Published in final edited form as:

Head Neck. 2010 May ; 32(5): 599–606. doi:10.1002/hed.21224.

Comprehensive IMRT Plus Weekly Cisplatin for Advanced Head and Neck Cancer: The University of Wisconsin Experience

Anne M. Traynor¹, Gregory M. Richards², Gregory K. Hartig³, Deepak Khuntia², James F. Cleary¹, Peggy A. Wiederholt², Søren M. Bentzen², and Paul M. Harari²

¹ Section of Hematology and Medical Oncology, University of Wisconsin Paul P. Carbone Comprehensive Cancer Center, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin

² Department of Human Oncology, University of Wisconsin Paul P. Carbone Comprehensive Cancer Center, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin

³ Department of Surgery – Otolaryngology, University of Wisconsin Paul P. Carbone Comprehensive Cancer Center, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin

Abstract

Background—We retrospectively examined the treatment efficacy and toxicity profile of intensity modulated radiotherapy (IMRT) plus concurrent weekly cisplatin chemotherapy in patients with locoregionally advanced squamous cell carcinoma of the head and neck (HNSCC).

Methods—57 patients with stage III or IV HNSCC were treated with IMRT and concurrent weekly cisplatin (dosed at 30 mg/m²) between 11/01 and 5/07. The median prescription dose to the gross tumor volume was 70 Gy (using 2.0–2.2 Gy daily fractions).

Results—In-field tumor control at 2 years was 89.1%, loco-regional control was 85.5%, and overall survival was 86.9%. The median radiation dose delivered was 70 Gy. The mean dose intensity of cisplatin administered was 25.7 mg/m²/week.

Conclusions—Comprehensive head and neck IMRT to 70 Gy delivered with weekly cisplatin chemotherapy (30 mg/m²) is feasible and generally well tolerated.

Keywords

head and neck cancer; combined modality therapy; intensity modulated radiotherapy; cisplatin; chemotherapy

INTRODUCTION

Concurrent chemoradiation has become a standard of care in the definitive treatment of patients with locoregionally advanced squamous cell carcinoma of the head and neck (HNSCC), with the expectation of improving locoregional tumor control and overall

Correspondence/Request for reprints: Anne M. Traynor MD, University of Wisconsin Paul P. Carbone Comprehensive Cancer Center, K6/568 CSC, #5669, 600 Highland Avenue, Madison, Wisconsin, 53792. Phone: 608.262.5092. Fax: 608.265.8133. amt@medicine.wisc.edu.

Presented in part at the 47th Annual Meeting of the American Society for Therapeutic Radiation and Oncology (ASTRO), October 16-20, 2005 in Denver, CO.

survival (1–7). Two recent meta-analyses indicate that concurrent chemoradiation yields an 8% absolute increase in overall survival at 5 years compared to radiotherapy alone (hazard ratio 0.81, $p < 0.0001$) (8,9). Acute toxicities, namely hematologic, nausea and vomiting, and renal dysfunction, are increased by concurrent chemotherapy (4–7), although not all reports confirm this (2,3,10). The incidence of late toxicities has been reported less thoroughly. Even though randomized chemoradiation trials have not reported a striking increase in chronic complications (3,6,7,10), subsequent symptom-specific studies have detected significant rates of swallowing dysfunction, aspiration, and sensorineural hearing loss in patients treated with concurrent dual modality therapy (11).

The updated MACH-NC meta-analysis of concurrent chemoradiation in HNSCC confirms that either single agent chemotherapy, utilizing a platin compound, or combination chemotherapy improves efficacy outcomes (8). Cisplatin can be administered with concurrent radiation for HNSCC as monotherapy or as part of combination chemotherapy, as well as in a variety of dose and administration schedules. The most common schedules for cisplatin monotherapy in HNSCC include 100 mg/m² every 21 days for 2 or 3 cycles or weekly, at doses ranging from 30 to 80 mg/m²/week (12–15). Cisplatin can also be given daily at 6 mg/m² (4,16), or at 100 mg/m² spread over several days (2,10).

