Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2009 July 15; 74(4): 1040–1046. doi:10.1016/j.ijrobp.2008.09.053.

Long-Term Outcomes and Toxicity of Concurrent Paclitaxel and Radiation in the Treatment of Locally Advanced Head and Neck Cancer

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Abstract

Purpose—To report the long-term outcomes and toxicity of a regimen of infusional paclitaxel delivered concurrently with radiotherapy in patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN).

Methods—Between 1995 and 1999, 35 patients with non-metastatic stage III or IV SCCHN were treated with 3 cycles of paclitaxel as a 120-hour continuous infusion beginning days 1, 21, and 42 concurrent with radiation. The initial 16 patients received 105 mg/m²/cycle, and the subsequent 19 patients received 120 mg/m²/cycle. External beam radiation was delivered to 70.2–72 Gy in 5 fractions per week. Patients were followed to evaluate disease outcomes and the late toxicity of this regimen.

Results—Median follow-up for all patients is 56.5 months. The median survival was 56.5 months and the median time to local recurrence was not reached. Fifteen patients (43%) developed hypothyroidism. Eleven of the 33 patients who underwent percutaneous endoscopic gastrostomy tube (PEG) placement were PEG-dependent until death or last follow-up. Five patients (14%) required a tracheostomy until death, while 3 patients (9%) suffered from severe esophageal stricture.

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Conflict of Interest: The authors report no conflicts of interest.

This work was presented in part at the American Society of Therapeutic Radiology and Oncology in 2007.

All evaluated long term survivors exhibited salivary hypofunction. Fibrosis in the radiation field occurred in 24 patients (69%).

Conclusion—Concurrent chemo-radiation therapy with a 120-hour infusion of paclitaxel provides long-term local control and survival in patients with SCCHN. Xerostomia, hypothyroidism, esophageal and pharyngeal complications, and subcutaneous fibrosis were common long-term toxicities; however, the vast majority of toxicities were grade 1 or 2.

Keywords

paclitaxel; radiation; toxicity; head and neck

INTRODUCTION

Therapy for locally advanced squamous cell carcinoma of the head and neck (SCCHN) has the major goals of eradicating locoregional disease, treating distant micrometastases, preserving organ function, and minimizing toxicities. Because of the aggressive nature of SCCHN, and the consequences of local failure, intensive treatment regimens have become standard. Prospective trials evaluating concurrent platinum based chemoradiation regimens have demonstrated improved disease control rates compared to those obtained using radiotherapy alone, with the cost of increased high grade mucositis, weight loss, and hematologic toxicity.^{1–3}

In an attempt to improve outcomes and identify agents lacking the renal toxicity of cisplatin, a variety of radiosensitizing chemotherapies have been delivered concurrently with radiation therapy in patients with SCCHN. Paclitaxel was shown to be a radiosensitizer for human squamous cell cancer (SCC) in preclinical studies. This led to the evaluation of concurrent radiation and paclitaxel, either alone or with other chemotherapeutic agents for the treatment of SCCHN.^{4–12} Although the acute toxicities of these regimens are well-described, the long-term disease outcomes and late toxicities are not often reported due to the challenges of patient attrition and long-term data collection.

Combined modality regimens are now standard of care for cancers at a number of anatomic sites and it remains critically important to evaluate and report the long-term outcomes. Late toxicity from chemo-radiotherapy may take months to years to develop, requiring long-term follow-up to adequately describe late toxicities in survivors. As regimens become increasingly efficacious, the number of patients surviving with toxicities will increase.

In 1995, a prospective study of concurrent infusional paclitaxel and radiation therapy for SCCHN was initiated at the intramural program of the National Cancer Institute (NCI). The objectives of this study were to (1) assess the feasibility of concurrent treatment with radiation and a 120 hour infusion of paclitaxel; (2) assess speech and swallowing post-treatment; and (3) evaluate pretreatment predictors of outcome. The response rates, local control, and pharmacokinetic data obtained in this trial were reported previously.¹³ We now report the long-term disease control rates and late toxicity associated with this regimen.

