.3 Quality of life, functional assessment, and performance status of the Head and Neck cancer patient.

For the quality of life and functional assessment we will use the FACT-H&N instrument developed at Rush University. This instrument in its most recent version 3 contains 34 general and 11 head and neck specific self-reported questions rated on a 0 to 4 Likert type scale. These items assess and describe patient functioning in six areas: physical well-being, social and family well-being, relationship with doctor, emotional well-being, functional well-being, and head and neck related symptoms. The validity of this instrument in the evaluation of head and neck patients has been tested and shown to be discriminatory between good and poor performance patients, with a coefficient α of internal consistency of 0.89 for the general section and 0.7 for the Head and Neck subscale. To assess the performance status we will use the scale developed by List for head and neck cancer patients (PSS-HN). The PSS-HN scale is a physician-rated instrument consisting of three subscales: normalcy of diet, understandability of speech, and eating in public (patient input is incorporated in this category). Each item is scored from 0-to 100, with higher scores indicating better performance. This scale was tested and confirmed to be more sensitive to the unique problems of head and neck cancer patients when compared to the Karnofsky status, providing independent and additional information. The complete FACT-H&N version 3 and the PSS-HN with the revised normalcy of diet scale are included in the Appendix section.

3.0 DRUG INFORMATION

3.1 Docetaxel

3.1.1 Mode of Action: Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules, while simultaneously inhibiting their disassembly, thereby resulting in inhibition of mitosis.

3.1.2 Supply, Reconstitution, and Administration: Docetaxel is a white to almost-white powder, which is highly lipophilic and almost insoluble in water. Taxotere® (docetaxel) for Injection Concentrate is a clear yellow to brownish-yellow viscous solution. Taxotere® is available in single-dose vials containing 20 mg (0.5 ml) or 80 mg (2.0 ml) anhydrous docetaxel. Each ml contains 40 mg docetaxel (anhydrous) and 1040 mg polysorbate 80. Taxotere® should be stored at 4 C away from light. Taxotere® for Injection Concentrate requires dilution prior to use. The diluent for Taxotere® contains 13% ethanol in Water for Injection, and is supplied in 1.5mL and 6.0 ml vials, to be used with 20 mg and 80 mg Taxotere® for Injection Concentrate, respectively. Prior to administration, Taxotere® is first diluted to prepare a premix solution at a concentration of 10 mg/ml. Further dilution

is then made in either 5% dextrose or 0.9% sodium chloride for injection to achieve a final Taxotere® concentration </= 1 mg/ml. The drug is stable for up to 8 hours from the time the premix solution is prepared. In order to minimize patient exposure to the plasticizer DEHP (di-(2-ethylhexyl)phthalate) which may be leached from polyvinylchloride (PVC), Taxotere® for infusion should be prepared in non-PVC bags and administered through non-PVC containing administration sets. In this study, docetaxel will be administered by IV infusion over 1 hour.

3.1.3 Toxicity: myelosuppression (dose-limiting neutropenia), nausea, vomiting, dermatologic toxicity, asthenia, fluid retention (including pleural effusion, cardiac tamponade, and ascites), mucositis, neuropathy, diarrhea, fever, myalgia, alopecia, hypersensitivity reactions, and nail changes.

3.2 Cisplatin (CDDP)

3.2.1 Mode of Action: The dominant mode of action of cisplatin is by formation of DNA cross-links.

3.2.2 Supply, Reconstitution, and Administration: Cisplatin is available as 10mg and 50 mg vials of dry powder which are reconstituted with 10 ml and 50 ml of sterile water for injection USP, respectively. Due to a lack of preservatives, the solution should be used within eight hours of reconstitution. The solution may be further diluted in a chloride containing vehicle such as D5NS or NS (precipitation occurs in D5W). Cisplatin can react with aluminum needles, producing a black precipitate within 30 minutes. In this study, cisplatin will be administered by IV infusion over 3 hours.

3.2.3 Toxicity: myelosuppression, nausea, vomiting, nephrotoxicity, hypokalemia, hypomagnesemia, hypocalcemia, allergic reactions, hearing loss, tinnitus, loss of muscle or nerve function, and loss of taste.

3.3 5 Fluorouracil

3.3.1 Mode of Action: 5-fluorouacil is an inhibitor of thymidylate synthetase and thereby limits the supply of thymidylate available for cell growth and DNA repair. 5-flourouracil may also be incorporated into DNA leading to potentially damaging cycles of insertion, excision, and reexcision. It may also be incorporated into RNA with potentially damaging effects.

3.3.2 Supply, Reconstitution and Administration: 5-fluorouracil is commercially available in 500mg vials consisting of 10cc of aqueous solution with pH adjusted to 9.2 with sodium hydroxide. No dilution is necessary. The drug is given intravenously. The solution should be inspected for particulate matter or discoloration. Normally, the solution is colorless, to faintly yellow. If a

precipitate occurs due to low temperature, the drug may be resolubilized by heating to 140 degrees with shaking. Solution may be administered when it cools to body temperature.

3.3.3 Toxicity: Mucositis, diarrhea, and neutropenia are common toxicities. Nausea, vomiting, thrombocytopenia, anemia, photosensitivity, rash, alopecia, and neurologic symptoms (i.e. a cerebellar syndrome) may result. Increased pigmentation of the skin, hand-foot syndrome, and tear duct stenosis may occur. Myocardial ischemia has been associated with 5-FU on occasion.

3.4 Calcium Leucovorin:

3.4.1 Mode of Action: Calcium leucovorin is a mixture of diastereomers of the 5-formyl derivative of folic acid. It is able to bind in addition to 5-fluorouracil to thymidylate synthetase to form a stable complex thereby enhancing the activity of 5-fluorouracil.

3.4.2 Supply, Reconstitution, and Administration: Calcium leucovorin is supplied in vials of 50, 100, and 350 mg. It is reconstituted with a sterile diluent and should be used immediately. If it is reconstituted with Bacteriostatic Water, it may be used within 7 days.

3.4.3 Toxicity: Allergic sensitization has been noted including anaphylactoid reactions and uticaria

3.5 Gemcitabine

3.5.1 Mode of Action: The cytotoxic effect of gemcitabine is due to a combination of the actions of the diphosphate (dFdCDP) and the triphosphate (dFdCTP) nucleoside analogs that lead to inhibition of DNA synthesis. Gemcitabine diphosphate inhibits ribonucleotide reductase. Gemcitabine triphosphate is incorporated into DNA, ultimately resulting in chain termination.