Cisplatin dosed at 100 mg/m² every 21 days in combination with concurrent comprehensive head and neck radiation is associated with significant acute toxicities, including azotemia and dehydration. Due to the acute toxicities associated with cisplatin administered at 100 mg/m², treatment compliance reported from past studies ranges from 74% to 85%; this translates roughly into a weekly dose intensity of administered cisplatin that approaches 24 mg/m² (5–7). In addition, two recent investigations of the weekly cisplatin schedule at a planned dose of 40 mg/m² in combination with concomitant boost radiation for locally advanced HNSCC yielded actual dose intensities of 25.3 and 29 mg/m²/week due to toxicity (12,13). Between 1982 and 1987, the Head and Neck Intergroup conducted a phase III trial comparing radiation therapy alone with radiation and concurrent weekly cisplatin at 20 mg/m². Although the response rate was higher in patients receiving cisplatin, the median survival was only 13 months and was not statistically distinct between the two groups. As such, this concurrent weekly cisplatin chemoradiation regimen, dosed at 20 mg/m², was not adopted as standard of care (5,17).

Intensity-modulated radiotherapy (IMRT) offers the potential to deliver highly conformal dose-intense radiation to target regions, while sparing adjacent critical non-malignant tissue. The improved shaping of high dose distributions with IMRT potentially mitigates treatment-related toxicities. For example, the use of IMRT has been associated with increased preservation of parotid salivary flow, although improvements in patient reported xerostomia have been modest (18–21). The use of IMRT in HNSCC is increasing, and early reports confirm its ability to secure excellent local and regional disease control (22–26). Caution must be exercised, however, when comparing outcome data using IMRT with historical controls due to biases inherent in such comparisons, including an imbalance in the duration of follow-up (27).

We herein report a retrospective review of the University of Wisconsin experience of 57 patients with stage III or IV HNSCC treated with comprehensive IMRT to 70 Gy with concurrent cisplatin chemotherapy at a planned weekly dose of 30 mg/m². Our purpose in doing so is to examine the outcome efficacy and tolerability of this regimen in the setting of IMRT, which aims to limit toxicity to normal tissues while maintaining tumor control.

MATERIALS AND METHODS

Patient and staging evaluation

Our series consisted of 57 consecutive patients with stage III or IV HNSCC who were treated with comprehensive IMRT and concurrent weekly cisplatin chemotherapy between November 2001 and May 2007 at the University of Wisconsin. All patients signed an institutional written consent for their clinical information to be entered in an institutional review board-approved comprehensive computerized database for research purposes. All patients also signed an institutional written consent for treatment. All patients were treated with definitive chemoradiation with curative intent; there were no cases in this report of post-operative adjuvant radiotherapy. Patients were selected for IMRT treatment according to the institutional practice pattern, including the use of IMRT in patients with unilateral neck metastases in whom it was desired to spare the contralateral parotid gland, in patients with bilateral neck disease well below the parotid glands, and in patients with superior pharyngeal disease where it was desired to spare the central nervous system and optic structures. In addition, patients had to be medically eligible for concurrent weekly cisplatin chemotherapy.

Pre-treatment evaluation included a comprehensive history and physical exam, including either direct or fiberoptic visualization of the oral cavity, oropharynx, nasopharynx, hypopharynx and larynx, a thorough dental evaluation with extractions as required, a high quality CT of the head and neck with intravenous contrast, a head and neck MRI for selected patients, radiographic imaging of the chest (x-ray or CT), complete blood counts, and positron emission tomography (PET) scans for selected patients. Patients were staged according to the 1998 American Joint Committee on Cancer staging classification.

Chemotherapy

Chemotherapy was administered under the care of two medical oncologists (AMT and JFC). Patients received intravenous cisplatin dosed at 30 mg/m² weekly throughout the duration of their radiation. They were evaluated weekly by the nursing staff and typically seen every other week by the treating physician. Treatment included 1 liter of normal saline pre-hydration, followed by dexamethasone and a 5HT₃ antagonist anti-emetic. In addition, promethazine and lorazepam anti-emetics were added as needed. Cisplatin was mixed in 1 liter of normal saline and infused over 1 hour. A complete blood count and a serum creatinine were obtained with each weekly treatment. Cisplatin was administered only if the absolute neutrophil count $\geq$ 1500/uL and platelets $\geq$ 100,000/uL. The cisplatin dose was reduced to 20 mg/m² in the event of grade 2 nephrotoxicity, nausea, or vomiting. Cisplatin was held if the above hematologic parameters were not met, or with any grade 3 non-hematologic toxicity occurring during the preceding week.