PATIENTS AND METHODS

Patient Eligibility

All patients were enrolled on an Institutional Review Board approved protocol at the NCI and provided informed consent. Eligible patients had biopsy proven stage III or IV SCCHN without distant metastasis (American Joint Committee on Cancer, 4th edition), and were either ineligible for curative resection or refused surgery. Additional eligibility criteria included

ECOG performance status of less than or equal to 2, age of at least 18 years, absolute granulocyte count of at least 2,000/mm³ and platelet count of at least 100,000/mm³, serum bilirubin less than 2.0 mg/dL, AST less than four times the upper limit of normal, and serum creatinine less than 1.5 mg/dL.

Pretreatment Evaluation

Pretreatment evaluation included examination under anesthesia with biopsies to determine disease extent, chest radiography (CXR), computerized tomography (CT) and/or magnetic resonance imaging of the head and neck, CT scan of the chest, complete blood cell count (CBC) with differential, serum chemistries, coagulation panel, HIV antibody test in all patients, and bone scan if clinically indicated.

Protocol Therapy

Paclitaxel was initiated at least one hour before radiotherapy and delivered as a 120-hour continuous intravenous infusion by portable pump beginning on days 1, 21, and 42 concurrent with radiotherapy. The first 16 patients received 105 mg/m²/cycle of paclitaxel and 19 additional patients received 120 mg/m²/cycle.

Radiation therapy was delivered by a high energy linear accelerator in 1.8 to 2 Gy daily fractions delivered 5 days a week. The radiation treatment plan typically included opposed laterals and a low neck field with a single isocenter technique. Uninvolved nodal groups received 50 Gy. The primary tumor and involved lymph nodes received a total dose of 70 to 72 Gy with conformal boosting. Three patients with oral cavity primary tumors received a 30 to 35 Gy brachytherapy boost following 50.4 to 54 Gy delivered with external beam radiation. Patients with resectable regional nodal metastases staged as N2 or greater with histologically proven CR at the primary site were recommended to receive a neck dissection at least eight weeks after treatment.

Follow-up and Evaluation

Patients were followed weekly by a multidisciplinary team while receiving treatment; then monthly for the first year, bimonthly during the second year, and every 3 to 6 months thereafter until the current evaluation or death. Outside records were obtained from all patients receiving follow up care at outside facilities. Follow-up evaluation included an interval history, physical examination, CT of the primary tumor site, neck and chest, fiberoptic nasopharyngoscopy, CBC with differential, and serum chemistries. A thyroid panel was obtained yearly. Swallowing evaluations including modified barium fluoroscopy were completed prior to therapy and serially during follow-up. Dental evaluations were completed at baseline and as clinically indicated. Standard supportive care including counseling on smoking cessation was offered to all patients.

Prophylactic PEG tubes were inserted when deemed necessary to maintain patient nutrition during treatment. Patients with PEG tubes were encouraged to continue oral intake until swallowing became too painful, difficult, or unsafe, and were encouraged to resume oral intake when symptoms resolved and swallowing safety was confirmed. Structured swallowing therapy was not administered on a routine basis. A registered dietitian followed every patient.

Long-term Toxicity Assessments

Toxicity and adverse events were evaluated on all 35 patients enrolled to determine the long-term effects attributable to the regimen. The duration of PEG dependence and the need for tracheotomy were recorded. The incidence of major complications definitely, probably, or possibly related to protocol therapy such as fibrosis within the radiation field, skin changes,

xerostomia, hypothyroidism, osteoradionecrosis, development of fistulae, and new onset cerebrovascular disease were recorded. Patients experiencing toxicity related to the treatment regimen received standard of care interventions.

Ten of the 12 surviving patients who continue to receive care at our facility were comprehensively evaluated with our usual follow up assessments, salivary flow measurement, and swallowing evaluation. The highest toxicity that occurred during follow-up was scored using RTOG/EORTC Late Radiation Morbidity Scoring Scale¹⁴ for the following sites: skin, mucous membrane, salivary, spinal cord, brain, eye, larynx, thyroid, lung, bone, and joint. ECOG performance status during the most recent follow-up was recorded.

