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"Rare Head and Neck Tumors"

Retrospective Study

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Simultaneous Fractionated Cisplatin and Radiation Therapy in the Treatment of Advanced Operable Stage III and IV Squamous Cell Carcinoma of the Larynx

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ABSTRACT

Background: Evaluation of simultaneous fractionated cisplatin and radiation therapy in treatment of advanced operable Stage III and IV squamous cell carcinoma (SCCHN) of the larynx.
Methods: 36 patients with SCCHN of the larynx underwent chemoradiotherapy of two types. Treatment group (CTRT, n=21) received pre-operative cisplatin, 20 mg/M^2 intravenous fusion for 4 consecutive days during weeks 1, 4, and 7 of radiotherapy. CTRT was compared to a control group (CONTROL, n=15) for clinical course, clinical (CCR) and histologic (HCR) complete response of tumor, recurrence, and survival.
Results: CTRT experienced less high grade toxicity (14% *vs*. 41%, $p<0.05$). CCR and HCR were 67% CTRT and 13% CONTROL ($p<0.05$). More CTRT patients are either alive or died disease-free compared to CONTROL (74% *vs*. 30%, $p<0.05$). Cancer recurred in 26% CTRT compared *vs*. 80% CONTROL ($p<0.01$).
Conclusions: In Stage III and IV laryngeal cancer, CTRT achieves higher CCR, HCR, and survival, lower recurrence, and reduced toxicity compared to CONTROL. CTRT should be considered for initial therapy of advanced operable SCCHN of the larynx.

KEY WORDS: Larynx; Carcinoma; Cisplatin; Squamous; Chemoradiotherapy.

ABBREVIATIONS: SCCHN: Squamous Cell Carcinoma; CCR: Clinical Complete Response; HCR: Histologic Complete Response.

INTRODUCTION

Squamous cell carcinomas of the head and neck (SCCHN) make up approximately 3% of all cancer cases in the United States.[1] SCCHN are most common in the larynx, pharynx, and oral cavity. These cancers are curable, but most patients present with locally advanced Stage III or IV disease, when treatment is complex and multidisciplinary.[2] Traditional therapies for SCCHN involve radical surgery and/or post-operative radiotherapy.[3] More recently, multi-modality therapies involving chemotherapy, radiation therapy and surgery have become useful for im-

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proving locoregional control and organ preservation, although survival is still poor.[2] However, the roles of each technique are not yet standardized.

While no single treatment regimen has been defined as most effective in managing SCCHN, several studies have identified certain multi-modality combinations that produce greater success in terms of organ preservation, survival, locoregional control, and toxicity to treatment. Common multi-modality treatments include, among others, docetaxel plus cisplatin followed by fluorouracil infusion for 4 days every 3 weeks; high-dose cisplatin given on days 1, 22, and 43 of radiotherapy; daily low-dose concomitant cisplatin; and a weekly combination of carboplatin and taxol.[2,4-6] Thus, it is difficult to determine which treatment is best for the patients.

In recent years, investigators have found that concurrent chemotherapy and radiation prior to surgery show synergistic effects in tumor treatment, improving overall disease control and survival.[3] Organ preservation, which is highly valued by most patients, is also improved due to less post-chemoradiotherapy surgery. Several pilot investigations have suggested that low-dose, fractionated cisplatin administered simultaneously with concomitant high-dose radiotherapy may be effective in curing cancer while preserving head and neck function.[7-9] The objective of the present study was to evaluate patients with advanced operable Stage III and IV SCCHN who were treated up front with 20 mg/M^2 IV cisplatin given on 4 consecutive days every 3 weeks during high-dose irradiation therapy (CTRT), reserving radical surgery for residual disease post-CTRT.