Radiation Treatment Planning and Delivery

Radiation therapy was administered under the care of two radiation oncologists (PMH and DK). All patients underwent a treatment planning CT scan with intravenous contrast. Patients were fitted with a customized thermoplastic mask to immobilize the head and neck. Patients treated with linear accelerator-based 7-field IMRT were fitted with a custom maxillofacial bite tray system embedded with optical fiducial markers to facilitate highly precise localization and delivery of radiation treatments as previously described (28). Patients treated with helical tomotherapy IMRT underwent daily megavoltage computed tomography treatment scans for position verification and adjustment as needed prior to each radiation treatment delivery.

CT-based treatment planning was performed using the Pinnacle³™ treatment planning system (Pinnacle, Philips Medical Systems, Andover, MA) for 7-field IMRT linac plans. For tomotherapy plans, all volumes were contoured in Pinnacle and then transferred into the TomoTherapy Hi Art treatment planning system (TomoTherapy, Madison, WI). All areas of gross disease, including the primary disease and all positive lymph nodes, were contoured as GTV. The clinical target volume (CTV), defined as areas at risk for microscopic disease outside of the GTV, was also contoured. The high-risk CTV (CTV₁) typically encompassed the GTV plus a margin and the regional lymphatics at highest risk for subclinical disease. In patients with unilateral nodal disease a lower-risk CTV (CTV₂) encompassed the contralateral neck lymphatics. An additional lower-risk CTV (CTV₃) was created for the low-neck and supraclavicular lymph nodes for patients treated with helical tomotherapy; the low-neck and supraclavicular lymph nodes were commonly treated with an AP field for patients receiving linac based IMRT.

Planning target volumes (PTV) were generated to account for set-up error and organ motion. Normal anatomic structures, including the parotid glands, spinal cord, brainstem, optic nerves, and lens of the eye were contoured. Typical dose constraints to normal structures included: contralateral parotid ≤ 22.5 Gy to 30% volume, spinal cord max dose ≤ 35 Gy, brainstem max dose ≤ 50 Gy, lens max dose ≤ 2 Gy. Dose-volume histograms were generated and reviewed by the treating physician for each case to ensure individual optimization of constraints. IMRT treatments were delivered using either continuous optical guidance during treatment (7-field IMRT) or daily megavoltage CT scanning prior to treatment (helical tomotherapy) to enhance set up precision. Treatments were delivered using 6 MV photons. Linac-based IMRT was performed using a step-and-shoot technique.

Surgery

No definitive surgery, aside from diagnostic biopsy, was performed on the primary site of disease in any patient within this report. One patient underwent a modified radical neck dissection prior to chemoradiation as part of his diagnostic evaluation at an outside institution. Thirty patients underwent a post-chemoradiation neck dissection. Surgical salvage was considered for patients who experienced local or regional disease recurrence.

Follow-up

Post-treatment evaluations were performed every 1–2 months for the first 6 months, then every 2–3 months for the first two years, biannually for years three through five, and annually thereafter. Clinical examination included indirect mirror exam or fiberoptic nasopharyngoscopy visualizing all head and neck mucosal surfaces, and careful evaluation of the cervical and supraclavicular nodal areas. Radiographic follow-up commonly included a CT scan within the first six months post-treatment, followed by annual chest x-rays. Additional imaging studies were ordered as clinically indicated. The median follow-up for all patients is 27 months.

Statistical methods

All statistical analyses, including Kaplan-Meier curves, were performed using MedCalc v9.3.2.0 (MedCalc Software, Belgium). Clinical data were collected retrospectively from reviews of patients' charts performed by 3 clinical research associates and reviewed by the first and second authors. These data were then entered into our computerized database for research purposes, and analyzed by the first and second authors for this report. Toxicities were evaluated and scored using the NCI CTCAE version 3.0.