Oral Examination and Salivary Flow

Surviving patients underwent a structured oral examination and salivary flow assessment at the most recent follow-up. The oral exam focused on the oral and oropharyngeal mucosa and soft tissues, the salivary glands and their orifices. Saliva collections were obtained after subjects had refrained from eating, drinking and performing oral hygiene for a minimum of 2 hours. Salivary flow rates (microliters/min/gland) for whole saliva and all major glands were measured under unstimulated and stimulated conditions using methods previously described.^{15,16} Normal values for saliva production were defined as greater than the 10th percentile for healthy adults.¹⁶ Patients subjectively rated their salivary function with a validated five-item questionnaire employing a 10 cm visual analogue scale (VAS)¹⁸ at their latest follow-up.

Speech and Swallowing Function

At the most recent follow-up, the surviving patients underwent comprehensive evaluation by a speech language pathologist (SLP). Along with answering queries about changes or difficulty with swallowing or speech, patients completed the Performance Status Scale for Patients With Head and Neck Cancer.¹⁷ Modified barium swallow studies were performed to assess hyolaryngeal elevation, retention of contrast in the vallecula and pyriform sinuses, piecemeal deglutition, and repeated swallows for both liquid and puree textures with function scored on a four point Likert scale (1=normal; 2=mild deficit 3=moderate deficit; 4=severe). The SLP comparatively analyzed pre- therapy and latest swallowing assessments.

Statistical Methods

Survival, disease-free survival, time to local recurrence, and duration of PEG-tube dependence were calculated using Kaplan-Meier methodology. Survival was defined as the time from registration on study to death. Disease-free survival was defined from the end of treatment to recurrence or death. Locoregional control was defined as the time from the end of treatment to local recurrence, treating death as a censored outcome. The duration of PEG use was defined as the time from PEG insertion to PEG removal or death.

RESULTS

Patient Characteristics and Treatment

A full description of adherence to protocol therapy and toxicity of the regimen was reported at a time when two of the 35 patients had yet to reach an evaluable point of follow-up.¹³ For this reason, they were not included in the original report but are included in this analysis. The characteristics of the study population are summarized in Table 1. The median age of enrolled patients was 55 years (range=25 to 78). Most patients were male with a history of smoking and/or alcohol use. The majority of patients had lymph node involvement and T3 or T4 disease.

Median follow-up for the entire study population is 56.5 months. Median follow-up for surviving patients (n=12) is 117.1 months (range=88.0 to 138.3 months). No patients were lost

to follow-up with respect to survival and tumor control information. Twelve of the 35 patients were alive at the time of this evaluation.

Local-Regional Control and Survival

The median duration of local-regional control was not reached (Figure 1). The proportion of patients without a local recurrence at 100 months is 0.66 (95% CI: 0.51 to 0.83). The majority of local recurrences occurred within two years of treatment.

The median overall survival of the entire study population was 56.5 months (Figure 2A). The median disease-free survival of the study population is 54.4 months (Figure 2B). Fourteen of the 23 deceased participants died of the index cancer; 4 with local disease recurrence, 7 with local and distant disease, and 3 with distant disease only. Four patients who persisted in smoking tobacco died of a secondary aerodigestive malignancy. Eight patients with persistent disease at the completion of therapy died early (range of survival=3 to 39 months). Cardiovascular disease was the most common non-tumor cause of death (n=3).

Toxicity

The most common RTOG late toxicities involved irradiated skin, subcutaneous (SQ) tissues, and mucous membranes. The majority of skin and SQ toxicities were grades 1 or 2 (n=22), with only two grade 3, and no grade 4 toxicities observed. Twenty-four patients experienced grades 1 or 2 late mucosal toxicity. No patient developed grade 5 toxicity. Of the 6 patients who underwent neck dissection, one experienced grade 3 SQ fibrosis, 4 experienced grade 2, and one had none. There was no correlation between common toxicities and taxol dose.