3.5.2 Supply, Reconstitution, and Administration: Gemcitabine is supplied in vials containing either 200mg or 1000mg of gemcitabine HCl formulated with mannitol (200 or 1000mg respectively) and sodium acetate (12.5 or 62.5 mg respectively) as a sterile lyophilized powder. To reconstitute, 5 ml or 25 ml respectively of 0.9% sodium chloride is add. These dilutions each yield a gemcitabine concentration of 40mg/ml. The appropriate amount of drug may be administered as prepared or further diluted to a concentration as low as 0.1 mg/ml. Gemcitabine solutions are stable for 24 hours at room temperature.

3.5.3 Toxicity: Myelosuppression, nausea, vomiting, diarrhea, and stomatitis are noted. Also, increased liver function tests, rash, alopecia, fever, flu-like symptoms, edema and paresthesias have been noted. A syndrome of dyspnea has been reported.

4.0 STAGING

All patients will be staged according to American Joint Committee on Cancer, 1993, criteria.

5.0 ELIGIBILITY CRITERIA

5.1 Patients must have histologically proven squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx.

5.2 Patients with clinical stage III or IV squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx are study eligible. Patients with Stage II squamous cell carcinoma of the larynx, hypopharynx, or base of tongue will also be eligible for treatment on this protocol. Measurable disease is required.

5.3 Patients must have resectable tumors (as determined by the attending surgeon) which are potentially curable with surgery and radiation therapy.

5.4 No prior chemotherapy or radiation therapy for head and neck cancer is allowed.

5.5 Patient Karnofsky performance status must be $\geq$ 60%.

5.6 Patients must have an absolute neutrophil count (ANC) $\geq$ 1500/μL and platelet count $\geq$ 100,000/μL.

5.7 Serum creatinine $\leq$ 1.5 mg/dl or the 24-hour creatinine clearance must exceed 60 cc/hr.

5.8 Serum bilirubin $\leq$ 1.5 mg/dl.

5.9 Transaminases (ALT or AST) may be up to 2.5 x institutional upper limits of normal (ULN) if alkaline phosphatase is $\leq$ ULN, or alkaline phosphatase may be up to 4 x ULN if transaminases are $\leq$ ULN. However, patients who have both transaminase elevation > 1.5 x ULN and alkaline phosphatase > 2.5 x ULN are not eligible for this study (due to decreased clearance of docetaxel and increased risk of toxicity)

5.10 Patients must be free of serious infection.

5.11 Women of child-bearing potential should have a negative pregnancy test and use effective birth control.

5.12 Written informed consent must be obtained.

5.13 EXCLUSION CRITERIA

5.13.1 Patients with unresectable disease (as determined by the attending surgeon) are ineligible.

6/13/01

5.13.2 No prior malignancy is allowed for purposes of determining disease free or overall survival except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer for which the patient has been disease-free for five years. Patients with other prior malignancies or with concurrent curable malignancies may be enrolled for determination of response and tolerance of treatment if they otherwise are eligible.

5.13.3 Patients with unstable angina, history of congestive heart failure, or an acute myocardial infarction within 6 months prior to study entry are ineligible.

5.13.4 No current symptomatic, Grade 2 or greater neurosensory or neuromotor toxicity or other significant medical or psychiatric condition incompatible with the protocol.

6.0 DESCRIPTIVE FACTORS

6.1 Patients will be described according to:

6.1.1 Primary site: oral cavity vs. oropharynx vs. hypopharynx vs. larynx.

6.1.2 T & N staging: T1 and T2 vs. T3 vs. T4; N0 vs. N1 vs. N2 vs. N3

6.1.3 Karnofsky performance status

7.0 TREATMENT PLAN

7/9/01

7.1 All study candidates will undergo consultation by a member of the Department of Radiation Oncology, Surgical Oncology, and Medical Oncology prior to initiation of treatment on this protocol. Complete dental evaluation will also be performed prior to initiation of radiation therapy.

7.2 Pretreatment studies

7.2.1 All pretreatment studies specified in the study calendar will be performed prior to initiation of chemotherapy.

7.2.2 At diagnosis, staging will include examination under anesthesia with laryngoscopy, bronchoscopy and esophagoscopy (triple endoscopy); biopsy

of any abnormal-appearing areas will be performed (these procedures are optional and to be done at the discretion of the treating physicians). Biopsy or cytologic aspiration of neck masses sufficient to determine nodal stage is optional.

7.3 Clinical response evaluation will be performed following the second course of chemotherapy. Patients with less than a partial response at the primary site or with N2 or greater disease at the neck will immediately proceed to surgery according to established guidelines; all other patients will proceed with a 3rd cycle of protocol chemotherapy. Response evaluation (examination under anesthesia with biopsy) will be performed within three weeks of completion of the neoadjuvant chemotherapy. Patients in complete response after neoadjuvant chemotherapy will proceed to concurrent chemoradiotherapy which will commence within three weeks of biopsies, given ANC > 1500/uL, and platelets > 100,000/uL. Patients with a partial response at the primary site may undergo surgery prior to the chemoradiotherapy if in the judgment of the surgeon this will not result in a major functional deficit and there will not be a delay in the initiation of the chemoradiotherapy. In patients with N1 disease a lymph node neck dissection will be performed before chemoradiotherapy in patients who require surgery for the primary. In all other patients neck lymph node dissection will be performed following chemoradiotherapy only for persistent disease.

7.4 The choice of antiemetics will be left to the attending physician.

7.5 Neoadjuvant chemotherapy

7.5.1 Chemotherapy schema

Day 0 Begin dexamethasone 8 mg po b.i.d. to continue for a total of 3 days (docetaxel premedication).

Day 1
1) Docetaxel 60 mg/m² IV over one hour
2) Cisplatin 25 mg/m²/day IV, to begin after completion of docetaxel. To continue q day x 4 for a total dose of 100 mg/m^2.
3) Leucovorin 500mg/m^2/day as a continuous infusion for 4 days.
4) 5-fluorouracil 700mg/m^2/day as a continuous infusion for 4 days.

Day 2 –4 Continuing therapy with cisplatin, 5-fluorouracil, and leucovorin

Day 27 Begin docetaxel premedication.

Day 28 Repeat chemotherapy

Day 55 Begin docetaxel premedication.

Day 56 Repeat chemotherapy.

7.5.2 After day 1, subsequent chemotherapy courses will be administered provided the patient has an ANC ≥ 1500/uL and platelet count ≥ 100,000, and recovery from prior toxicity to Grade 1 or less has occurred. If blood counts have not sufficiently recovered by the scheduled day of chemotherapy administration, blood counts will be obtained weekly, and treatment initiated when counts satisfy the above criteria. A maximum chemotherapy delay of 14 days will be allowed. If the ANC and platelet count do not meet the above criteria after 14 days delay, the patient will be removed from protocol therapy.

