Published in final edited form as:

Head Neck. 2010 February ; 32(2): 221–228. doi:10.1002/hed.21179.

Docetaxel, cisplatin and fluorouracil induction chemotherapy followed by accelerated fractionation/concomitant boost radiation and concurrent cisplatin in patients with advanced squamous cell head and neck cancer: A Southwest Oncology Group phase II trial (S0216)

David J. Adelstein, M.D.¹, James Moon, M.S.², Ehab Hanna, M.D.³, P.G. Shankar Giri, M.D.⁴, Glenn M. Mills, M.D.⁵, Gregory T. Wolf, M.D.⁶, and Susan G. Urba, M.D.⁶

¹Cleveland Clinic Taussig Cancer Institute, Cleveland, OH

²Southwest Oncology Group Statistical Center, Seattle, WA

³M.D. Anderson Cancer Center, Houston, TX

⁴Baylor College of Medicine, Houston, TX

⁵Louisiana State University Health Science Center, Shreveport, LA

⁶University of Michigan Medical Center, Ann Arbor, MI

Abstract

Background—In an effort to optimize non-operative therapy in patients with locoregionally advanced head and neck squamous cell cancer, the Southwest Oncology Group conducted a phase II trial combining three-drug taxane-containing induction chemotherapy with accelerated fractionation/concomitant boost radiation and concomitant single-agent cisplatin.

Methods—Two induction courses using docetaxel (75 mg/m² day 1), cisplatin (100 mg/m² day 1), and fluorouracil (1000 mg/m²/day continuous intravenous infusion days 1-4) were given, 21 days apart. Stable or responding patients received definitive accelerated fractionation/concomitant boost radiation with concurrent cisplatin (100 mg/m²) on day 1 and 22 of radiation.

Results—There were 74 eligible and evaluable patients enrolled between 3/1/03 and 8/15/04; 52 (70%) had stage IV disease. At least one grade 3-4 toxicity was experienced by 63 (85%) during induction. A total of 61 patients completed induction and began concurrent chemoradiotherapy; 50 (68%) completed all planned treatment. At least one grade 3-4 toxicity was noted in 53 of the 58 patients (91%) evaluated for toxicity from concurrent chemoradiotherapy. Two patients died during induction, and 2 during chemoradiation. With a median follow-up of 36 (range: 14-50) months, the 2-year and 3-year overall survival estimates are 70% and 64%, with 2-year and 3-year progression-free survival estimates of 66% and 61% respectively.

Conclusions—Three drug induction chemotherapy followed by accelerated fractionation/concomitant boost radiation and concurrent cisplatin is toxic but feasible within a cooperative group.

Address for editorial correspondence: David J. Adelstein, M.D., Cleveland Clinic Taussig Institute, Department of Solid Tumor Oncology, Desk R-35, 9500 Euclid Ave., Cleveland, OH 44195, Phone: 216-444-9310; Fax: 216-444-9464, adelstd@ccf.org; Address for other inquiries: Group Chair's Office, Southwest Oncology Group, 24 Frank Lloyd Wright Dr., PO Box 483, Ann Arbor, MI 48106-0483, Phone: 734-998-7187; Fax: 734-998-7118, arlausk@med.umich.edu.

Presented, in part, at the 43rd Annual Meeting of the American Society of Clinical Oncology, June 1-5, 2007, Chicago, IL.

In this patient cohort with advanced head and neck squamous cell cancer, overall and progression-free survivals were encouraging, justifying further study of this approach.

