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Single Arm Phase II Trial of Elective Nodal Dose Reduction for Patients with Locoregionally Advanced Squamous Cell Carcinoma of the Head and Neck

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Abstract

Purpose—To evaluate a novel chemoradiotherapy (CRT) regimen for patients with squamous cell carcinoma of the head and neck (SCCHN) incorporating a lower intensity modulated radiation therapy (IMRT) dose to electively treated neck lymph nodes than is currently standard.

Methods and Materials—Eligible patients had locally advanced SCCHN of the oral cavity, oropharynx, larynx, or hypopharynx. The seven week CRT course consisted of weekly cisplatin at 35 mg/m² concurrent with sequential boost IMRT: 36 Gy to high and low risk planning target volumes (PTV) followed by a sequential boost to high risk PTV to 70 Gy. The primary endpoint was elective nodal failure (ENF). Secondary endpoints were survival, toxicity, feeding tube duration, and QOL evaluated by FACT-HN and QOL-RTI surveys.

Results—Between 2011 and 2014, 54 patients were enrolled, 31 (57%) of whom had HPV+ disease. Thirty-five (65%) patients had stage IVa disease. Median follow-up for survivors was 36 months (range 12 – 66 months). No patient developed ENF. Actuarial three-year survival for the entire cohort was 91 % (95% confidence interval [CI] 0.79–0.96); HPV– 85% (95% CI 0.61–0.95), and HPV+ 96% (95% CI 0.77–0.99). Common grade three toxicities were dysphagia 79%, mucositis/stomatitis 41%, nausea 20%, xerostomia 13%, vomiting 11%, and neutropenia 10%. Median feeding tube duration was 142 days. Patient FACT-HN scores were higher at three, six, and 12 months vs. end of treatment ($p < 0.0001$). Total FACT-HN scores returned to pre-treatment baseline by six months. Overall QOL-RTI scores were lower from pretreatment to end of treatment through 12 months ($p = 0.0001$).

Conclusion—This CRT regimen for patients with advanced SCCHN demonstrated the potential feasibility of reducing the elective dose to the neck, a topic that requires additional study in future clinical trials.

Introduction

Current nonsurgical treatment for patients with locally advanced SCCHN consists of IMRT with concurrent cisplatin chemotherapy. In a recently published phase III trial of definitive

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CRT for SCCHN, the standard IMRT dose to high risk PTV was 70 Gy in 35 fractions of 2 Gy each delivered in six fractions per week. Protocol specified doses to lower risk regions in the neck ranged from 56 – 63 Gy at 1.6 – 1.8 Gy per fraction or 50 Gy at 2 Gy per fraction.¹ Current National Comprehensive Cancer Network guidelines continue to recommend similar doses. These recommendations for elective nodal irradiation (ENI) are based upon historical data utilizing RT alone.^{2,3} However, there is evidence that concurrent chemotherapy may equate to between four and 12 Gy of RT dose, delivered in 2 Gy daily or 1.2 Gy twice daily fractions, in terms of acute effects including tumor cell kill.⁴⁻⁶ Moreover, several decades of clinical data indicate that CRT regimens utilizing ENI doses of 30 – 45 Gy at 1.7 – 1.8 Gy per fraction to treat squamous cell cancers of the cervix and anus result in consistently low rates of elective nodal failure (ENF).⁷⁻⁹

Modern CRT regimens incorporating today's standard IMRT dosing to treat advanced SCCHN yield high locoregional control and survival rates, though generally with significant toxicity and poor QOL for patients. When cancer recurs, the pattern of failure is essentially bimodal: within sites of initial gross disease or distant metastases.¹⁰ The ENF rate with today's CRT regimens incorporating standard IMRT ENI doses is 0–1%.^{11,12}

The authors' historical clinical trial approach to CRT for patients with advanced SCCHN has been a stepwise movement to decrease toxicity and maintain efficacy. These efforts have included utilizing concurrent cisplatin low dose weekly rather than in high doses q3 weeks, as well as lower ENI doses in a hyperfractionated schedule.^{13,14} Since the aforementioned modern CRT regimens using 50 – 63 Gy ENI doses to treat advanced SCCHN have resulted in rare ENF and there is evidence indicating potential efficacy of lower ENI doses in the setting of concurrent chemotherapy, we hypothesized that IMRT doses utilized for ENI within current CRT regimens may be excessive. The trial reported herein tests a CRT regimen incorporating a de-intensified regimen delivered to the low risk PTV encompassing electively treated neck lymph nodes. We anticipated this regimen would maintain high efficacy including an ENF rate of < 5 – 7%, while potentially decreasing toxicity and improving QOL for these patients.