7.6 Surgical Guidelines

7.6.1 Surgical Evaluation of extent of disease

7.6.1.1 Evaluation of the primary disease

The diagnosis and extent of the primary disease will be determined with an examination under general anesthesia using direct laryngoscopy , bronchoscopy, and esophagoscopy whenever indicated. Multiple biopsies of the primary site will be obtained as well as biopsies of the normal mucosa for histologic diagnosis and molecular studies (see appendix). Biopsy specimens will be sent for routine pathological studies as well as for molecular studies. Samples obtained for molecular studies will be snap frozen in liquid nitrogen, and kept in appropriately labeled containers at -80 C° until the studies are performed. Accurate description of the primary site as well as of the extent of the tumor will be documented in the operative report and in the ad hoc protocol form (see appendix). An examination (under anesthesia if required) will be repeated on the last day of the first course of chemotherapy and within three weeks after the completion of the neoadjuvant chemotherapy. Tumor and normal mucosa samples will be obtained at that time; tissue samples will be processed as described above. Following the second course of chemotherapy, clinical response will be determined and documented by the surgeon and medical oncologist. Three months after the completion of all treatment dictated by the protocol or sooner if persistent disease is suspected, a new examination under anesthesia will be performed to document complete histologic response, tissue biopsies will be obtained

and processed as described above.

7.6.1.2 Saliva sample and oral rinse

7/9/01 Prior to the initial diagnosis and at six months intervals for the first three years a sample of saliva and an oral rinse with 20 cc of normal saline will be collected (these studies will be optional). Cells will be pelleted immediately by centrifugation, and slides for cytological diagnosis will be prepared. Supernatant will be frozen, aliquoted, and kept at - 80 C° for future studies.

7.6.1.3 Surgical evaluation of the Neck disease

At the time of the initial diagnosis needle biopsy or surgical biopsy of palpable lymph node(s) should be performed to
7/9/01 document pathologically tumor stage (this procedure is optional and to be done at the discretion of the treating physicians).

7.6.2 Resection of the primary tumor

7.6.2.1 General Guidelines

Following the completion of neoadjuvant chemotherapy the primary tumor will be treated according to treatment response and location of the primary site. Radical resection that includes all sites of initial tumor involvement will be reserved for patients with stable disease or disease progression following the second cycle of chemotherapy. In all other patients a functional resection will be performed in an attempt to preserve organ function (speech, swallowing, mastication, cosmesis). The presence of a final positive microscopic margin will not be cause for protocol exclusion, and patients should complete chemoradiation prior to being considered for further surgical resection.

7.6.2.2 Stable disease or disease progression following the second cycle of chemotherapy

Radical surgical resection will be performed according to standard surgical guidelines followed by chemoradiation.

7.6.2.3 Complete clinical response or partial clinical response to a tumor size of T1 or less according to AJCC criteria following the completion of all chemotherapy

Patients with no residual disease at the primary site, or with

clinical response equal to T1 or less according to the AJCC will not require primary surgery, unless in the judgment of the primary surgeon the surgery can be performed without significant functional deficit and without delaying subsequent treatment more than 4 weeks. These patients will be treated with chemoradiation, reserving surgery for salvage.

7.6.2.4 Partial clinical response to tumor size larger than T1 according to AJCC criteria, but to less than 50% of the initial tumor size following the completion of all chemotherapy

Patients with a partial response, but to a size larger than T1 should have a radical resection of the primary followed by chemoradiation according to protocol guidelines. If in the judgment of the surgeon adequate surgical resection of the primary will include a total laryngectomy or a total glossectomy, chemoradiation will be administered according to protocol and surgery will be reserved for salvage.

7.6.3 Surgical Management of the Neck

7.6.3.1 General Guidelines

Management of the neck will be determined by the initial tumor stage and by the response of the primary and the neck to neoadjuvant chemotherapy. Radical Neck Dissection shall include neck nodes from levels 1-5, internal jugular vein, sternocleidomastoid and spinal nerve. All other dissections will be considered Modified Neck Dissections, and the operative report and the ad-hoc surgical protocol form (see appendix) should accurately state the extent of the resection. In patients with palpable node(s) at least one level above and below the palpable node(s) should be dissected. In patients with bilateral nodes, staged or simultaneous neck lymph node dissections may be performed.

7.6.3.2 N2 or N3 Neck following the completion of the second course of chemotherapy

Patients will not receive course #3 of chemotherapy. A radical lymph node dissection will be performed according to standard surgical guidelines followed by chemoradiation according to protocol.

7.6.3.3 N0 Neck at diagnosis

There will be no lymph node neck dissection in patients with no palpable enlarged lymph nodes and without evidence of enlarged (>1 cm) lymph nodes by CT scan. Patient may proceed to chemo-radiation if there is no indication for surgical treatment of the primary.

7.6.3.4 N1 Neck following the completion of chemotherapy

Following the completion of the neoadjuvant chemotherapy if there is clinical N1 disease, or evidence of enlarged lymph nodes by CT scan (>1 cm), patients will be evaluated for surgical treatment of the neck. Patients who initially presented with clinically positive neck nodes, will also be evaluated for surgery even if they obtain a complete or near complete response.

7.7 Concurrent Chemotherapy and Radiation Therapy

7.7.1 Chemotherapy

7.7.1.1 Patients with persistent disease at the primary or neck will receive chemoradiation.

7.7.1.2 Drug cycle schema: On day 1, cisplatin 25 mg/m² IV over 1 hour will be administered (to commence with radiation therapy). It will be followed with gemcitabine 25mg/m^2 over 30 minutes. Cisplatin and gemcitabine will be repeated on a weekly basis during radiation for a total of 7 planned doses.

7.7.1.3 Chemotherapy will be administered weekly provided the patient has an ANC $\geq$ 1500/μL and platelet count $\geq$ 100,000/μL. If blood counts have not sufficiently recovered by the scheduled day of chemotherapy administration, blood counts will be obtained weekly, and gemcitabine/cisplatin will be administered when counts satisfy the above criteria. If the ANC and platelet count do not meet these criteria within 21 days of scheduled chemotherapy administration, chemotherapy will be discontinued.

7.7.1.4 Chemotherapy will be held if radiation is held due to toxicity. It will also be held if grade III mucositis or oropharyngeal toxicity occur.