Keywords

Chemotherapy; Radiation; Chemoradiotherapy; Induction; Concomitant

Introduction

Multiple studies of both single agent and combination chemotherapy administered with concomitant definitive radiation have now been reported and have demonstrated a clear survival and locoregional control benefit when compared to radiation therapy alone.¹ The best studied concurrent chemoradiotherapy regimen is radiation and single agent cisplatin which has been well-established as a standard of care in the management of patients with unresectable head and neck cancer,² nasopharyngeal cancer,³ and in post-operative patients with poor prognostic features.⁴⁻⁶ It has also proven to be the most successful strategy for non-operative larynx preservation.⁷ These conclusions have been confirmed and strengthened by the results of the large Meta-Analysis of Chemotherapy on Head and Neck Cancer (MACH-NC) which reported a 5-year 8% overall survival benefit ($P < 0.0001$) with concurrent chemoradiotherapy regimens when compared to radiotherapy alone.^{8,9}

Along with the improved survival and locoregional control that has resulted from these aggressive concomitant treatment schedules has been an apparent shift in the pattern of treatment failure. Historically, locoregional disease control has been the most important concern in disease management. Distant metastases were a relatively uncommon event. Recently, several single institution phase II trials of aggressive concurrent chemoradiotherapy and altered fractionation radiation have reported locoregional control rates in excess of 90%, with distant metastases representing the most frequent cause of treatment failure.^{10,11} This observation has suggested a possible role for additional systemic chemotherapy in an effort to improve overall treatment success by decreasing this incidence of distant recurrence.^{12,13} Given the difficulties associated with the administration of adjuvant chemotherapy after completion of definitive chemoradiotherapy, re-exploration of the use of induction therapy would seem reasonable.

Induction therapy is hardly a new concept in the treatment of head and neck cancer. A large number of phase III studies have been conducted comparing induction chemotherapy followed by definitive surgery and/or radiation to definitive management alone. Response rates as high as 90% using well established treatment regimens, have been reported.¹³ Although individual studies have failed to demonstrate any consistent improvement in locoregional control or survival, meta-analysis has been able to identify a small survival benefit (hazard ratio 0.88, 95% CI 0.79-0.97) for induction regimens containing fluorouracil and a platin, the most widely tested chemotherapy combination used in this setting.⁸ In several of these induction chemotherapy trials it was also noted that distant metastases were reduced in those patients who received the chemotherapy.¹⁴⁻¹⁶ Thus the argument can be made that the sequential use of aggressive multi-agent induction therapy followed by optimal definitive chemoradiotherapy might successfully improve both locoregional and distant control and further improve overall survival.^{13,17}

Recent work has produced evidence that the incorporation of a taxane, either paclitaxel or docetaxel, into the well tested fluorouracil and cisplatin combination can produce additional benefit. Hitt,¹⁸ Vermorken,¹⁹ and Posner²⁰ have reported results from three separate phase III studies comparing induction fluorouracil and cisplatin with induction fluorouracil, cisplatin and a taxane followed by definitive therapy. Improvements in overall response rate, complete

response rate, organ preservation, and survival were reported. Thus, a three drug combination of fluorouracil, cisplatin and either paclitaxel or docetaxel can be considered to be the most effective induction chemotherapy combination for this disease, and as such, would be the appropriate choice for this kind of sequential treatment regimen.

The optimal radiation therapy fractionation schedule has also been an unresolved question for many years. Results from a large Radiation Therapy Oncology Group trial (RTOG 9003) as well as other phase III studies appear to demonstrate a locoregional control benefit from altered fractionation treatment schedules when compared to conventional once-daily treatment.²¹ Meta-analysis has confirmed this conclusion.²² Although the best altered fractionation approach is as yet undefined, RTOG 9003 suggested a benefit from the accelerated fractionation/concomitant boost treatment schedule.

The hypothesis behind this phase II Southwest Oncology Group Trial was that optimal non-operative therapy should address both locoregional control and distant metastases and should therefore sequentially employ the most effective multi-modality components available to achieve each of these ends. An induction taxane, fluorouracil, and cisplatin combination chemotherapy regimen was chosen followed by concurrent chemoradiotherapy using single-agent cisplatin and altered fractionation radiation therapy with the accelerated fractionation concomitant boost schedule. We chose to give only two cycles of induction chemotherapy, rather than the three^{18,20} or four¹⁹ cycles used by previous investigators, because of concern about the potential for cumulative cisplatin neurotoxicity.