Additional toxicities included hypothyroidism (n=15, 43%), osteoradionecrosis (n=5, 14%), cerebrovascular accident (n=4, 11%), and pharyngocutaneous fistula (n=3, 9%). Of the 5 patients who developed osteoradionecrosis, 2 were managed with surgical debridement and antibiotics while 2 required additional pentoxifylline, tocopherol and hyperbaric oxygen. Exposed mandibular bone in one additional patient resolved with conservative management. A patient treated for nasopharyngeal cancer developed exposed bone in the auditory canal and chronic rhinosinusitis requiring two sinus surgeries.

Medical management of toxicities included levothyroxine for hypothyroidism and pilocarpine or saliva substitutes for xerostomia. Fibrosis was managed medically or surgically: two patients with laryngeal and SQ fibrosis received pirfenidone on a clinical trial;¹⁸ four received pentoxifylline and tocopherol. Five patients (14%) required a tracheostomy until death, while 3 patients (9%) had esophageal strictures requiring a chronic gastrostomy tube or serial dilations.

Table 2 details toxicity scoring for the 10 long-term survivors. Skin, SQ, mucous membrane, salivary gland, and laryngeal toxicities were common. Patients with grades 3 or 4 SQ toxicity also experienced the worst pharyngeal, laryngeal, and esophageal toxicities. For example, a long-term survivor of T4N3 hypopharyngeal cancer, whose tumor-infiltrated epiglottis was absent post treatment, experienced chronic aspiration, late grade 2 upper esophageal stricture, and late grade 3 SQ and laryngeal fibrosis requiring tracheotomy.

Oral Examination and Salivary Flow

Four of the 10 survivors available for evaluation presented with partial papillary atrophy on the dorsal tongue with no other oral mucosal abnormalities. All of the 10 had abnormal unstimulated total salivary flow. Only one survivor had normal stimulated salivary flow in one parotid gland while another survivor had normal flow from the submandibular and sublingual glands (Table 3). Responses to each question on the VAS questionnaire were on average less

than 10, reflecting patients' subjective perceptions of substantial salivary hypofunction (Table 4).

Speech and Swallowing Function

Thirty-three of the 35 patients received PEG-tube placement prior to therapy with the median duration of use being 11.3 months (range=1.9 to 109 months). Eleven patients died with PEG tubes in place. The proportion of surviving patients requiring PEG was 22/33 at 6 months, 15/31 at 1 year, 8/26 at 2 years, and 1/19 at 3 years. The surviving patient that continued to require the PEG tube for nutrition at 3 years remained PEG dependent until last follow up at greater than 9 years. Fourteen of the 33 patients that were PEG dependent at 6 months died within 3 years of treatment, many with evidence of recurrent or persistent disease.

Eleven surviving patients completed the Performance Status Scale for Head and Neck Cancer with three reporting no functional limitations. For the eating in public subscale, 4 of 11 patients reported no restriction (mean=72.7; range=25 to 100). For the understandability of speech subscale, 6 of 11 patients reported their speech was always understandable (mean=86.4; range=50 to 100); no patient reported their speech was difficult to understand or that they required written communication. For the normalcy of diet subscale, 6 of 11 patients reported no restrictions (mean=85.4; range=5 to 100).

Eight of the 10 patients who returned for follow-up participated in a videofluoroscopic swallowing evaluation. One patient was excluded from participation due to chronic PEG dependence with a history of life threatening barium aspiration, while the other declined evaluation. The primary tumor locations for patients who underwent swallowing evaluations included the oropharynx (n=3), larynx (n=3), hypopharynx (n=1), and oral tongue (n=1).

Comparison of pre-treatment and latest swallowing evaluations revealed difficulties in hyolaryngeal elevation at the late time point in five of eight patients (oropharyngeal primary n=2, larynx primary n=2, oral tongue primary n=1); three demonstrated mild deficits and two demonstrated severe deficits. These five patients all demonstrated a deterioration of 1–2 severity levels with increased retention in the vallecula and pyriform sinuses when swallowing liquids and purees, requiring repeated swallows to clear the bolus. Despite the documented swallowing abnormalities, all 8 patients maintained swallowing function adequate to maintain oral nutrition. Statistical analyses were not performed due to small patient numbers.