Methods and Materials

Patients

Non-pregnant patients > 18 years old, with Zubrod performance status 0–1, adequate bone marrow, liver, and renal function, and previously untreated, histologically proven SCCHN, stage III-IVa were eligible for enrollment. Patients with T2N0 cancers of the base of tongue were eligible. Patients with T1-2N1 oral cavity and tonsil primaries, the majority of whom would not standardly require ENI to the contralateral neck, were ineligible. Patients with N2c or bilateral N3 disease were also ineligible. Other ineligibility criteria were: prior invasive malignancy (other than non-melanoma skin) within the past two years, prior cisplatin chemotherapy or radiotherapy, or any symptomatic coronary disease within the prior six months.

Initial work-up included evaluation by otolaryngology, radiation oncology, and medical oncology. Oral surgery was consulted for prophylactic dental care and teeth extractions as

warranted. Histologic confirmation of SCCHN included p16 status to evaluate for HPV - associated disease. Laboratory evaluation included blood count, metabolic profile, and creatinine clearance. In addition to direct fiberoptic laryngoscopy by both otolaryngology and radiation oncology, pre-treatment imaging included CT of the neck, fluorodeoxyglucose PET/CT, and modified barium swallow. Staging was via TNM classification of the American Joint Commission on Cancer (7th edition). Prophylactic endoscopic gastrostomy (PEG) feeding tube placement was at the discretion of the treating radiation oncologist and patient. In general, PEG was recommended prior to treatment for patients with any baseline weight loss or poor nutrition, our practice standard.

This trial was approved by the hospital institutional review board. All patients provided written informed consent prior to study entry. They completed two quality of life (QOL) questionnaires, the FACT-HN and the QOL-RTI, prior to treatment.

Treatment Planning

At the time of imaging for IMRT planning, head, neck, and shoulders were immobilized utilizing the Accufix device to ensure minimal in-field motion. CT imaging consisted of 3 mm axial slices from the top of the head through the aortic arch. PET/CT image data sets were imported for image fusion planning. General definitions of gross tumor volume (GTV), clinical target volume (CTV) and PTV were employed for outlining tumor targets. Primary and nodal GTV included all cancer that was visible or palpable on physical exam, greater than one cm or visibly necrotic on neck CT, and/or hypermetabolic on PET/CT. The GTV was expanded 5 – 10 mm to include adjacent tissue at risk for harboring microscopic cancer, creating the CTV70. Expansion of CTV70 by 5 mm to account for organ and patient motion, shaved off skin by 3 mm in the absence of gross skin involvement, generated the PTV70. Clinically uninvolved, elective neck nodal regions bilaterally at risk for harboring microscopic disease were contoured as CTV36. The combination of CTV36 + CTV70, + 5 mm margin to account for patient and organ motion, shaved off skin by 3mm in absence of gross skin involvement, generated PTV36. Standard dose constraints were employed to minimize dose to adjacent critical organs at risk.

Treatment and Follow-up

Patients received IMRT daily utilizing a sequential boost approach. The primary plan was delivered in 18 fractions of 2 Gy each to PTV36, followed by a sequential boost of 17 fractions of 2 Gy each to PTV70. The IMRT course was five days per week for seven weeks. Image guidance consisted of KV matching daily and cone beam CT weekly. Following standard premedication, cisplatin at 35 mg/m², our institutional standard, was delivered one day per week during the first six weeks of the IMRT course. Delivery of a seventh weekly cycle of cisplatin was at the discretion of the treating medical oncologist. Receipt of five total cycles of cisplatin was considered a minor protocol violation, while four or fewer cycles was a major violation. Acute and late toxicities of CRT were recorded according to the Common Terminology Criteria for Adverse Events (CTCAE).