The objectives of this trial were to 1. Assess the overall survival in patients with advanced head and neck squamous cell cancer treated with this multimodality treatment regimen. 2. Estimate the clinical complete response rate after both induction therapy and concomitant chemoradiotherapy, and 3. Evaluate the toxicities of induction chemotherapy and of this entire multi-modality treatment approach.

Patients and Methods

Enrollment on this trial required the diagnosis of a previously untreated stage III or IV (M0) head and neck squamous cell cancer with an identified primary site excluding the lip, nasopharynx, paranasal sinus, or salivary gland. Patients were eligible if deemed appropriate for radiation therapy with curative intent. A Zubrod performance status of 0 or 1, adequate hematologic, renal, and hepatic function, and a chest radiograph that did not demonstrate any metastatic disease were also required. Pre-treatment evaluation by radiation oncology, medical oncology, head and neck surgery and dentistry, and documentation of disease extent by either computed tomography or magnetic resonance imaging were mandated. Positron emission tomography scans were not routinely requested for this study. An examination under anesthesia was required if deemed necessary by the head and neck surgeon. Those patients with pre-existing peripheral neuropathy were excluded. Similarly, patients with any prior malignancy were also ineligible for this trial, excluding those with adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, or adequately treated stage I or II cancer in remission for five years.

This study was conducted under the auspices of the Southwest Oncology Group and approved by the local Institutional Review Boards of all participating institutions. Written informed consent, in accordance with institutional and federal guidelines, was required from all patients before entering onto this protocol.

The treatment schema is depicted in Figure 1 and consisted of induction chemotherapy followed by concurrent chemoradiotherapy. Induction chemotherapy utilized a three drug combination of intravenous docetaxel 75mg/m² on day 1, cisplatin 100mg/m² on day 1, and

fluorouracil 1000mg/m²/day as a continuous 24 hour intravenous infusion for four days beginning on day 1. Two courses of this treatment regimen were given 21 days apart. Patients received 10 days of prophylactic ciprofloxacin after chemotherapy administration and standard anti-emetics, hydration and diuresis.

Three weeks after completion of the second cycle of induction chemotherapy, a response assessment was made using the same technique performed to document baseline disease. An examination under anesthesia was not required at this time. Patients with stable or responding tumor were then treated with concurrent chemoradiotherapy. Patients with progressive disease during or after induction chemotherapy were considered for surgical resection, if possible, with appropriate post-operative radiation therapy. If surgery was not possible in these patients, chemoradiotherapy was administered as per the protocol.

Radiotherapy consisted of the RTOG accelerated fractionation, concomitant boost schedule. Patients were given 54 Gy in 30 daily fractions, five days per week at 180 cGy per fraction to the total treatment volume. Concomitant with the last 12 treatments, a boost volume was treated to 18 Gy at a rate of 150 cGy per day. The total volume included the primary tumor, neck nodes and all areas at risk for microscopic disease. Boost volume included the primary tumor with a 1.5 cm margin, and any clinically enlarged lymph nodes. A minimum of six hours was required between the radiation administration to the total volume and to the boost volume on the last 12 concomitant treatment days. Only megavoltage equipment was allowed and the use of intensity modulated radiation therapy (IMRT) was not permitted on this study. Maximum dose to the spinal cord was 45 Gy. Two doses of concurrent cisplatin 100mg/m² were given on day 1 and day 22 of the radiation therapy along with standard hydration and anti-emetic therapy.

Between 8 and 12 weeks after completion of concomitant chemoradiotherapy, all patients underwent a comprehensive clinical and radiological assessment of response. The response assessment was again based on the same technique used at baseline. Those patients who achieved a complete response to concomitant chemoradiotherapy were followed for disease recurrence. Surgical resection was considered after concomitant chemoradiotherapy for those patients with histologically confirmed residual or recurrent disease at the primary site. Neck dissection was considered for all patients with clinical evidence of residual neck node disease after chemoradiotherapy and for patients with N2 or greater disease at presentation irrespective of their clinical response.