METHODS

With the approval of the Inspira Health Network Institutional Review Board, medical records of 21 patients with Stage III and IV squamous cell carcinoma of the larynx who received CTRT were reviewed retrospectively and compared with an unselected CONTROL group of 15 patients who underwent other treatment regimens, receiving at least part of their care at the Inspira Health Network, Vineland, NJ, USA. CTRT chemotherapy consisted of cisplatin, 20 mg/M^2 as a continuous intravenous infusion daily for 4 consecutive days during weeks 1, 4, and 7 of radiotherapy. The Southern New Jersey Head and Neck Treatment Network is a group of medical oncologists and radiation oncologists who have treated patients of the senior author (GJS) with CTRT, based on the successes of previously published pilot trials of this regimen and their positive clinical experiences with it.[7-9] Conversely, CONTROL chemotherapy consisted of several regimens: cisplatin, 75 mg/M^2 intravenously on days 1, 22, and 43 of radiotherapy (2 patients); carboplatin, 100 mg/M^2 and taxol, 45 mg/M^2 once per week during radiotherapy (10 patients); or CTRT regimen following surgery (3 patients), each of which were administered at the discretion of each patient's physicians (Table 1). Although, this was not a true homogeneous control cohort, the authors compared these outcomes with CTRT as a reflection of community practice standard of care. Both the CTRT and CONTROL groups were treated between June 1992 and October 2011. Determination of whether patients received CTRT or CONTROL regimens was at the discretion of the treating physician. Due to the retrospective nature of the study, the definition of need for surgery was not controlled. However, all operations at all institutions were performed by trained head and neck surgical oncologists.

Radiation therapy in the earlier portion of the study consisted of single daily fractionation with 6 MV photons and 3D treatment planning. This was then followed by a boost, in which patients were treated with a hyperfractionated (two fractions/day) regimen, with concurrent chemotherapy. In 2006, patients were treated with normal fractionation to a higher total dose, between 70-74 Gy. In the latter part of the treatment study, the patients were treated with a field-within-a-field technique utilizing head and neck IMRT. PTVs were treated between 70-74 Gy. Most treatment regimens were delivered with 6 MV photons with either customized blocks or multi-leaf collimator generated blocks. This progression reflected technological advances in radiation therapy hardware and software, and in clinical application. The constant factor in this investigation was the regimen of fractionated cisplatin that facilitated the same high response rates of primary and lymphogenous SCCHNN of

Table 1: Clinical Characteristics of 36 Patients Who Received Treatment for Stage III and IV Squamous Cell Carcinoma of the Larynx Between June 1992 and October 2011.

Patient Characteristics	CTRT (SD) n=21	CONTROL (SD) n=15	*p* value
Age	56.9 (10.8)	62.2 (9.7)	0.457
Sex (male/female)	19/2	8/7	<0.05
Race (white/other)	15/6	10/5	0.759
Alcohol use	17	7	<0.05
Tobacco use	20	14	0.805
Tumor stage (III/IV)	4/17	5/10	0.329
Tumor grade (I/II/III)	6/6/5	1/7/4	0.739
Treatment Regimens			
Cisplatin 20	21	0	
Cisplatin 75	0	2	
Carboplatin/Taxol	0	10	
CTRT following surgery	0	3	

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the larynx for all of the radiation regimens described, without variation by the modest changes in radiation application. Verification was performed using port films and later changed to stereoscopic imaging followed by cone beam computed tomography (CT).

The study variables included age, sex, race, vital status, alcohol use, tobacco use, tumor site, tumor grade, clinical stage, surgery, chemoradiotherapy regimen, clinical response, post-CTRT biopsy result, recurrence, and toxicity to treatment. Clinical stage was determined according to the classification of the American Joint Committee on Cancer Staging.[18] Post-chemoradiotherapy biopsy determined whether or not patients whose cancers regressed completely clinically (Clinical Complete Response – CCR) had achieved either a histologically complete response (HCR) or still had residual tumor. Patients with residual disease were recommended for curative surgery. Toxicity to treatment was determined according to the NCI Common Terminology Criteria for Adverse Events.[19]

Statistical analysis was performed using the chi-squared equation for categorical variables. Analysis of variance (ANOVA) was used to compare age. Overall survival and disease-specific survival were analyzed by the Kaplan-Meier logarithmic rank test. Median follow-up was 20 months, with a range of 1 to 128 months. The level of significance was set as $p<0.05$ (SAS/STAT(R) 9.22 User's Guide).

RESULTS

Patient demographics and tumor characteristics for CTRT and CONTROL are displayed in Table 1. No significant differences between CTRT and CONTROL regarding age, race, tobacco use, tumor site, clinical stage, or tumor grade was found. Male: female ratio and alcohol abuse were higher in CTRT. In the CTRT group, 8 patients (38%) had N0 disease, compared to 9 (60%) patients in the CONTROL group. The remaining patients had nodal disease: CTRT had 3 (14%) N1 tumors, 7 (33%) N2 tumors, and 3 (14%) N3 tumors; CONTROL had 1 (7%) N1 tumors, 5 (33%) N2 tumors, and 0 N3 tumors.