RESULTS

Patient Characteristics

Fifty-seven consecutive patients with stage III or IV head and neck cancer were treated with comprehensive IMRT to 70 Gy and concurrent weekly cisplatin at a dose of 30 mg/m².

Table 1 lists demographic and clinical characteristics of the treatment cohort.

Treatment Details and Compliance

The overall treatment compliance for patients in this study was quite good (Table 2). The median radiation dose delivered to the high risk PTV was 70.0 Gy with dose per fraction ranging from 2.0 – 2.2 Gy (median 2.1 Gy). The median doses to PTV₆₀, PTV₅₄, and PTV₅₀ were 60 Gy, 54 Gy, and 50 Gy respectively. The median overall treatment time for IMRT was 45 days (range: 41–56 days). No patient required a treatment break greater than 2 consecutive days. One patient had a total of 4 days of treatment breaks, each occurring on single, nonconsecutive days due to transportation difficulties. All patients received the prescribed radiation dose.

The median number of chemotherapy cycles delivered per patient was 5.5, thereby yielding a mean dose intensity of 25.7 mg/m²/week (range: 5–34.3 mg/m²). Of 369 planned cisplatin doses, 311 (84.2%) were delivered and 15.7% were omitted. One patient received one dose beyond that initially planned. Nine (3%) of the 311 delivered planned doses were administered at an adjusted dose of 20 mg/m² due to treatment related toxicity. Thirty-three patients (57.9%) received at least 6 cisplatin cycles; only 5 patients (8.7%) received fewer than 4 cycles. Nine patients (15.8%) received a seventh dose and 1 patient received an eighth dose due to the timing and duration of their IMRT course.

Post-chemoradiation neck dissections were performed in 30 patients: 27 selective neck dissections and 3 modified radical neck dissections. One patient underwent a modified radical neck dissection prior to chemoradiation treatment as part of his diagnostic evaluation at an outside institution. Salvage surgical resections were performed in 3 patients. One patient who had a local hypopharynx recurrence underwent total laryngopharyngectomy with bilateral selective neck dissection. A second patient was found to have persistent local disease involving the tongue base at the time of his planned post-treatment neck dissection; therefore, he underwent a composite resection of the tongue base, right oropharynx, and right soft palate, as well as a right modified radical neck dissection. Finally, a third patient with left neck recurrence underwent a revision neck dissection consisting of a modified radical neck dissection with extension to remove infraclavicular lymph nodes.

Treatment Outcome

With a median follow up of 27 months, there have been 7 local failures, 2 of which manifested as incomplete tumor regression (persistence) following primary treatment. Two of these 7 local failures (29%) occurred in patients with nasopharyngeal primaries. Five patients experienced recurrent disease in the neck. With a median follow up of 27 months, the Kaplan-Meier estimate as depicted in Table 3 shows in-field tumor control at 2 years of 89.1%, regional control in the neck of 90.6%, locoregional control of 85.5% (Figure 1), freedom from distant metastases of 88.9%, and overall survival of 86.9% at 2 years (Figure 2).

Toxicities

Twelve patients (21%) were hospitalized during treatment: 9 for nausea, vomiting, and dehydration, 1 for febrile neutropenia, 1 for candidal esophagitis, and 1 for a feeding tube complication. Twenty-four patients (42%) experienced grade 2, and 29 (51%) developed

grade 3, mucositis. All cases of mucositis fully resolved by 12 weeks. Two patients (4%) experienced grade 3 hyperkalemia; there were no occurrences of nephrotoxicity. Table 4 lists the acute treatment-related toxicities that occurred in at least 5% of patients. The median weight loss during treatment was 8.2 kg (range: 0.9–18.2 kg), with 24 patients (42%) losing greater than 10% of their pretreatment body weight. Chronic treatment-related toxicities are listed in Table 5. Of the 34 patients in whom a percutaneous gastrostomy tube was placed prior to treatment, 7 (20%) retained the tube at 6 months post-treatment, and 1 patient (3%) had it at 12 months.