Statistical considerations

Based on the results reported from RTOG 9003²¹, it was assumed that this treatment approach would not warrant further study if the true 2-year overall survival probability was 45% or less. If, however, the true 2-year overall survival probability was at least 61% it would be of considerable interest in the treatment of advanced head and neck cancer. With 60 eligible patients enrolled over two years and an additional two years of follow-up, the power of a 1-sided log rank test to detect an increase in 2-year survival from 45% to 61% was 83% with an alpha of 0.05. An observed 2-year survival probability of 58% or greater would be considered sufficient evidence to justify further study of this treatment approach, provided other factors, such as progression-free survival and toxicity, also appeared favorable.

Response at the primary, in the neck, and overall were each documented separately after the completion of induction chemotherapy and again after the completion of concurrent chemoradiotherapy. Sixty patients would be sufficient to estimate each of these clinical complete response rates to within 13% (95% confidence intervals). Sixty patients would also be sufficient to estimate any toxicity rate to within 13% (95% confidence interval). Any toxicity with at least a 5% chance of occurring was likely to be seen at least once with 95% probability.

Overall survival and progression-free survival estimates were calculated using the method of Kaplan-Meier.²³ Survival times were calculated from the date of registration (no more than 5 working days prior to the initiation of induction chemotherapy) to the date of death due to any cause. Patients last known to be alive were censored at date of last contact. Progression-free survival times were calculated from the date of registration to date of first documentation of progression (as defined by RECIST), symptomatic deterioration (global deterioration of health status requiring discontinuation of treatment) or death due to any cause. Patients who had not been observed experiencing one of these events were censored at date of last contact.

Results

Between March 1, 2003 and August 15, 2004, 76 patients were entered on this clinical trial. Two of these patients were deemed ineligible due to the presence of metastatic disease at entry, leaving 74 eligible and evaluable patients. Forty-one of these patients were entered from seven member institutions of the Southwest Oncology Group. Thirty-five of these patients were entered from 15 different community affiliates of Southwest Oncology Group member institutions.

The patient characteristics are displayed in Table 1. Tumor and nodal disease extent based on the 6th edition of the American Joint Committee Cancer Staging Manual²⁴ is displayed in Table 2. Overall, 70% of patients had stage IV disease; 15% with stage IVB tumors.

Patient accounting is detailed in Figure 2. Of the 74 eligible patients who began induction chemotherapy, 68 (92%) completed it. Sixty-one of these 68 patients (or 82% of the original 74) began concurrent chemoradiotherapy, all but one within 3-4 weeks of induction chemotherapy as specified by the protocol. Fifty patients (or 68% of the original 74) finished both induction cycles and all planned radiation. Both concurrent chemotherapy doses could be given to 45 of these 50 patients. Reasons for premature treatment discontinuation are indicated in the Figure and were related to treatment toxicity in 14 patients. Five patients were taken off study because of progressive disease during therapy. No statistically significant differences in patient or tumor characteristics could be identified between the 50 patients who completed their treatment and the 24 who did not.

Table 3A details the acute toxicity experienced by the 74 patients who underwent induction therapy. Grade 3-4 neutropenia was experienced by 59% of patients, and required hospitalization for neutropenic fever in 18%. There were two toxic deaths, one due to febrile neutropenia and one from a cardiac cause. Overall, at least one grade 3 or greater toxicity occurred in 85% of patients. Table 3B details the acute toxicity during concurrent chemoradiotherapy in the 58 patients for whom data is available. Grade 3-4 mucositis was experienced by 48% of patients and grade 3-4 neutropenia by 31%. Hospitalization for neutropenic fever was required in 5% of patients. There were two additional toxic deaths during concurrent chemoradiotherapy, one from febrile neutropenia and one from a cardiac cause. Overall, 91% of patients experienced at least one grade 3 or greater toxicity during concurrent chemoradiotherapy.

After induction therapy an unconfirmed clinical complete response was identified at the primary site in 12 patients (16%), and in the neck in 8 of the 65 patients (12%) with lymph node involvement at baseline. An overall complete response was documented in 5 patients (7%). After concurrent chemoradiotherapy a primary site complete response was noted in 25 (34%) patients, a complete response in the neck was noted in 20 of 65 (31%) patients with nodal involvement at baseline, and an overall complete response was documented in 21 patients (28%).