7.7.2 Radiation Therapy Parameters

7.7.2.1 Radiation Dose

Treatment to the primary tumor and upper neck will be given at 1.8-2.0 Gy per fraction, once a day, five days a week to a total dose of 70 Gy in 35 to 39 fractions in seven to eight weeks. Fields must be reduced to exclude the spinal cord at 40-44 Gy at the midplane. However, the entire neck must be irradiated to a dose of at least 44 Gy (even in N0 stage) at anatomical levels of lymph nodes usually 2-4 cm below the skin surface. Patients with multiple nodes, extracapsular extension, lymph node(s) greater than 3 cm, or positive lymph nodes on surgical dissection should receive a minimum dose of 60 Gy to the ipsilateral neck postoperatively. Electrons will be used to supplement the dose to the posterior neck. The anterior lower neck field will be treated at 1.8-2.0 Gy per fraction once a day, to a total dose of at least 44 Gy. The total dose to the primary tumor and clinically positive nodes will be 70 Gy in 35 to 39 fractions in 7 to 8 weeks.

An isodose plan must be performed to document close homogeneity at multiple levels. Dose inhomogeneity my not exceed 110%.

7.7.2.2 Physical Factors

7.7.2.2.1 Equipment: linear accelerators with appropriate photon (6 MV to 18 MV) and electron energies (6 MeV to 20 MeV) for supplemental boosting to the nodes.

7.7.2.2.2 Patients will be treated with treatment distance at 100 cm SAD for upper neck fields and 100 cm SSD for the anterior lower neck field.

7.7.2.3 Localization Requirements

7.7.2.3.1 Simulation of all fields is mandatory. Patients must be reproducibly immobilized using Aquaplast headmask or equivalent technique. The use of customized blocks to shape the treatment fields is recommended.

7.7.2.3.2 Beam verification (port) films must be obtained for each field prior to the first radiation treatment and every 1-2 weeks thereafter.

7.7.2.3.3 Either portal verification, simulation or Polaroid films must verify electron fields utilized for supplemental nodal boosting.

7.7.2.4 Target Volume Irradiation Portals

A combination of lateral opposing fields, anterior and lateral wedged fields, or several beam-directed fields will be used for the primary tumor site at the discretion of the attending radiation oncologist. A single anterior field will be used to treat the neck below the fields for the primary tumor. When there are positive nodes in the lower neck, an additional posterior field may be necessary to deliver a supplemental dose to the positive node(s). The lower neck and supraclavicular field should abut the primary field at the skin. Independent jaw technique for the field junction with junction shift every 15 Gy is recommended. For oral cavity and oropharynx primaries, a midline block 2 cm wide and at least 2 cm in length on the skin surface may be placed in the anterior lower neck field to shield the larynx and the spinal cord in the junction region. For larynx and hypopharynx primaries, a lower lateral block, 2 cm in height could be placed in the lateral upper neck fields to shield the areas of potential overlap of diverging beams over the spinal cord. The primary treatment fields should encompass the pre-chemotherapy tumor volume with adequate margins (minimum 1.5 cm) along with sites of known and/or suspected lymph node disease in the upper neck. At least field two reductions are recommended. The first field reduction off the spinal cord occurs at 40-44 Gy, and the second field reduction at 50-60 Gy encompassing tumor volume with 1.0-1.5 cm margins depending on the dose delivered to the regional lymph nodes (see 7.9.2.1). The primary treatment fields by tumor site and the lower neck field are as follows:

7.7.2.5 Oral tongue and floor of mouth

The lateral fields should include the primary tumor bed, the submandibular and upper jugular nodes. Boost irradiation of the posterior chain is not indicated unless there are clinically positive cervical nodes.

7.7.2.6 Anterior tonsillar pillar and retromolar trigone

Both ipsilateral and contralateral posteriorcervical nodes must be irradiated to a minimum of 50 Gy if the primary tumor is T2-T4 or if there are clinically positive nodes in the anterior chain.

7.7.2.7 Oropharynx

Both the ipsilateral and contralateral posterior cervical nodes must be irradiated to a minimum of 50 Gy if the primary tumor

is T2-T4 or if there are clinically positive nodes in the anterior chain.

7.7.2.8 Larynx

7.7.2.8.1 The upper border of the field includes the upper jugular nodes. Two cm. of the mandible is to be included to obtain adequate coverage for N0 neck, or one cm. above the tip of the mastoid process when N+, or involvement of the pyriform sinus and/or lateral hypopharyngeal wall, to include the retropharyngeal nodes.

7.7.2.8.2 The lower border of the field encompasses the larynx usually at the inferior border of the cricoid cartilage.

7.7.2.8.3 If there is subglottic extension, the inferior border should extend to the upper trachea (2 cm. below disease).

7.7.2.8.4 Both ipsilateral and contralateral posterior nodes should be treated to a minimum of 50 Gy if there are T2-T4 or clinically positive nodes in the anterior chain.

7.7.2.9 Hypopharynx

7.7.2.9.1 The superior border is placed at the base of the skull (above C1) to include the retropharyngeal nodes. Nodes in the upper jugular region and posterior triangle are included. Two cm. of the mandible is to be included to obtain adequate coverage.

7.7.2.9.2 The lower border of the field encompasses the primary lesion with margin (as low as possible without treating shoulders).

7.7.2.10 Lower neck

7.7.2.10.1 A single anterior lower neck field will be used to treat the neck and the supraclavicular fossa below the fields for the primary tumor. When there is (are) positive node(s) in the lower neck, an additional posterior field may be necessary to deliver a supplemental dose to the positive node(s).

7.7.2.10.2 For all patients with clinically positive nodes greater than 6 cm, positive supraclavicular nodes, or pyriform sinus tumors that are T3 or T4 or have clinically positive nodes, a mediastinal T field may be used. The lateral limbs of the T extend to 1 cm below the clavicle and the central portion of the field extends 5 cm more inferiorly to include the upper mediastinum.

7.7.2.11 Photon beam portal arrangements

7.7.2.11.1 The following portal arrangements require dose specifications as follows:

For two opposed coaxial equally weighted beams: on the central ray at mid-separation of beams.

For arrangement of two or more intersecting beams: at the intersection of the central ray of the beams.

7.7.2.12 Electron beam dose specifications:

The energy and field size shall be chosen so that the target volume is encompassed within 90% (or other appropriate minimum dose) of the prescribed dose.

7.7.2.13 Dose calculations

7.7.2.13.1 Doses are specified as mid-depth at central axis when parallel opposed techniques are used or at the intersection of the central axis for other techniques. Dose to the supraclavicular field is calculated at 3 cm depth. Complete isodose curves are required.