DISCUSSION

Our experience suggests that comprehensive head and neck IMRT to 70 Gy delivered with concurrent weekly cisplatin chemotherapy at 30 mg/m² is feasible and generally well tolerated in patients with locoregionally advanced HNSCC.

Given the substantial limitations of comparing retrospective single institution data with prospective multi-institution phase III results, our 2 year efficacy outcomes are encouraging, compared to those from chemoradiation trials incorporating standard (non-IMRT) radiotherapy (2–5,10). In addition, we identified lower rates of acute toxicity compared to those seen in phase III trials using non-IMRT treatment. This finding is consistent with reports of modest improvements in xerostomia and quality of life from prospective studies comparing IMRT treatment with standard radiotherapy (18,21). The limitations of comparing our single institution retrospective data with prospective results are significant, and include variances in toxicity evaluation and reporting, patient population, duration of follow-up, and treatment intensity (27). Nonetheless, it is possible to speculate that the conformal dose distributions seen with IMRT may lower rates of acute toxicity to skin, mucosa and salivary glands when combined with weekly cisplatin. However, expertise in head and neck IMRT target design, normal tissue dose constraints, patient immobilization and treatment delivery are all critical elements that can influence outcome.

Comparisons of our experience with that from larger single institution retrospective series of chemoradiation using IMRT are limited by differences in treatment populations and the variable types of chemotherapy used (although most incorporated cisplatin at 100 mg/m² on a 21 day schedule) (22–26,29,30). Nonetheless, our efficacy results at 2 years are comparable with these series, and our toxicity analyses suggest reduced rates of acute adverse events. For example, in a series of 41 patients undergoing IMRT with concurrent chemotherapy (usually cisplatin at 100 mg/m² every 21 days) for stage III and IV oropharyngeal cancer, Lee et al. describe rates of at least grade 3 acute toxicities (mucositis, skin reactions, hematologic, nausea and vomiting) that exceed those in our series (23). Treatment-related xerostomia was the primary chronic toxicity consistently reported in these series, with grade 2 xerostomia ranging from 3% to 32% (23,29,30). Forty-six percent of our patients experienced grade 2 xerostomia. This higher rate of xerostomia may be due to treatment, or possibly to more consistent rates of follow-up evaluations occurring in our cohort of predominantly local patients, who have high rates of adherence to follow-up. Regarding rates of other chronic treatment-related toxicities, low grade laryngeal edema was observed in 26% of patients in this series, particularly in patients in whom the primary tumor resided within or directly contiguous to the larynx. For oropharynx patients (69% in this series), we employed conformal IMRT techniques that specifically limited dose to the larynx in an effort to minimize laryngeal edema and dysfunction. Forty percent of patients in this report manifested some degree of soft tissue thickening and low grade fibrosis in the neck. This was seen more commonly in patients who underwent a neck dissection. However, no advanced cases of cervical fibrosis or necrosis have been observed. Two patients developed grade 3 esophageal stricture requiring endoscopic dilatation. Aside from these 2

patients, there were no additional cases of grade 3 or greater chronic toxicities identified in this series to date. However, our median follow up is only 27 months and these late complications can certainly emerge with longer term follow up.

Our retrospective review of the use of IMRT and weekly cisplatin chemotherapy in locally advanced HNSCC is limited by several variables. Patient selection factors may well have contributed to favorable results in this report, given that patients had disease distributions amenable to IMRT treatment, therefore likely favoring a population with a lower percentage of bulky bilateral disease. In addition, our patients were predicted to tolerate concurrent chemotherapy. Nonetheless, we hope our findings serve to identify the need for randomized comparisons of weekly cisplatin in IMRT-based prospective trials in the treatment of HNSCC.

Any consideration of our efficacy outcomes must also take into account that 69% of patients in this report had oropharyngeal primaries. Although HPV status was not evaluated in these patients, HPV is common in this group and is a favorable prognostic factor that may have contributed to the favorable treatment results for this group as a whole (31). In addition, while only 6 (11%) of our 57 patients had a nasopharyngeal primary site of disease, they accounted for 2 (29%) of the local recurrences (both patients had T₄N₂ disease). Therefore, we elected to keep these 6 patients in our efficacy analyses since they did not favorably influence the overall outcome.