Immediately upon completion of CRT, patients completed a second round of QOL-RTI and FACT-HN surveys. Patients were evaluated in radiation oncology at one, three, six, 12, 18,

and 24 months post-CRT. Either neck CT or PET/CT (choice at discretion of the treating radiation oncologist) restaging was performed at 10–12 weeks post-CRT. Patients with residual disease on either physical examination or restaging imaging at this time underwent selective neck dissection between 12 and 20 weeks post-CRT. Biopsy was not performed prior to neck dissection. Both QOL-RTI and FACT-HN were completed again at three, six, and 12 months post-CRT. Modified barium swallow and recording of any persistent PEG tube dependence were scheduled for six and 12 months post-CRT.

Statistical Analysis

The primary study endpoint was ENF, defined as tumor recurrence within CTV36. The baseline ENF rate for reported studies utilizing standard CRT regimens in the treatment of patients with locally advanced SCCHN has been 0–1%. Thus, the authors set the control event (ENF) rate at 1%. We felt that a clinically unacceptable ENF rate would be between 5% and 10%, so we chose 7% as the experimental event threshold. In order to detect an increase in ENF rate from the current 1% baseline to 7% with 80% power and an alpha of 0.05, a sample size of 47 patients was required. Secondary endpoints were survival, CTCAE grade three to five toxicity, and patient reported QOL.

Actuarial survival was calculated using the Kaplan-Meier method. Comparison of survival between groups based on HPV status was tested using both a log rank comparison and a Wilcoxon rank sum test. Repeated Measures Two-Way ANOVA tests were performed to compare survey QOL scores over time. Analysis between individual time periods used Turkey-Kramer adjustment for family wise comparisons. Tests were two-tailed as appropriate and p-value of <0.05 was considered significant.

An interim analysis was planned after the first 20 enrolled patients had a minimum of one year follow-up. The trial would be halted if the ENF rate was >5%. After completion of trial accrual, final analysis was to be performed once all patients had a minimum follow-up of one year.

Results

Patient Characteristics and Protocol Adherence

Between 2011 and 2014, 54 patients were enrolled, all of which were analyzable. Patient characteristics are shown in Table 1. Thirty-one (57%) patients had HPV+ disease. All patients completed the IMRT course to 70 Gy per protocol. Forty-eight (89%) patients received the minimum required six weekly doses of cisplatin. Five patients received five weekly cycles of cisplatin and there was one major protocol violation for a patient receiving four cycles.

Elective Nodal Failure (ENF), Pattern of Failure, and Survival

Two patients who presented with N2b neck disease in ipsilateral levels 2–3 underwent selective neck dissections after completion of CRT due to concerns of persistent disease within the initial high risk CTV70. One patient had 17 negative nodes. The other had two

persistent matted nodes peeled off the internal jugular vein, subsequently developed recurrence, and died of disease.

Four patients were lost to follow-up at various time points following completion of CRT. Seven patients have died. After a median follow-up for surviving patients of 36 months (range 12 – 66), no patient has developed an ENF. None of the patients who died had developed an ENF. Four patients with HPV– disease developed recurrence: two in the lungs and two within the initial high risk CTV70. Two patients developed second primary cancers. Actuarial three-year survival for the entire cohort was 91 % (95% confidence interval [CI] 0.79–0.96); for the HPV– group was 85% (95% CI 0.61–0.95), and for the HPV+ group was 96% (95% CI 0.77–0.99). There was no significant difference in survival between the groups by HPV status (log-rank $p = 0.173$; Wilcoxon rank sum $p = 0.174$).

Toxicity

The most common grade three acute toxicities were dysphagia 80%, mucositis/stomatitis 41%, nausea 20%, xerostomia 13%, vomiting 11%, and neutropenia 10%. There were no grade four or five toxicities. Among the 44 patients (81%) who had PEG feeding tube placed, median duration from insertion to removal was 142 days (range 107 –208).