7.7.2.13.2 Variation within the target volume is not to exceed +/- 10% of the target dose.

7.7.2.13.3 Fields must encompass the primary tumor and its suspected projections with a minimum 1.5 cm margin in all directions. This tumor (target) volume should receive 90% or greater of the central axis mid-depth dose.

Fields must be reduced to exclude the spinal cord at a dose of 40-44 Gy at the mid-saggital plane. To

supplement the dose to gross adenopathy in the neck, boost techniques may include electrons, wedge pairs, oblique fields, or interstitial implants.

7.7.2.14 Time and dose modifications

Treatment interruptions are strongly discouraged and should be allowed only for healing of severe normal tissue reactions. Treatment interruptions, and the reason for these must be clearly indicated in the treatment record.

7.7.2.15 Anticipated side effects and toxicities

7.7.2.15.1 Reversible mucositis, epilation and various degrees of skin reaction in the treatment area are expected. Side effects within 90 days of the start of treatment should be graded according to the Acute Radiation Morbidity Scoring Scale. Radiation effects persisting beyond or appearing after the first 90 days are measured on the Late Effects Scale (see Appendix).

7.7.2.15.2 Other expected acute reactions include xerostomia, hypogeusia, and dysphagia. Unusual severity of any of these reactions should be noted.

7.7.2.15.3 Late effects include permanent xerostomia in almost all patients and occasionally persistent dysphagia. Mandibular osteoradionecrosis will occur in 5 % or less of the patients, but can be reduced by thorough dental evaluation before irradiation, which is mandatory. Pretherapy extraction of badly diseased teeth should be carried out with conservation of restorable teeth where possible. Teeth extractions should be done at least 2 weeks prior to the start of irradiation.

7.7.2.15.4 Radiation-induced myelopathy can occur in less than 1% of patients providing cervical spinal cord dose remains below 40-44 Gy in 20 fractions in 4 weeks. Transient radiation effects, manifested by L'Hermittes sign, may be more frequent and should be fully documented.

7.8 Criteria for Removal from Protocol Treatment

7.8.1 Disease progression.

7.8.2 Delay in treatment of > 2 weeks for chemotherapy or radiation therapy.

7.8.3 Unacceptable toxicity.

7.8.4 Patients may withdraw from the study at any time for any reason.

7.9 All patients will be followed until death.

8.0 TOXICITIES MONITORED AND DOSAGE MODIFICATIONS

8.1 Patients will be examined and toxicity graded on the first day of each chemotherapy cycle. Chemotherapy-associated toxicities will be monitored according to the NIH Common Toxicity Criteria, Version 2.0 (see Appendix).

8.2 Acute and chronic radiation morbidity will be graded according to RTOG/EORTC criteria (see Appendix).

8.3 Dose Modifications: Neoadjuvant Chemotherapy

8.3.1 Hematologic toxicity

8.3.1.1 At Day 28 and 56: Chemotherapy will be postponed for seven days for ANC < 1500/uL or platelet count < 100,000/uL. The patient will be removed from protocol therapy if the ANC and platelet count do not satisfy these criteria within 14 days of scheduled administration (see Section 7.7.2).

8.3.1.2 Should febrile neutropenia occur after the first cycle of neoadjuvant chemotherapy, there will be a 20% reduction in the dose of docetaxol. Support with G-CSF may be considered in place of a dose reduction if the episode of neutropenic fever was uncomplicated, and if there were no other significant toxicities (i.e. no other toxicities greater than grade 2).

8.3.2 Hypersensitivity reactions

Docetaxel infusion should be stopped immediately if a patient develops anaphylaxis manifested by bronchospasm or hypotension sufficient to require parenteral therapy. Acute anaphylaxis should be treated with standard emergency medical regimens. Patients who develop anaphylaxis or grade 3 hypersensitivity reaction will be removed from the protocol. Any hypersensitivity reaction should be recorded as an adverse event. In case of late-occurring hypersensitivity symptoms (e.g., appearance within 1 week after treatment of a localized or generalized pruritis), symptomatic treatment may be given (e.g., oral antihistamine). Additional oral or

parenteral premedication with antihistamine may also be given for the next cycle of treatment, depending on the intensity of the reaction observed. No dose reductions will be made in any case.

8.3.2.1 MANAGEMENT OF SUBSEQUENT CYCLES

Patients with hypersensitivity reactions to Taxotere® are at risk for recurrent reactions. These patients must be informed of the potential risk of recurrent allergic reactions and must be carefully monitored.

Management of Hypersensitivity Reactions (Taxotere®)
Management of Hypersensitivity Reactions

Severity of Symptoms	Treatment Guidelines
Mild symptoms: localized cutaneous reactions such as mild pruritus, flushing, rash	• consider decreasing the rate of infusion until recovery from symptoms, stay at bedside and monitor patient • then, complete Taxotere infusion at the initial planned rate
Moderate symptoms: any symptom that is not listed above (mild symptoms) or below (severe symptoms) such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic BP > 80 mm Hg	• interrupt Taxotere infusion • give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV; monitor patient until resolution of symptoms • resume Taxotere infusion after recovery of symptoms; depending on the physician's assessment of the patient, Taxotere infusion should be resumed at a slower rate, then increased incrementally to the initial planned rate, (eg. infuse at an 8 hour rate for 5 minutes, then at a 4-h rate for 5 minutes, then at a 2-h rate for 5 minutes, then finally, resume at the 1-h infusion rate) • depending on the intensity of the reaction observed, additional oral or IV premedication with an antihistamine should also be given for the **next cycle** of treatment, and the rate of infusion should be decreased initially and then increased back to the recommended 1-hour infusion, (eg. infuse at an 8 hour rate for 5 minutes, then at a 4-h rate for 5 minutes, then at a 2-h rate for 5 minutes, and finally, administer at the 1-h infusion rate)
Severe symptoms: any reaction such as bronchospasm, generalized urticaria, systolic BP ≤ 80mm Hg, angioedema	• immediately discontinue Taxotere infusion • give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV and/or epinephrine as needed; monitor patient until resolution of symptoms • the same treatment guidelines outlined under moderate symptoms (i.e. the third and fourth bullets) should be followed.
Anaphylaxis (NCI grade 4 reaction)	• NO FURTHER STUDY DRUG THERAPY

8.3.3 Renal toxicity

The dose of cisplatin during neoadjuvant therapy will be based on serum creatinine and calculated creatinine clearance values on the scheduled treatment days:

Serum Creatinine	Creatinine Cl(calculated)	% Cisplatin Dose
≤ 1.5 mg/dl and	> 50 cc/hr	100%
1.6-2.0 or	30-50 cc/hr	50%
> 2.0 or	< 30 cc/hr	No cisplatin

8.3.4 Mucositis, diarrhea, dermatitis

Grade 3 mucositis, diarrhea, or dermatitis occurring during the previous cycle will result in a 10% reduction in docetaxel dose as well as a 10% reduction in 5-fluorouracil.