DISCUSSION

Long term follow-up of survivors of chemoradiation regimens has revealed the impact of toxicity on quality of life (QOL)^{19,20} and function.^{21,22} We studied a regimen of infusional paclitaxel combined with conventionally fractionated radiation to test the hypothesis that this combination may provide a mechanism for improving disease outcomes. Paclitaxel has now been delivered concurrently with radiation for patients with head and neck cancer in a variety of schedules alone and in combination with other agents.^{23,24}

We found locoregional control and survival rates comparable to those obtained in other chemoradiotherapy regimens for SCCHN. Distant metastases or second primary tumors remained a major cause of failure for the study population, with most failures occurring early after treatment. Four patients died of a second malignancy, all of whom continued to smoke following treatment, highlighting the need for smoking cessation counseling throughout the treatment continuum.

The acute toxicity of paclitaxel containing regimens is significant, but the long-term disease control and late toxicities have been infrequently reported.²⁵ Previous reports of late outcomes

with taxane regimens have mainly focused on disease control and have rarely evaluated survivors' overall function and QOL. We aimed to evaluate not only long-term survival and local regional control, but also late toxicity and functional measures.

In regards to late toxicity, we found a significant number of patients treated with this regimen with skin and SQ fibrosis and hypothyroidism at late follow-up. The rate of hypothyroidism observed in this study is within the expected range as a sequelae of chemoradiotherapy.²⁶ Four of the ten survivors who returned for late follow-up exhibited grade 3 skin/SQ toxicity. Although the number of long-term survivors is not large enough to draw any firm conclusions, clustering of high-grade toxicities (> grade 3) of the skin, SQ tissues, larynx, and esophagus occurred in a subset of patients suggesting that these patients may have been more susceptible to late toxicity with this regimen for reasons yet undefined.

One of our objectives was to evaluate the effects of the treatment regimen on long-term swallowing function based on the high rate of acute grade 3 dysphagia. In the entire study population, PEG dependence was used to provide a surrogate of swallowing dysfunction. For long-term survivors, we evaluated late swallowing function with history, questionnaires, and fluoroscopic swallowing evaluations. While our study is limited by the lack of pre-treatment functional evaluations, it is strengthened by the longitudinal evaluation of swallowing function and other outcomes at our facility spanning years.

PEG dependence was present in two-thirds of surviving patients at 6 months, in almost half of surviving patients at one year, and in one-third of patients at 2 years. By three years, less than 10% of surviving patients were PEG dependent. The decrease in PEG dependence between 6 months and 3 years primarily resulted from death due to tumor and not resolution of dysphagia allowing PEG removal, suggesting that a significant component of PEG dependence resulted from local tumor effects in addition to regimen related toxicity. As a result PEG dependence may be a better correlate of local disease control in this population.

Both salivary hypofunction and pharyngeal/laryngeal dysmotility/fibrosis may have contributed to swallowing dysfunction in our population. Altered pharyngeal phase swallowing was seen in a significant portion of the patients and all surviving patients experienced late xerostomia by subjective and objective measures. Salivary gland sparing was not possible due to the use of a conventional three-field single isocenter technique and the need to include adjacent areas within the target volume. Newer techniques such as intensity modulated radiation therapy may improve these outcomes.

An interesting observation with relevance for toxicity scoring is that many patients reported persistent mild or no swallowing deficits with direct questioning; however, most were noted on fluoroscopic examination or on validated questionnaires to have functional impairment. Many of our patients reported that they had learned to cope with their functional deficits and did not consider them to have a major impact on quality of life. This attitude may alter the ability to score toxicity as questioning a patient is the gold standard for AE evaluation. These findings confirm the need to integrate functional measures and patient reported outcomes measures into toxicity assessment, as is the trend in the oncology community.²⁷

In summary, this concurrent infusional paclitaxel and radiation regimen proved feasible and provided reasonable rates of local and regional control. The toxicity observed included acute and chronic swallowing dysfunction and late fibrosis in the radiation treatment field. This regimen has been used as the backbone for investigational regimens employing targeted agents in this population at our institution (unpublished data).