Quality of Life

Overall QOL-RTI scores over time are shown in Figure 1A. Scores were significantly lower between pre-treatment and end of treatment ($p < 0.0001$) through 12 months ($p = 0.0001$). Both FACT-HN total and head and neck (H&N) subsection scores over time are shown in Figure 1B. Scores at end of treatment were significantly lower than pretreatment for total ($p < 0.0001$) and H&N subset ($p < 0.0001$). Scores at three, six, and 12 months were significantly higher than end of treatment for total ($p < 0.0001$) and H&N subset ($p < 0.0001$). Total FACT-HN scores returned near baseline by 6 months. Median total score differences between end of treatment and subsequent follow-up time points at 3, 6, and 12 months are shown in Table 2.

Dosimetry

The authors chose to perform a sequential rather than concurrent boost, in order to isolate the single variable of total ENI dose, 36 Gy (at 2 Gy per fraction), to be examined. The sequential boost to the high risk PTV70 had the potential to deliver increased dose to adjacent, grossly uninvolved first echelon nodes (FEN) within the low risk PTV36. Therefore, the primary author contoured post hoc both an FEN structure (within the PTV36) and a second echelon nodes (SEN) structure on 49 of 54 plans that could be restored. The mean and median for this group of individual mean FEN composite doses were 45.5 Gy (range 40.0 – 59 Gy) and 44.9 Gy. The mean FENV45Gy for the group was 47%. Differential between intended prescribed dose of 36 Gy and actual composite dose received of 45 Gy was 9 Gy to FEN. This 9 Gy delivered over 17 fraction sequential boost equates to 0.53 Gy per fraction to FEN. The mean and median for the mean SEN composite doses were 38.6 Gy (range 36–44) and 36.7 Gy. An example of the coronal dose distribution for one of the patients is shown in Figure 2.

Discussion

Sparse data exist regarding ENI dose to treat potential sites of microscopic disease in neck lymph nodes for patients with advanced SCCHN. The authors found three references addressing this question, all of which were published during the course of the current trial. Nuyts et al performed a randomized trial of 40 Gy versus 50 Gy ENI dose with the primary endpoint of acute toxicity.¹⁵ This trial, which enrolled 100 patients onto each arm, revealed no significant difference in acute toxicity but did show a difference in grade three+ dysphagia at three months: 2% in the 40 Gy arm versus 11% in the 50 Gy arm ($p=0.03$). “Concurrent chemotherapy was allowed” but not discussed, nor did the authors report ENF rate. A recent retrospective review by van den Bosch et al of 264 patients with T2-4N0-2 SCCHN treated with IMRT alone, utilizing an ENI dose of 50.3 Gy at 1.48 Gy per fraction, revealed an ENF rate of 5.1% at two years.¹⁶ Lastly, Bedi et al reported, in abstract form only to date, their experience treating 69 patients with IMRT doses of 70 Gy at 2 Gy per fraction to the high risk region and 50 Gy at 1.48 Gy per fraction ENI.¹⁷ Some type of concurrent chemotherapy was delivered to 77%. There were no regional relapses. Thus, the available data indicates that an ENI dose of 50 Gy at low dose per fraction yields an ENF rate of 0–5%, possibly dependent upon whether concurrent chemotherapy was delivered or not, while a lower ENI dose of 40 Gy results in less severe dysphagia than 50 Gy.

The trial reported herein prospectively evaluated a reduced ENI dose, with a primary endpoint of ENF. The selected ENI dose of 36 Gy IMRT represents a 20% decrease from the lowest standard currently acceptable and is 10% lower than the lowest reported in the medical literature as noted above. Despite this reduction in ENI dose, none of the 54 patients in the current trial developed an ENF after a median follow-up for survivors of three years.

Secondary endpoints of the current study were survival, grade three to five toxicity, feeding tube duration, and patient reported QOL. Patients with bilateral neck disease, N2C or bilateral N3, were specifically excluded from this trial. Since the primary site and both sides of the neck would receive 70 Gy in these cases, the remaining ENI volume would be small (eg. – level 4 supraclavicular region only), as would the potential clinical benefit of reducing ENI dose for these patients. Therefore, compared to other trials of CRT for locoregionally advanced SCCHN reported in the medical literature, our patient population had less advanced nodal disease, probably a major contributing factor to the relatively high 3-year survival on this trial.