Grade 4 mucositis, diarrhea, or dermatitis during the previous cycle will require a 20% reduction in docetaxel dose and a 20% reduction of the 5-fluorouracil dose

8.3.5 Neurotoxicity

Doses of docetaxel and cisplatin will be modified based on the most severe neurotoxicity during the previous cycle:

Neurotoxicity Grade	Dose Adjustment
0 - 2	None
3	Hold chemotherapy until recovery to ≤ Grade 1, then decrease docetaxel and cisplatin by 25%
4	Patient removed from study

If neurotoxicity does not improve to ≤ Grade 1 after a 2 week delay, the patient will be removed from protocol treatment.

8.3.6 Fluid retention

No dose reduction is planned. Patients developing new onset or symptomatic edema, or other signs of fluid retention, should be treated with

oral diuretics. The choice of diuretics will be at the discretion of the attending physician.

8.3.7 Abnormal liver function tests

Patients who develop abnormal liver function tests while on the study, for any reason, will have the following docetaxel dose reductions:

Bilirubin	Alkaline phosphatase	ALT/AST	Action
1) > ULN	or >5 x ULN	or >5 x ULN	Wait ≤ 2 weeks.

If recovered, reduce dose by 25%. If not, off study.

2) ≤ ULN	≤ 5 x ULN	and	≤ 5x ULN	Dose reduce 25%.

8.4 Dose Modifications: Concurrent Chemotherapy (and radiation therapy)

8.4.1 Hematologic toxicity

At the beginning of each week of radiation therapy, gemcitabine and CDDP will be held if ANC < 1500, or PLT < 100,000.

8.4.2 Renal toxicity

The dose of cisplatin will be based on serum creatinine and calculated creatinine clearance values on the scheduled treatment days:

Serum Creatinine	Creatinine Cl(calculated)		% Cisplatin Dose
≤ 1.5 mg/dl	and	> 50 cc/hr	100%
1.6-2.0	or	30-50 cc/hr	50%
> 2.0	or	< 30 cc/hr	No cisplatin

If renal function declines to the point that cisplatin is placed on hold, gemcitabine with also be held.

8.4.3 Neurotoxicity

In the event of a grade 3 or greater neurotoxicity, CDDP will be held until recovery to toxicity level ≤ Grade 1, then subsequent cisplatin doses will be reduced by 25%. Therapy with gemcitabine alone may continue.

8.5 Ototoxicity

Audiograms will be performed if subjective hearing loss develops. Significant (>40 dB) loss in the speech frequency range is an indication to discontinue cisplatin.

8.6 Radiation Therapy Treatment Interruption

Skin reaction, mucositis, ulceration, edema or other acute radiotherapy complication may necessitate interruptions in radiotherapy. The interruption should not exceed two weeks.

8.7 If > 3 patients are unable to receive at least 4 of the planned 7 weekly chemotherapy treatments, or if >3 patients require radiation interruptions of more than 2 weeks, then this part of the protocol will be reevaluated for feasibility. Accrual to the protocol will continue, but patients will be treated with radiation alone.

8.8 ADVERSE EVENT REPORTING

Adverse events will be reported as outlined in appendix . In addition, Rhône-Poulenc Rorer, the manufacturers of Taxotere, has requested the following guidelines included as additional information.

8.8.1 Definitions

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

The definition of serious adverse event (experience) also includes important medical event. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.8.2 Reporting

In IND studies, all docetaxel serious, related, unlabeled, (unexpected) adverse events will be reported to the FDA, by the investigator, as required by 21 CFR 312.32.

In IND studies, Rhône-Poulenc Rorer Pharmaceuticals, Inc., will be provided with a copy of all docetaxel serious, related adverse event reports. These reports should be filed utilizing the Form FDA 3500A (MedWatch Form). This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. These reports must be sent by FAX to Rhône-Poulenc Rorer Drug Product Safety (610-454-2190), within 24 hours of receipt by investigator / sponsor

For Comparator Drugs / Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer, by the investigator.

In IND-exempt studies, Rhône-Poulenc Rorer Pharmaceuticals, Inc., will be provided with a copy of all docetaxel serious, related adverse event reports. These reports should be filed utilizing the Form FDA 3500A (MedWatch Form). This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. These reports must be sent by FAX to Rhône-Poulenc Rorer Drug Product Safety (610-454-2190), within 24 hours of receipt by investigator / sponsor.

For Comparator Drugs / Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer, by the investigator.

9.0 STUDY PARAMETERS

	Prestudy	Before each Chemotherapy Cycle	During Chemoradiation	After 2nd Chemotherapy/After all Chemotherapy/After Radiotherapy
History & Physical Examination	X	X	q2wk	0/X/X
Tumor Measurements	X	0	0	X/X/X
Performance Status	X	X	q2wk	0/X/X
CBC, platelet count and differential AΦ	X	X	qwk	0/X/X
Chem 18, MagnesiumΦ	X	X	qwk	0/X/X
Creatinine Clearance (actual)	X	0	0	0/X/X
Creatinine Clearance (calculated)	X	X	qwk	0/0/0
Triple Endoscopy*	X*	0	0	0/0/0
Tumor Biopsy *(when feasible)	X*	0	0	X*/X*/X*
Oral Rinses*	X*	0	0	0/X*/X*
Serum Specimen *(peripheral blood)	X*	0	0	0/0/X*
CT or MRI of Neck *(optional)	X*	0	0	0/X*/X*
Chest X-ray	X	0	0	0/0/X
Quality of Life Assessment	X	0	0	0/X/X
Audiogram	X	0	0	0/0/X

7/9/01

ϕ- labs should be repeated on day 8 –12 to determine nadir and electrolyte status, and should be drawn otherwise as clinically indicated.
* - tests are optional.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 Disease status

10.1.1 Measurable disease: Bidimensionally measurable lesions with clearly defined margins by 1) medical photograph (skin or oral lesions) or plain

x-ray, with at least one diameter .5 cm or greater (bone lesions not included) or 2) CT, MRI, or other imaging scan, with both diameters greater than the distance between cuts of the imaging study or 3) palpation, with both diameters 1 cm or greater.