Toxicity from chemotherapy and radiation is displayed in Table 2. High toxicity (Grade III-V) included dehydration, bleeding, hypoxemia, and/or hospitalization. Grade III toxicity occurred in 3 (14%) CTRT patients and in 4 (33%) CONTROL patients. CONTROL also saw 1 (8%) patient with grade V toxicity. Thus, overall high-grade toxicity was higher in CONTROL ($p<0.05$). Grade 0 toxicity was noted in 6 (29%) CTRT patients, while no CONTROL patients had Grade 0 toxicity ($p<0.05$). No difference was noted for low-grade toxicity (Grade I-II).

Response to pre-operative treatment is listed in Table 3. A clinically complete response was seen in 67% (14/21) of CTRT patients *vs*. 13% (2/15) in CONTROL ($p<0.01$). Post-chemoradiotherapy biopsy revealed a histologically complete

Table 2: Toxicity to Chemotherapy/Radiation Therapy (Determined by the NCI Common Terminology Criteria for Adverse Events)

Toxicity grade	CTRT n=91	CONTROL n=12*	Total	*p* value
No toxicity				
0	6 (29%)	0	6	<0.05
Low grade toxicity				
1	4 (19%)	2 (17%)	6	0.079
2	8 (38%)	5 (42%)	13	
High grade toxicity				
3	3 (14%)	4 (33%)	7	
4	0	0	0	<0.05
5	0	1 (8%)	1	
Total	21	12	33	

*Note: 3 CONTROL patients were unavailable for toxicity determination.

Table 3: Response to Treatment.

Treatment response	CTRT n=21	CONTROL n=15	*p* value
Clinical response			
Clinically complete Response	14 (67%)	2 (13%)	<0.01
Partial response	5 (24%)	7 (47%)	
Biopsy result			
Histologically complete response	14 (67%)	2 (13%)	<0.01
Residual disease	5 (24%)	7 (47%)	
Type of surgery			
Radical surgery	5 (24%)	4 (27%)	
Neck dissection only	3 (14%)	1 (7%)	0.915
No surgery	13 (62%)	10 (67%)	

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response in 14 out of 21 CTRT patients (67%), and in only 2 out of 15 CONTROL patients (13%) ($p<0.01$).

Curative cancer surgery results are seen in Table 3. CTRT and CONTROL did not differ in the number of patients who required curative surgery (8/21 *vs*. 5/15; $p=0.769$). Three CTRT patients had neck dissection only, and 1 CONTROL patient had neck dissection only. Thus, organ preservation was achieved in 76% of CTRT, and in 73% of CONTROL ($p=0.845$).

Cancer recurrence and survival data are tabulated in Table 4. Median follow-up time was 20 months, with a range from 1 to 128 months. Recurrences developed in 5 out of 19 (26%) CTRT, and in 7 out of 10 (70%) CONTROL ($p<0.01$). The CONTROL group had no distant metastases, whereas CTRT had 40% distant metastases ($p=0.05$). Regarding vital status, 3 CTRT patients are still alive and 11 died disease-free, *versus* only 2 CONTROL patients alive and 1 who died disease free (74% *vs*. 30%, $p<0.05$).

Overall survival is depicted in Figure 1. For CTRT, overall survival was 54.55% for CTRT versus 20.00% in CONTROL patients ($p=0.66$). Figure 2 displays the disease-free Kaplan-Meier survival for patients with squamous cell carcinoma of the larynx. With a median follow-up of 20 months, disease-free survival was 72.73% for CTRT and 46.67% in the CONTROL group ($p=0.62$).

DISCUSSION

The results of this study that the simultaneous administration of low-dose fractionated cisplatin chemotherapy and high-dose irradiation (CTRT) may be an effective primary treatment for patients with advanced operable Stage III and IV SCCHN of the larynx. High grade toxicity to treatment was significantly lower with CTRT compared with CONTROL ($p<0.05$). Additionally, no toxicity at all was reported by a significant portion of the CTRT treatment group ($p<0.05$). Post-treatment biopsy revealed more histologic complete responses in CTRT compared to CONTROL ($p<0.01$). No differences were found regarding curative surgery; however, there was a trend toward better organ preservation in CTRT patients. CTRT had fewer recurrences *versus* CONTROL ($p<0.01$). Furthermore, patients who underwent CTRT remained disease-free and expired of other causes more frequently than did the CONTROL group ($p<0.05$). Lastly, the Kaplan-Meier survival curves indicate a trend toward better disease-free survival among CTRT patients. Our review of the literature indicates that these treatment effects of CTRT on Stage III and IV SCCHN compared with other cancer protocols have not been reported previously and are significant findings of this study.