Acute grade three dysphagia and mucositis remained the most common toxicities of this CRT regimen, likely attributable to the unchanged dose of 70 Gy to the high risk PTV encompassing the pharynx. However, the median duration from PEG tube insertion to removal of 142 days in this trial compares favorably with both the authors’ historical results as well as others reported utilizing modern CRT regimens. The authors have a low threshold for recommending pre-CRT PEG placement. Our experience has been that the risk to benefit ratio for PEGs is quite low. The vast majority of patients fare better overall during and immediately post-CRT due to improved nutrition. As noted, the median duration from insertion to removal of PEG was 4 months.

Both overall and head and neck specific QOL, as measured by the FACT-HN instrument, were favorable with this regimen. Scores for both improved from end of treatment to three, six, and 12 months post-treatment. Total FACT-HN mean scores returned to pre-treatment baseline by six months, similar to both the authors' historical results and other reported modern CRT regimens. The magnitude of median increase in FACT-HN scores between end of treatment and subsequent follow-up points out to 12 months does appear to be clinically meaningful.^{18,19}

There are a couple of limitations to this reported trial. First and foremost, the N of 54 is small, with the majority of patients having biologically more favorable HPV+ cancers of the oropharynx, which limits the study's application to patients with HPV- disease. Patients with HPV+ disease have higher cure rates than those with HPV negative disease using CRT regimens with standard RT dosing.²⁰⁻²² Therefore, conservative readers who want to utilize this regimen may want to limit its use to patients with HPV+ cancers of the oropharynx. Early reports utilizing lower IMRT doses to treat the high risk PTV for these patients certainly appear favorable.^{23,24} Multiple phase III trials are underway evaluating de-intensification strategies for patients with HPV+ disease and our group enrolled patients onto the HN002 trial.²⁵ That said, the authors are unaware of any published difference between the ENI doses required to eradicate microscopic disease for HPV+ vs. HPV- subgroups.

A second limitation of this trial is restrictive eligibility criteria. The rationale for excluding patients with N2c or bilateral N3 neck disease is explained above. Among patients with earlier stage SCCHN, those with T1-2N1 tonsil and oral cavity (mostly well lateralized) cancers have very low baseline risk for developing contralateral neck disease with no RT dose delivered. The appropriate contralateral ENI dose for the vast majority of these patients is 0, not 36 Gy. Since the authors felt inclusion of these patients would "stack the deck" in favor of the treatment regimen 36 Gy ENI dose being tested, they were excluded. On the other hand, patients with T2N0 base of tongue cancers were eligible because they have a high baseline risk for developing neck disease bilaterally, so it is standard of care to treat with ENI bilaterally.

A third limitation is the phase II nature of this trial. While comparisons to previously reported trials may be interesting, they are no substitute for a prospective randomized trial comparing treatment arms. While the authors believe that patient QOL as measured by FACT-HN was favorable (eg. - trend of returning near pre-treatment baseline by 6 months) on this trial, for instance, we cannot state that it is superior to CRT regimens utilizing NCCN standard ENI doses of 50 – 63 Gy. That said, it is highly unlikely that a phase III trial will ever be performed for patients with advanced SCCHN to evaluate ENI dose with the primary endpoint of ENF rate.

Lastly, there are two IMRT plan considerations worth mentioning to readers who may consider utilizing this regimen. First, the authors utilized dosimetric expansions of GTV + 5–10 mm to create CTVs and CTV + 5mm to create PTVs. The higher end of this range is generous by today's standards. These larger treatment volumes, particularly for PTV70, may have provided greater margin for error in coverage of immediately adjacent tissues. When

this trial was written, however, these margins were fairly standard. For instance, the RTOG 0522 trial published in 2014 utilized GTV + 10 mm to create CTV1 and GTV + 20 mm to create CTV2, expanding 3 – 5 mm to create PTVs. The HN002 trial for patients with favorable HPV+ disease, closed to accrual in 2016, utilized GTV + 5 mm to create CTV6000 and GTV + 10 mm to create CTV5400, expanding 3 – 5 mm to create PTVs.