10.1.2 Evaluable disease: Unidimensionally measurable lesions, masses with margins not clearly defined, lesions with both diameters less than 0.5 cm, lesions on scan with either diameter smaller than the distance between cuts, palpable lesions with either diameter less than 2 cm, bone disease. Markers that have been shown to be highly correlated with extent of disease are also considered to be evaluable.

10.2 Objective status

If an organ has too many measurable lesions at each evaluation, choose three to be followed before the patient is entered on study. The remaining measurable lesions in that organ will be considered evaluable for the purpose of objective status determination.

10.2.1 Complete response (CR): Complete disappearance of all measurable and evaluable disease. No new lesions. No disease-related symptoms. No evidence of non-evaluable disease, including normalization of markers and other abnormal lab values. All measurable, evaluable, and non-evaluable lesions and sites must be assessed using the same technique as baseline. Refers to clinical CR. (When restaging surgery is required, a separate pathologic response variable is incorporated in the response data).

10.2.2 Partial response (PR): Applies only to patients with at least one measurable lesion. Greater than or equal to 50% decrease under baseline in the sum of products of perpendicular diameters of all measurable lesions. No progression of evaluable disease. No new lesions. All measurable and evaluable lesions and sites must be assessed using the same techniques as baseline.

10.2.3 Stable/No response: Does not qualify for CR, PR, or progression, All measurable and evaluable sites must be assessed using the same techniques as baseline.

10.2.4 Progression: 50% increase OR an increase of 10 cm^2 (whichever is smaller) in the sum of products of all measurable lesions over smallest sum observed (over baseline if no decrease) using the same techniques as baseline, OR clear worsening of any evaluable disease, OR reappearance of any lesion that had disappeared, OR appearance of any new lesion/site, OR failure to return for evaluation due to death OR deteriorating condition (unless clearly unrelated to this cancer). For

scan-only bone disease, increased uptake does not constitute clear worsening. Worsening of existing non-evaluable disease does not constitute progression.

10.2.4.1 Exceptions:

10.2.4.1.1 In cases for which initial tumor flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), either symptoms must persist beyond 4 weeks or there must be additional evidence of progression.

10.2.4.1.2 Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.

10.2.5 Clinically Significant Response (CSR): patients achieving a complete response (as defined in section 10.2.1) of the primary tumor, or a partial response of the primary tumor less than or equal to T1 by AJCC staging and neck metastases staged as NO or N1. A clinically non-significant response would include patients achieving a partial response at the primary tumor greater than T1, stable disease, progression or metastatic disease in the neck greater than N1.

10.3 Best Response: Best response is determined from the sequence of objective statuses.

10.3.1 Disease assessment every 4 weeks. Two objective status determinations of CR before progression are required for a best response of CR. Two determinations of PR or better before progression, but not qualifying for a CR, are required for a best response of PR. Two determinations of PRNM or better before progression, but not qualifying for CR, are required for PRNM. Two determinations of stable/no response or better before progression, but not qualifying as CR, PR or PRNM, are required for a best response of stable/no response; if the first objective status is unknown, only one such determination is required. Patients with an objective status of progression on or before the second evaluation (second AFTER the prestudy evaluation) will have a best response of increasing disease. Best response is unknown if the patient does not qualify for a best response of increasing disease and if all objective statuses after the first determination and before progression are unknown.

Use of the definition is illustrated in Table 1 with several sequences of objective statuses and the corresponding best response.

Table 1. Sequences of objective statuses with corresponding best response

1st objective status	2nd objective status	3rd objective status	Best response
3-6 week assessment interval			
Progression			Progression
Stable, PR, CR, unk	Progression		Progression
Stable[a]	Stable	Progression	Stable
Stable, unk[a]	PR, CR	Progression	Stable[e]
Stable, unk	Unknown[d]	Progression	Unknown
PR[b]	PR	Progression	PR
PR[b]	CR	Progression	PR
PR, CR	Unknown[d]	Progression	PR (Unconfirmed)
CR[c]	CR	Progression	CR
Unknown[a]	Stable	Progression	Stable

[a]Best response is the same if these sequences are preceded by the objective statuses of unknown or stable, or if unknowns separate the first objective status from the second.
[b]Best response is the same if these sequences are preceded by the objective statuses of unknown, stable or PR, or if unknowns separate the first objective status from the second.
[c]Best response is the same if these sequences are preceded by the objective statuses of unknown, stable, PR or CR, or if unknowns separate the first CR from the second.
[d]Best response is the same if followed by additional unknowns.
[e]Evaluation codes allow identification of these patients with best response of stable or unknown who had unconfirmed PR or CR.

10.4 ENDPOINT DEFINITIONS

10.4.1 Overall Survival. Defined as the time from first day of treatment to time of death due to any cause. If a patient is still alive, survival time is censored at the time of last follow-up.

10.4.2 Disease-Free Survival. Defined as the time from first day of treatment to the first observation of disease recurrence or progression or death due to any cause. If a patient has not progressed or died, disease-free survival is censored at the time of last follow-up.

10.4.3 Disease-Free Interval. Defined as the time from first day of treatment to the first observation of disease recurrence or progression or death due to disease. If failure has not occurred, failure time is censored at the time of last follow-up.

10.4.4 Duration of response. Defined as the time from first objective status assessment of response to the first time or progression or death due to any cause. If a responding patient has not progressed or died, duration is censored at the time of last follow-up.

11.0 TISSUE HANDLING

11.1 Tumor Tissue Procurement

Tumor tissue specimens and normal mucosa will be obtained by the surgical service via biopsy (or excision) of primary tumors or regional lymph nodes at diagnosis, on day 2 of the first chemotherapy cycle, at the completion of the neoadjuvant chemotherapy, and at the time of the definitive surgical resection if indicated. All tissue obtained will be transported in an iced container to anatomic pathology for immediate processing. A surgical pathologist will review portions of all specimens to confirm malignant histology. Dr. Sharon Wilczynski, from the Division of Pathology at COH, will supervise the handling of the tissues obtained. Using standard methods, each biopsy will be divided longitudinally: half of the tissue will be placed in buffered formalin for routine histology and for immunohistochemical evaluation. Half of the tissue will be immediately frozen and sent to Dr. Doroshow's laboratory for DNA and protein extraction for future molecular studies. Specimens obtained at the time of surgical resection and future staging procedures will be processed under the same conditions.

In cases where tissue is not available at City of Hope, a request will be made for access to an outside paraffin block. In addition, a request will be made for a blood sample to further as correlate with tissue parameters.