With a median follow up of 36 (range 14-50) months, the two-year and three-year progression-free survival estimates are 66% (95% confidence interval 55-77%) and 61% (95% confidence interval: 50-73%) respectively (Figure 3A). The two-year and three-year overall survival estimates are 70% (95% confidence interval 60-81%) and 64% (95% confidence interval 52-75%) (Figure 3B).

Analysis of patterns of failure is displayed in Table 4 but is not terribly revealing. Disease progression or death occurred in 29 patients; 12 of whom died before disease progression could be documented. Second primary malignancies have been identified in four patients; two with lung cancer, and one each with kidney and colon cancer. All four patients were alive, without evidence of their head and neck cancer, at the time of this analysis.

Discussion

In this cohort of patients with locoregionally advanced squamous cell head and neck cancer, this aggressive sequential treatment schedule produced very encouraging two year progression-free and overall survival rates. It should be pointed out that a significant fraction of these patients were entered from community-based oncology affiliates of larger Southwest Oncology Group member institutions suggesting that this kind of intensive treatment can be successfully administered in the community.

At first glance, the overall complete response rates of only 7% after three-drug induction chemotherapy, and 28% after concurrent chemoradiotherapy seem disappointingly low, particularly in a patient population being treated with curative intent. These results must be viewed with caution however, given the constraints of the RECIST definition of a complete response. Furthermore, residual radiographic abnormalities of measurable lesions are frequently found after chemotherapy and radiation and often do not reflect residual cancer. Many of the patients who did not achieve a formal complete response remain alive and progression free, years after completing treatment. In patients with this disease, the progression-free and overall survivals are far better measures of treatment effect than the complete response rate.

It must be stressed, however, that this is a very toxic treatment regimen. More than 90% of patients experienced at least one grade 3 or greater toxicity, and many patients experienced multiple such toxicities. Four of the 74 patients (5%) entered on this trial died from treatment-related complications. Although this toxicity is in keeping with that observed in other similar multi-modality treatment trials, it clearly strains the limits of acceptability for any clinical treatment program. This toxicity and the potential for toxic death underscore how important it is that both treating physician and institution are familiar with this approach to head and neck cancer, and with the necessary supportive care.

The treatment could be completed, and therefore proved feasible in 68% of patients entered on the study. It is important, however, to examine this notion of feasibility within the context of other recent trials in this disease, particularly those conducted in a cooperative group setting. Feasibility has been reported from similar cooperative group studies of chemotherapy and radiation for squamous cell head and neck cancer. In studies using radiation and single agent cisplatin, even when that radiation is administered using an altered fractionation schedule, the feasibility has, in general, ranged from 83-85%.^{2,4,25} When treatment becomes more complex, however, utilizing adjuvant chemotherapy,³ concurrent multi-agent chemotherapy,² or sequential treatment regimens similar to this trial,²⁰ the feasibility drops to between 55-73%, results more in keeping with this study. Clearly there is a trade-off between the aggressiveness and complexity of a treatment regimen and the likelihood that it can be completed. The obvious

concern is that these more aggressive and more complex treatment regimens may ultimately not improve outcome if the treatment cannot be completed.

It should be noted that 30% of the patients in this trial had stage III tumors. These patients may well have been successfully treated with less intensive or less complicated regimens. It is of critical importance that we continue to attempt to identify selection factors that might better suggest which patients require the most aggressive therapies and which patients should be treated less intensively, or, alternatively, with surgery. The University of Michigan group has, for example, suggested that in larynx cancer, failure to respond to a single course of induction chemotherapy may identify a patient less likely to do well with chemoradiotherapy who might be better treated surgically.²⁶

This phase II trial reports the feasibility and toxicity of this kind of sequential treatment approach and suggests that there is considerable efficacy in this patient population. This kind of sequential treatment schedule, however, remains investigational. Although theoretically attractive, the value of induction chemotherapy prior to definitive concurrent chemoradiotherapy has not been firmly established. We await the results of the phase III randomized trials currently being conducted that address this question.¹³