Second, the FEN at highest risk for containing microscopic disease within the PTV36 ENI volume received additional dose during the sequential boost of the PTV70 high risk volume. After the initial 36 Gy in 18 fractions of 2 Gy, approximately 9 Gy in 17 fractions of 0.53 Gy was delivered to FEN for a composite dose of 45 Gy for the “average patient” on this trial. How does the biologic effect of this ENI dose compare to the current standard of care? Assuming an alpha/beta of 10, the commonly prescribed 56 Gy in 35 fractions of 1.6 Gy equates to 54 Gy in 27 fractions, while 36 Gy in 18 fractions of 2 Gy plus 9 Gy in 17 fractions of 0.53 Gy equates to 44 Gy in 22 fractions. The authors will leave it to the reader to decide whether 9 Gy in 17 fractions is clinically equivalent to 8 Gy in 4 fractions.

Conclusions

The current trial evaluating reduced dose elective nodal irradiation in patients with locally advanced head neck cancer shows intriguing early results. This small phase 2 study warrants further evaluation in additional prospective trials. Future studies may focus on more homogeneous patient populations but would likely require the collaboration of multiple institutions in order to enroll a sufficient number of patients to demonstrate safety.

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Summary

Current standard chemoradiotherapy (CRT) regimens use doses of 50 Gy IMRT to control microscopic cancer within electively treated neck nodes for patients with advanced squamous cell carcinoma of the head and neck (SCCHN). This trial evaluated a novel CRT regimen for patients with SCCHN incorporating a much lower nodal IMRT dose than is standard.

Figure 1.

(A) Patient-reported QOL-RTI total scores over time.

(B) Patient-reported FACT HN total (red) and H&N subsection (blue) scores over time.

Figure 2.

Coronal dose distribution for sample patient with cT1N2B oropharynx cancer. Contours displayed are planning target volume receiving 70 Gy (PTV70; purple), first echelon nodes (FEN; white), and second echelon nodes (SEN; yellow). Isodose curves displayed are 70 Gy (red), 60 Gy (light green), 50 Gy (blue), 45 Gy (purple), 40 Gy (dark green), and 36 Gy (orange). Note the purple 45 Gy and orange 36 Gy isodose curves in relation to white FEN and yellow SEN structures.

Patient Characteristics		N = 54
Age		
Median		60 (56–66)
Race		
Caucasian		51 (94%)
African American		3 (6%)
Gender		
Male		47 (87%)
Female		7 (13%)
Insurance		
Commercial/Medicare		43 (80%)
Medicaid		6 (11%)
No Insurance		5 (9%)
Primary Site		
Oral Cavity		3 (6%)
Oropharynx		43 (80%)
Hypopharynx		4 (7%)
Larynx		4 (7%)
T Stage		
T1		14 (26%)
T2		24 (44%)
T3		13 (24%)
T4		3 (6%)
N Stage		
N0		8 (15%)
N1		13 (24%)
N2a		12 (22%)
N2b		21 (39%)
AJCC Stage		
II	T2N0	2 (4%)
III		17 (31%)
	T3N0	6
	T1N1	2
	T2N1	6
	T3N1	3
IVa		35 (65%)
	T4aN0	0
	T4aN1	2
	T1N2	12
	T2N2	14
	T3N2	6
	T4aN2	1

Patient Characteristics	N = 54
HPV Status & Smoking History	
Positive, p16	31 (57%)
Nonsmoker	13
Smoker	18
Negative, p16	22 (41%)
Unknown	1 (2%)
PEG Duration	
Median, days	142 (107–208)

QOL Instrument	Follow-up Time	Median (Range) Score Increase from End of Treatment
FACT-HN	3 month	7.5 (–26 to 29)
	6 month	8 (–30 to 36)
	12 month	11 (–18 to 28)
QOL-RTI	3 month	0 (–82 to 69)
	6 month	–5 (–72 to 66)
	12 month	1 (–53 to 74)