Samples will be submitted to:

Clinical and Molecular Pharmacology Laboratory
Kaplan Clinical Research Building
City of Hope National Medical Center
1500 E. Duarte Rd.
Duarte, CA 91010

12.0 STATISTICAL CONSIDERATIONS

This is a Phase II study. The first objective of this trial is to obtain preliminary estimates of the anti-tumor efficacy of three cycles of a preoperative combination of platinum-taxane-5-FU-LV chemotherapy in patients with stage III-IV resectable squamous cell carcinoma (SCC) of the head and neck (assessment of response at day 55). Patients will be considered evaluable for response and evaluable for toxicity as outlined in **section 10.0**. The second objective of the trial is to determine the tolerability and feasibility of a multimodality approach including combined chemoradiation after initial neoadjuvant chemotherapy and surgery. A further purpose is to explore whether biochemical parameters of tumor tissue correlate with response and outcome.

A maximum of 30 patients will be accrued to the trial. Justification of the samples size is provided below.

12.1 STUDY DESIGN AND JUSTIFICATION OF SAMPLE SIZE

A two stage design will be used to evaluate the anti-tumor efficacy (CR or PR) of the induction chemotherapy. It is assumed that a true response rate less than 50% would not warrant further study of this regimen and a response rate of 70% would be considered promising for further studies in these patients. In the first stage, 20 evaluable patients will be entered. If nine or less responses are observed, the accrual will stop with the conclusion that the regimen is not promising for further study. If ten or more responses are observed in the first 20 patients, an additional 10 patients will be accrued during the second stage of the study. Nineteen or more responses out of 30 patients will be considered as evidence warranting further study of the regimen providing other factors, such as toxicity and survival, also appear favorable. If less than 19 responses out of 30 patients are observed, further study of the regimen would not be warranted. The probability of falsely declaring an agent with a 50% response probability as warranting further study is 0.10 (alpha) and the probability of correctly declaring an agent with a 70% response probability as warranting further study is 0.84 (power). With 30 patients the true probability of response can be estimated with a maximum standard error equal to 9%.

Statistics on biochemical studies performed on biopsy specimens are planned to be exploratory. Trends noted on this study will be used to guide studies in future trials.

Based on current projections of patients evaluated in the Department of Medical Oncology and the Division of Surgery, it is estimated that accrual of 30 patients should be completed within a maximum of two years.

12.2 ANALYSIS OF RESULTS

12.2.1 Analysis of Anti-tumor Activity

The response rate is defined as the percent of evaluable patients who experience a CR or PR. Binomial confidence intervals (95%) will be [91]. Duration of response will be estimated using the product-limit method of Kaplan and Meier [92].

12.2.2 Summary of Toxicities and Side Effects

All observed toxicities and side effects will be recorded on flow sheets and the data collection forms. Toxicity information including the type, severity, time of onset and time of resolution, and probable association with the drugs will be recorded. Tables will be constructed to summarize the observed incidence by severity and type of toxicity.

12.2.3 Analysis of Survival and Disease-Free Survival

Overall and disease-free survival will be estimated using the product limit method of Kaplan and Meier.

12.2.4 Analysis of functional outcome

Data collected using the FACT-H&N quality of life questionnaire and the PSS-HN performance status scale for head and neck patients will be used. These instruments have been validated and used at other institutions for assessing quality of life in patients with head and neck cancer. Data will be analyzed using the psychometric and correlation analysis recommended by the developers of the instrument.

13.0 REGRISTRATION GUIDELINES

To register a patient, the treating physician should contact the responsible Clinical Research Associate (CRA) in Biostatistics or the protocol nurse to determine whether the patient meets all of the eligibility criteria, and to confirm the a Patient Informed Consent has been signed. After verifying the eligibility and receiving the signed informed consent, the CRA will register the patient on study.

14.0 RECORDS TO BE KEPT AND DATA SUBMISSION SCHEDULE

14.1 Confidentiality of Records: The original data collection forms will be stored in secure cabinets in the Department of Biostatistics.

14.2 Patient Consent Form: At the time of registration, three signed and dated copies of the patient Informed Consent form with the Human Rights must be available (for patient, patient's medical chart and one for the Biostatistics Office).

14.3 Registration Eligibility Worksheet: At the time of registration, the information requested on the On-Study/Eligibility Form will be submitted to Data Manager.

14.4 Data Collection Forms and Submission Schedule

All data will be collected using COH Biostatistics Information Tracking System (BITS) data collection forms. Copies of the completed forms will be submitted to City of Hope Department of Biostatistics for data entry and stored in a secure location. The original data collection forms will reside at the originating institution in secure location.

14.4.1 The data manager will complete the Eligibility Checklist Worksheet at the time of registration:

14.4.2 Within two weeks of registration, the data manager will complete the On-Study Form (Form OS).

14.4.3 Within four weeks of completion of each course of treatment, the data manager must complete the following:

14.4.3.1 Treatment and Adverse Event Form
14.4.3.2 Supplemental Data Form (if applicable)
14.4.3.3 Flow Sheets (These are to be submitted along with each treatment form.)

14.4.4 Each time a patient is evaluated for response and/or new follow-up information is obtained the data manager will complete the Response/Off-Study/Follow- Up Form.

15.0 MINORITIES AND GENDER STATEMENT

Recruitment is open to all minorities and both genders. Our recruitment procedures have been developed to enroll patients who are representative of the respective target population. The ethnic and gender distribution of cancer patients in the COH catchment area is given in Table 2. These neoplasms are more frequent in the male population in a ratio 4:1, so we expect a disproportionate accrual of male subjects, consistent with this frequency.

Table 2
Gender and Minority Breakdowns for COH Catchment Area[1]

Gender	Caucasian	Hispanic	African American	Asian	Other	Total
Males	18%	16%	2.5%	5.0%	8.5%	50.0%
Females	18%	16%	2.5%	5.0%	8.5%	50.0%
Total	36%	32%	5.0%	10.0%	17.0%	100.0%

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

All patients will have signed an informed consent for participation in research activities in accord with all institutional, NCI and Federal regulations, and will have been given a copy of the Experimental Subject's Bill of Rights.

When the results of this study are reported in medical journals or meetings, identification of those taking part will be withheld. Medical records of patients will be maintained in strictest confidence according to current legal requirements. However, they will be made available for review, as required by the FDA or other authorized users such as the National Cancer Institute, under the guidelines established by the Federal Privacy Act. Record may also be made available for review to Rhône-Poulenc Rorer, the manufacturers of Taxotere.

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