Table 4: Overall Survival, End-of-Life Status, and Recurrence Data.

Patient Characteristics	CTRT n=19	CONTROL n=10	*p* value
Vital status			
Died with disease	5 (26%)	7 (70%)	<0.05
Alive/Died disease-free	3/11 (74%)	2/1 (30%)	
Recurrence			
Local/Distant	5 (26%)/0	4/4 (80%)	<0.01
None	14 (74%)	2 (20%)	

Figure 1: Overall Survival Probability for Patients who Underwent CTRT Treatment (Dashed Line) *Versus* CONTROL Treatment (Straight Line). Kaplan-Meier Survival Curves Display the Number of Months after Treatment was Completed. Survival was 54.55% CTRT *Versus* 20.00% CONTROL. Log Rank Test $p=0.66$.

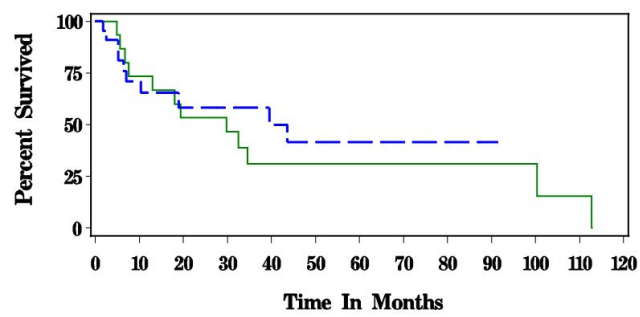
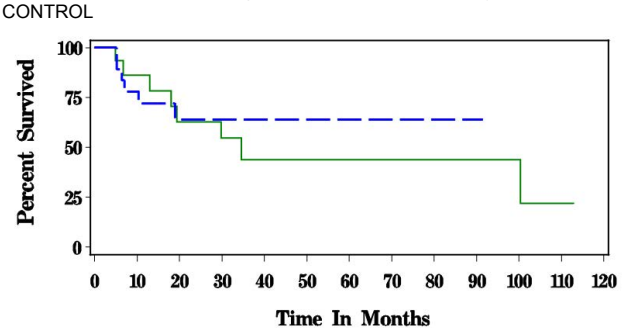


Figure 2: Disease-free Survival Probability for Patients who Underwent CTRT Treatment (Dashed Line) *Versus* CONTROL Treatment (Straight Line). Kaplan-Meier Survival Curves Display the Number of Months after Treatment was Completed. Survival was 72.73% for CTRT *Versus* 46.67% for CONTROL. Log Rank test $p=0.62$.



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While clinical adverse events were common among CONTROL patients who underwent other treatment regimens for SCCHN, CTRT toxicity was minimal. Only 14% of CTRT patients suffered grade 3 toxicity, and no patients experienced grade 4 or 5 toxicity. In addition, 29% of CTRT patients completed treatment with no toxicity at all. Previously published clinical trials of concomitant chemoradiotherapy almost universally have reported increased toxicities due to the potency of the drug combinations.[3] In their evaluation of high-dose 100 mg/M^2 cisplatin on days 2, 16, and 30 of radiotherapy plus 5-FU, Bourhis and colleagues observed grade 3 and higher toxicity in 83% of their patients.[10] Unfortunately, these very high rates of toxicity also are common among studies of high-dose cisplatin given every three weeks.[4,11] Alternatively, a study with weekly low-dose cisplatin (30 mg/M^2) during radiotherapy still observed grade 3 to 4 mucositis in 35.2%.[12] In contrast, an early pilot investigation of the regimen that became CTRT (20 mg/M^2 cisplatin on day 1 to 4 and 22 to 25 of radiotherapy) reported only 27% grade 3 toxicity and no grade 4 or 5 toxicity, similar to the present results.[9] The results of the present study suggest that chemoradiotherapy protocols in treating SCCHN need to move in the direction of low-dose chemotherapy in fractionated administrations so as to improve patient tolerance of treatment without compromising therapeutic effectiveness.