Acknowledgments

This investigation was supported in part by the following PHS Cooperative Agreement grant numbers awarded by the National Cancer Institute, DHHS: CA32102, CA38926, CA-04919, CA-105409, CA-58658, CA-27057, CA-12644, CA-35431, CA-16385, CA-67575, CA-35178, CA-37981, CA-14028, CA-42777, CA-67663, CA-35128, CA-76447, CA-68183, CA-46441, CA-45560, CA-22433, CA-74647, CA-7481 and supported in part by Sanofi-Aventis US Inc

References

1. Salama JK, Seiwert TY, Vokes EE. Chemoradiotherapy for locally advanced head and neck cancer. *J Clin Oncol* 2007;25:4118–4126. [PubMed: 17827462]
2. Adelstein DJ, Li Y, Adams GL, et al. An Intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. *J Clin Oncol* 2003;21:92–98. [PubMed: 12506176]
3. Al-Sarraf M, LeBlanc M, Shankar Giri PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: Phase III randomized Intergroup study 0099. *J Clin Oncol* 1998;16:1310–1317. [PubMed: 9552031]
4. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med* 2004;350:1937–1944. [PubMed: 15128893]
5. Bernier J, Dornge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med* 2004;350:1945–1952. [PubMed: 15128894]
6. Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: A comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (#9501). *Head Neck* 2005;27:843–850. [PubMed: 16161069]
7. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med* 2003;349:2091–2098. [PubMed: 14645636]
8. Pignon JP, Bourhis J, Dornge C, et al. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: Three meta-analyses of updated individual data. *Lancet* 2000;355:949–955. [PubMed: 10768432]
9. Pignon JP, Le Maitre A, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update. *Int J Radiation Oncology Biol Phys* 2007;69(Suppl.):S112–S114.
10. Vokes EE, Kies MS, Haraf DJ, et al. Concomitant chemoradiotherapy as primary therapy for locoregionally advanced head and neck cancer. *J Clin Oncol* 2000;18:1652–1661. [PubMed: 10764425]

11. Adelstein DJ, Saxton JP, Lavertu P, et al. Maximizing local control and organ preservation in stage IV squamous cell head and neck cancer with hyperfractionated radiation and concurrent chemotherapy. *J Clin Oncol* 2002;20:1405–1410. [PubMed: 11870186]
12. Forastiere A. Is there a new role for induction chemotherapy in the treatment of head and neck cancer? *J Natl Cancer Inst* 2004;96:1647–1649. [PubMed: 15547172]
13. Adelstein DJ, LeBlanc M. Does induction chemotherapy have a role in the management of locoregionally advanced squamous cell head and neck cancer? *J Clin Oncol* 2006;24:2624–2628. [PubMed: 16763275]
14. Paccagnella A, Orlando A, Marchiori C, et al. Phase III trial of initial chemotherapy in stage III or IV head and neck cancers: A study by the Gruppo di Studio sui Tumori della Testa e del Collo. *J Natl Cancer Inst* 1994;86:265–272. [PubMed: 8158680]
15. Schuller DE, Metch B, Mattox D, et al. Preoperative chemotherapy in advanced resectable head and neck cancer: Final report of the Southwest Oncology Group. *Laryngoscope* 1988;98:1205–1211. [PubMed: 3054373]
16. The Department of Veterans Affairs Laryngeal Cancer Study Group. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. *N Engl J Med* 1991;324:1685–1690. [PubMed: 2034244]
17. Posner MR, Haddad RI, Wirth L, et al. Induction chemotherapy in locally advanced squamous cell cancer of the head and neck: Evolution of the sequential treatment approach. *Semin Oncol* 2004;31:778–785. [PubMed: 15599855]
18. Hitt R, Lopez-Pousa A, Martinez-Trufero J, et al. Phase III study comparing cisplatin plus fluorouracil to paclitaxel, cisplatin, and fluorouracil induction chemotherapy followed by chemoradiotherapy in locally advanced head and neck cancer. *J Clin Oncol* 2005;23:8636–8645. [PubMed: 16275937]
19. Vermorken JB, Remenar E, van Herpen C, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. *N Engl J Med* 2007;357:1695–1704. [PubMed: 17960012]
20. Posner MR, Hershock DM, Blajman CR, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. *N Engl J Med* 2007;357:1705–1715. [PubMed: 17960013]
21. Fu KK, Pajak TF, Trotti A, et al. A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: First report of RTOG 9003. *Int J Radiat Oncol Biol Phys* 2000;48:7–16. [PubMed: 10924966]
22. Bourhis J, Overgaard J, Audry H, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: A meta-analysis. *Lancet* 2006;368:843–854. [PubMed: 16950362]
23. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457–481.
24. Greene, FL.; Page, DL.; Fleming, ID., et al., editors. *AJCC Cancer Staging Manual*. 6th edition. Springer-Verlag; New York, NY: 2002.
25. Ang KK, Harris J, Garden AS, et al. Concomitant boost radiation plus concurrent cisplatin for advanced head and neck carcinomas: Radiation Therapy Oncology Group phase II trial 99-14. *J Clin Oncol* 2005;23:3008–3015. [PubMed: 15860857]
26. Urba S, Wolf G, Eisbruch A, et al. Single-cycle induction chemotherapy selects patients with advanced laryngeal cancer for combined chemoradiation: A new treatment paradigm. *J Clin Oncol* 2006;24:593–598. [PubMed: 16380415]