In conclusion, our retrospective, single institution review suggests that comprehensive head and neck IMRT to 70 Gy delivered with concurrent weekly cisplatin chemotherapy at 30 mg/m² is feasible and generally well tolerated in patients with locoregionally advanced HNSCC. It has been over 2 decades since the Head and Neck Intergroup conducted a phase III trial comparing radiation therapy alone with radiotherapy and concurrent weekly cisplatin at 20 mg/m² (17). Interval advances in supportive care, patient characteristics (more HPV positive patients), and in radiation technologies suggest that a prospective, randomized comparison of weekly cisplatin versus every 3 week high dose treatment, administered concurrently with IMRT, would be helpful in order to provide the most rigorous evaluation of this treatment regimen.

Acknowledgments

The authors thank the patients who participated in this study. The authors also extend special thanks to Wendy Walker, Kerrin Palazzi-Churas, and Heather Geye for data extraction and organization for this project, as well as Melinda Baker for assistance in preparation of the manuscript.

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. Brizel DM, Albers ME, Fisher SR, et al. Hyperfractionated Irradiation With or Without Concurrent Chemotherapy For Locally Advanced Head and Neck Cancer. *N Engl J Med* 1998;338:1798–1804. [PubMed: 9632446]
3. Denis F, Garaud P, Bardet E, et al. Final Results of the 94–01 French Head and Neck Oncology and Radiotherapy Group Randomized Trial Comparing Radiotherapy Alone with Concomitant Radiochemotherapy in Advanced-State Oropharynx Carcinoma. *J Clin Oncol* 2004;22:69–76. [PubMed: 14657228]
4. Jeremic B, Shibamoto Y, Milicic B, et al. Hyperfractionated Radiation Therapy With or Without Concurrent Low-Dose Daily Cisplatin in Locally Advanced Squamous Cell Carcinoma of the Head and Neck: A Prospective Randomized Trial. *J Clin Oncol* 2000;18:1458–1464. [PubMed: 10735893]