In addition to significantly reducing toxicity, the CTRT regimen analyzed in this study was highly effective against the cancer. The CCR was 67%, and the negative biopsy HCR of the primary tumor site was 67% as well (p<0.01). These outcomes are favorable to those of Paccagnella et al, who treated SCCHN patients with either two cycles of cisplatin 20 mg/M^2, days 1-4, plus 5-FU 800 mg/M^2/day during weeks 1 and 6 of radiotherapy or docetaxel 75 mg/M^{2}plus cisplatin 80 mg/ M^2, day 1, and 5-FU 800 mg/ M^2/day every 3 weeks,[13] achieving rates of 21.2% and 50%, respectively. Another study tested 100 mg/ M^2 cisplatin every 3 weeks plus 5-FU versus the cisplatin regimen plus UFT 200 mg/M^2/d and vinorelbine 25 mg/M^2 every 21 days.[14] Again, CCR rates were only 36% and 31%, respectively. Conversely, a pilot CTRT study by Goodman et al in which patients were treated with cisplatin 20 mg/M^2 on days 1 to 4 and 18 to 20 during radiotherapy had an HCR rate of 54%.[15] Consequently, CTRT has better rates of complete response and negative biopsy than other studies regarding the treatment of SCCHN.

Radical curative head and neck surgery, with its high complication rates and resulting cosmetic and functional morbidities, has been a major concern in the treatment of SCCHN, particularly in elderly patients. Organ preservation is extremely important to the patient; however, organ function is often compromised when surgery is used to treat SCCHN. Additionally, patients with SCCHN frequently present with unresectable, advanced stage disease at diagnosis.[16] Thus, CTRT was specifically designed to eliminate surgery from the treatment regimen whenever possible. Patients who responded to this treatment not only had a negative biopsy, but also were able to retain full function of their upper aerodigestive tract. Furthermore, only 24% of patients who underwent CTRT required composite resections with complex reconstruction; thus organ preservation was achieved in 76% of CTRT patients. Conversely, a comparison study of two treatments, cisplatin 100 mg/M^2 on day 1, 23, and 45 during radiotherapy *versus* cisplatin 40 mg/M^2 weekly for 6 weeks, found that 44.6% and 37% of patients, respectively, required post-treatment surgery.[17] Thus, although CTRT did not differ from CONTROL regarding overall surgery, CTRT was more successful in reducing the need for post-treatment surgery when compared to other regimens.

The Kaplan-Meier curve for overall survival indicates a disease-free survival for 73% of CTRT patients compared to 47% of CONTROL patients at three years post-treatment. Cohen's review of eight prominent chemoradiotherapy studies for advanced stage SSCHN found survival percentages ranging from 17.5% to 55% for three year follow-up periods.[3] In the present investigation, this trend toward increased long-term survival as evidenced by both of the Kaplan-Meier curves for overall survival and disease-free survival suggest that CTRT is comparable with other treatment regimens in terms of survival, and may possibly be more successful. Future studies of CTRT should focus on consistent follow-up with patients for five to ten years.

There are several limitations in the present study. Of course, a retrospective review is lower on the evidence-based medicine scale than would be a prospective investigation. Incomplete information on individual patients and follow-up data that was not universal restricted analyses as well. Additionally, the CONTROL group was small and heterogeneous, and it was not enrolled by pre-established criteria. Therefore, the group varied widely in the treatments that were applied. Consequently, this study was not a strict two-armed study. Radiation therapy varied modestly within both patient groups. Over the course of the study, the radiation therapy technique varied as the technology changed. However, the CTRT chemotherapy regimen was administered consistently. Lastly, the sample sizes were limited by the retrospective nature of the study.

CONCLUSION

By comparing the CTRT regimen not only to our CONTROL group, but also to other SCCHN regimens and publications, the therapeutic benefits of CTRT and their potential for future application are identified. The impressively high CCR and HCR rates achieved in this study while simultaneously reducing toxicity are major improvements to the multi-modality treatment of squamous cell carcinoma of the head and neck. Reduced distant metastasis is another positive outcome from CTRT. Lastly, CTRT is comparable in terms of survival with other published regimens, adding effective disease control to minimized adverse treatment effects. Based on the results presented in this paper, we believe that fractionated low-dose cisplatin administered simultaneously with high-dose radiotherapy is a feasible and useful first line treatment for the management of advanced, operable Stage III and Stage IV SCCHN.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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