Figure 1.
S0216: Treatment schema

Figure 2.
S0216: Patient accounting

Figure 3.
Progression-free (A) and Overall (B) Survival.

Table 1

Patient characteristics (n=74)

		<u>No. (%)</u>
Gender:	Male	61 (82%)
	Female	13 (18%)
Race:	Caucasian	57 (77%)
	African-American	15 (20%)
	Other	2 (3%)
Performance status:	0	39 (53%)
	1	35 (47%)
Primary site:	Oral cavity	6 (8%)
	Oropharynx	35 (47%)
	Larynx	24 (32%)
	Hypopharynx	9 (12%)
Median age:	54 (range 37-75) years	

Table 2

Tumor (T) and nodal (N) distribution (n=74)

	T1	T2	T3	T4a	T4b	Total
N0			7	2	0	9
N1	2	4	9	3	0	18
N2a	0	2	4	0	0	6
N2b	1	3	7	5	1	17
N2c	2	4	2	6	3	17
N3	3	1	2	1	0	7
Total	8	14	31	17	4	74

Table 3Toxicity Grade ≥ 3

A. Induction chemotherapy (n=74)	
	No. (%)
Nausea, vomiting	19 (26%)
Anorexia	8 (11%)
Dehydration	11 (15%)
Renal dysfunction	1 (1%)
Mucositis	15 (20%)
Neutropenia	44 (59%)
with fever	13 (18%)
Thrombocytopenia	5 (7%)
Anemia	3 (4%)
Toxic death during induction	2 (3%)
Total with $\geq$ Grade 3 toxicity	63 (85%)
B. Concurrent chemoradiotherapy (N=58)	
Nausea, vomiting	14 (24%)
Anorexia	10 (17%)
Dehydration	13 (22%)
Renal dysfunction	5 (9%)
Mucositis	28 (48%)
Neutropenia	18 (31%)
with fever	3 (5%)
Thrombocytopenia	4 (7%)
Anemia	5 (9%)
Toxic death during chemoradiotherapy	2 (3%)
Total with $\geq$ Grade 3 toxicity	53 (91%)

Table 4

Patterns of Treatment Failure

	<u>No. patients</u>
Disease progression	17
Local failure	3
Regional failure	5
Local and regional failure	5
Distant metastases	4
Death without disease progression	12
Toxicity	4
Cardiac disease	2
Infection (unrelated)	2
Lung disease	1
Unknown (disease-free)	3