5. Adelstein D, Li Y, Adams G, 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]
6. 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]
7. 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]
8. Pignon JP, Le Maitre A, Bourhis J. Meta-Analyses of Chemotherapy in Head and Neck Cancer (MACH-NC): An Update. *Int J Radiat Oncol Biol Phys* 2007;69:S112–S114. [PubMed: 17848275]
9. Budach W, Hehr T, Belka C, Dietz K. A Meta-Analysis of Hyperfractionated and Accelerated Radiotherapy and Combined Chemotherapy and Radiotherapy Regimens in Unresected Locally Advanced Squamous Cell Carcinoma of the Head and Neck. *BMC Cancer* 2006;6:1–12. [PubMed: 16390557]
10. Huguenin P, Beer KT, Allal A, et al. Concomitant Cisplatin Significantly Improves Locoregional Control in Advanced Head and Neck Cancers Treated with Hyperfractionated Radiotherapy. *J Clin Oncol* 2004;22:4665–4673. [PubMed: 15534360]
11. Bentzen SM, Trotti A. Evaluation of early and late toxicities in chemoradiation trials. *J Clin Oncol* 2007;25:4096–4103. [PubMed: 17827459]
12. Medina JA, Rueda A, de Pasos AS, et al. A Phase II Study of Concomitant Boost Radiation Plus Concurrent Weekly Cisplatin for Locally Advanced Unresectable Head and Neck Carcinomas. *Radiother Oncol* 2006;79:34–38. [PubMed: 16626826]
13. Beckmann GK, Hoppe F, Pfreundner L, Flentje MP. Hyperfractionated Accelerated Radiotherapy in Combination With Weekly Cisplatin For Locally Advanced Head and Neck Cancer. *Head Neck* 2005;27:36–43. [PubMed: 15459918]
14. Kumar S, Pandey M, Lal P, Rastogi N, Maria Das KJ, Dimri K. Concomitant Boost Radiotherapy With Concurrent Weekly Cisplatin in Advanced Head and Neck Cancers: A Phase II Trial. *Radiother Oncol* 2005;75:186–192. [PubMed: 16086908]
15. Planting AS, de Mulder PH, de Graeff A, Verweij J. Phase II Study of Weekly High-Dose Cisplatin for Six Cycles in Patients With Locally Advanced Squamous Cell Carcinoma of the Head and Neck. *Eur J Cancer* 1997;33:61–65. [PubMed: 9071901]
16. Hoebbers FJ, Pameijer FA, de Bois J, et al. Prognostic value of primary tumor volume after concurrent chemoradiation with daily low-dose cisplatin for advanced stage head and neck carcinoma. *Head Neck* 2008;30:1216–1223. [PubMed: 18642295]
17. Haselow, RE.; Warshaw, MG.; Oken, MM., et al. Radiation Alone Versus Radiation with Weekly Low Dose Cis-Platinum in Unresectable Cancer of the Head and Neck. In: Fee, WE., Jr; Goepfert, H.; Johns, ME., et al., editors. *Head and Neck Cancer*. Vol. 11. Philadelphia, PF: Lippincott; 1990. p. 279-281.
18. Kam MK, Leung SF, Zee B, et al. Prospective Randomized Study of Intensity-Modulated Radiotherapy on Salivary Gland Function in Early-Stage Nasopharyngeal Carcinoma Patients. *J Clin Oncol* 2007;25:4873–4879. [PubMed: 17971582]
19. Eisbruch A. Reducing Xerostomia by IMRT: What May, and May Not, Be Achieved. *J Clin Oncol* 2007;25:4863–4864. [PubMed: 17971579]
20. Graff P, Lapeyre M, Desandes E, et al. Impact of Intensity-Modulated Radiotherapy on Health-Related Quality of Life for Head and Neck Cancer Patients: Matched-Pair Comparison With Conventional Radiotherapy. *Int J Radiat Oncol Biol* 2007;67:1309–1317.
21. Pow EHN, Kwong DLW, McMillan AS, et al. Xerostomia and Quality of Life After Intensity-Modulated Radiotherapy Vs. Conventional Radiotherapy for Early-Stage Nasopharyngeal Carcinoma: Initial Report on a Randomized Controlled Clinical Trial. *Int J Radiat Oncol Biol* 2006;66:981–991.
22. Lee N, Xia P, Fischbein NJ, Akazawa P, Akazawa C, Quivey JM. Intensity-Modulated Radiation Therapy for Head and Neck Cancer: The UCSF Experience Focusing on Target Volume Delineation. *Int J Radiat Oncol Biol Phys* 2003;57:49–60. [PubMed: 12909215]

23. Lee N, de Arruda FF, Puri DR, et al. A Comparison of Intensity-Modulated Radiation Therapy and Concomitant Boost Radiotherapy in the Setting of Concurrent Chemotherapy for Locally Advanced Oropharyngeal Carcinoma. *Int J Radiat Oncol Biol Phys* 2006;66:966–974. [PubMed: 17145527]
24. Chao KSC, Ozyigit G, Tran BN, Cengiz M, Dempsey JF, Low DA. Patterns of Failure in Patients Receiving Definitive and Postoperative IMRT for Head and Neck Cancer. *Int J Radiat Oncol Biol Phys* 2003;55:312–321. [PubMed: 12527043]
25. Yao M, Dornfeld KJ, Buatti JM, et al. Intensity-Modulated Radiation Treatment for Head and Neck Squamous Cell Carcinoma-The University of Iowa Experience. *Int J Radiat Oncol Biol Phys* 2005;63:410–421. [PubMed: 16168834]
26. Daly ME, YeeYie L, Pawlicki T, et al. Evaluation of Patterns of Failure and Subjective Salivary Function in Patients Treated With Intensity Modulated Radiotherapy for Head and Neck Squamous Cell Carcinoma. *Head Neck* 2007;29:211–219. [PubMed: 17111429]
27. Hodge CW, Bentzen SM, Wong G, et al. Are we influencing outcome in oropharynx cancer with intensity-modulated radiotherapy? An inter-era comparison. *Int J Radiat Oncol Biol Phys* 2007;69:1032–1041.
28. Hong TS, Tome WA, Chappell RJ, et al. The impact of daily setup variations on head-and-neck intensity-modulated radiation therapy. *Int J Radiat Oncol Biol Phys* 2005;61:779–788. [PubMed: 15708257]
29. Wolden SL, Chen WC, Pfister DG, Kraus DH, Berry SL, Zelefsky MJ. Intensity-Modulated Radiation Therapy (IMRT) for Nasopharynx Cancer: Update of the Memorial Sloan-Kettering Experience. *Int J Radiat Oncol Biol Phys* 2006;64:57–62.
30. Lee NY, O'Meara W, Chan K, et al. Concurrent and Intensity-Modulated Radiotherapy for Locoregionally Advanced Laryngeal and Hypopharyngeal Cancers. *Int J Radiat Oncol Biol Phys* 2007;69:459–468. [PubMed: 17493769]
31. Klussmann JP, Mooren JJ, Lehnen M, et al. Genetic Signatures of HPV-related and Unrelated Oropharyngeal Carcinoma and Their Prognostic Implications. *Clin Cancer Res* 2009;15:1779–1786. [PubMed: 19223504]