Conclusion

Concurrent radiation and paclitaxel delivered as a 120 hour infusion provides durable local control and survival at rates similar to those of platinum containing regimens. Late toxicities from this regimen are typical for those seen in the head and neck cancer population receiving chemoradiation and include xerostomia, hypothyroidism, and swallowing dysfunction. Late skin effects and SQ fibrosis were pronounced with this regimen.

Acknowledgements

This research was supported by the Intramural Research Program of the NIH.

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Figure 1. Local Regional Control

A. The median time to local or regional recurrence was not reached. At 100 months the proportion of patients without a local recurrence is 0.66 (95% CI : 0.51 to 0.83). The dotted lines are point-wise 95% Confidence intervals for the Kaplan-Meier estimated curve.

Figure 2. Survival and Disease Free Survival

A. The median survival from study enrollment until death is 56.5 months. B. The median disease free survival from the end of all treatment to disease or death is 54.4 months. The dotted lines are point-wise 95% Confidence intervals for the Kaplan-Meier estimated curve.

Table 1

Patient and tumor characteristics

Sex	Male	28 (80%)
	Female	7 (20%)
Age of Enrollment	Range	25–78 years
	Median	55 years
Primary Tumor Site	Oral cavity	6 (17%)
	Oropharynx	11 (31%)
	Hypopharynx	9 (26%)
	Larynx	6 (17%)
	Other	3 (9%)
Primary Tumor Stage *	T1	0
	T2	1
	T3	12
	T4	22
Nodal Stage *	N0	9
	N1	3
	N2a	4
	N2b	2
	N2c	5
	N3	12

* AJCC 4th edition

RTOG late toxicity in ten surviving patients that returned for follow-up

Table 2

SITE	Grade of late Toxicity				
	0	1	2	3	4
Skin	1	6	1	2	0
Subcutaneous	2	3	1	4	0
Mucous Membrane	0	3	5	2	0
Salivary Gland	0	2	7	1	0
CNS	10	0	0	0	0
Eye	10	0	0	0	0
Larynx	3	3	1	3	0
Lung	4	6	0	0	0
Esophagus	3	5	1	1	0
Bone	8	0	1	0	1
Joint	6	2	2	0	0

Table3**Salivary gland flow**

Number and percentage of patients with normal stimulated and unstimulated salivary gland flow. R = right, L = left, SM/SL = submandibular sublingual.

Type of saliva collected	Number of patients (total n=10) with normal function (%)
Unstimulated whole	0 (0%)
Unstimulated R parotid	0 (0%)
Unstimulated L Parotid	0 (0%)
Unstimulated SM/SL	0 (0%)
Stimulated R parotid	1 (10%)
Stimulated L parotid	0 (0%)
Stimulated SM/SL	1 (10%)

Table 4

Subjective assessments of salivary function measured with a visual analog scale (0 – 10 cm) in 11 surviving patients

Question	Mean $\pm$ SEM
How dry does your mouth feel most of the time? (0 = “dry as a desert” and 10 = “not at all”)	3.6 $\pm$ 1.0
How comfortable does your mouth feel most of the time? (0 = “extremely uncomfortable” and 10 = “comfortable”)	4.7 $\pm$ 1.1
How difficult is it to swallow dry food without additional liquids? (0 = “very difficult” and 10 = “easy”)	1.9 $\pm$ 0.7
How difficult is it to swallow any food without additional liquids? (0 = “very difficult” and 10 = “easy”)	6.0 $\pm$ 0.9
How difficult is it for you to speak without drinking liquids? (0 = “very difficult” and 10 = “easy”)	4.6 $\pm$ 0.7