Figure 1.
Kaplan Meier estimate of locoregional control at 2 years, with 95% confidence intervals.

Figure 2.
Kaplan Meier estimate of overall survival at 2 years, with 95% confidence intervals.

Table 1

Patient Characteristics, N=57

	N	(%)
Median Age (range) in years	55 (36–77)	
Gender		
Male	50	88
Female	7	12
Karnofsky Performance Status		
≥ 90	52	91
70–90	5	9
Tumor Site		
Nasopharynx	6	11
Oropharynx		
Base of Tongue	21	37
Tonsil	18	32
Larynx		
Glottis	1	2
Epiglottis	2	4
Hypopharynx		
Pyriform Sinus	1	2
Posterior Wall	1	2
Maxillary Sinus	2	4
H&N Unknown Primary	4	7
Other: Parotid	1	2
T Stage		
T0, Tx	4	7
T1	11	19
T2	20	35
T3	11	19
T4	11	19
N Stage		
N0	9	16
N1	4	7
N2a	3	5
N2b	30	53
N2c	4	7
N3	4	7
Overall Stage		
I	0	0
II	0	0

	N	(%)
III	6	11
IV	51	89

Table 2

Treatment Compliance

RADIOTHERAPY	
Median IMRT dose	70 Gy
Median dose/Fraction	2.1 Gy/Fraction (2.0–2.2)
Median treatment time	45 days (range 31–56)
Patients requiring treatment break ≥ 2 days	0
Patients who received prescribed IMRT dose	100%
CHEMOTHERAPY	
Weekly dose intensity	Cisplatin 30 mg/m ² /week
Weekly dose intensity	25.7 mg/m ² (5–34.3)
% of chemotherapy doses administered	84.2%
% of patients receiving at least 6 cycles	57.9%
% of patients receiving at least 4 cycles	91.3%

Table 3

Efficacy Outcomes at 2 Years

Median follow-up	27 months
Local tumor control	89.1% $\pm$ 4.2%
Regional neck control	90.6% $\pm$ 4.0%
Loco-regional control	85.5% $\pm$ 4.8%
Freedom from distant metastases	88.9% $\pm$ 4.8%
Overall Survival	86.9% $\pm$ 5.0%

Table 4

Acute Toxicity Occurring in at Least 5% of Patients

PERCENT OF PATIENTS (N = 57)				
Toxicity		Grade 2	Grade 3	Grade 4
Blood		50	14	4
	Leukopenia	25	7	2
	Neutropenia	11	5	2
	Anemia	14	2	0
Mucositis		42	51	0
Nausea and Vomiting		48	23	0
Anorexia		30	23	0
Dehydration		39	14	0
Fatigue		40	5	0

Table 5Chronic Toxicities: $\geq$ Grade 1

PERCENT OF PATIENTS (N = 57)			
Toxicity	Grade 1	Grade 2	Total
Xerostomia	48	46	94
Laryngeal edema	14	12	26
Neck fibrosis	10	30	40
Esophageal stricture	0	4	4
Osteoradionecrosis	0*	0*	0*

* 2 patients did develop small areas of exposed mandibular bone that healed with conservative management