HHS Public Access

Author manuscript

Head Neck. Author manuscript; available in PMC 2016 October 12.

Published in final edited form as:

Head Neck. 2013 May ; 35(5): 684–688. doi:10.1002/hed.23024.

Quantification of the effect of treatment duration on local-regional failure after definitive concurrent chemotherapy and intensity-modulated radiation therapy for squamous cell carcinoma of the head and neck

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Abstract

Background—The purpose of this study was to quantify the effect of treatment duration on locoregional progression after definitive concurrent chemoradiation (CCRT) for squamous cell carcinoma of the head and neck (SCCHN).

Methods—We conducted a retrospective chart review of patients treated between 2004 and 2010. After a prior analysis, measures were taken to limit therapy beyond 7 weeks. Comparison of outcomes were made between cohorts 1 (2004–2007, $n = 78$) and 2 (2007–2010, $n = 62$).

Results—Median therapy duration was statistically significantly different between cohorts as follows: 51 days, cohort 1 and 46 days, cohort 2 ($p < .01$). Locoregional progression in cohorts 1

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and 2 was 19% and 5% ($p = .01$), respectively. On multivariate analysis, patients with prolonged treatment (≥57 days) had an 8-fold increase in risk of locoregional progression compared to patients who completed on time ($p < .01$).

Conclusion—Treatment duration was a significant predictor of locoregional progression in patients with SCCHN who received definitive CCRT.

Keywords

concurrent chemoradiation therapy; squamous cell carcinoma of the head and neck; treatment delay; anemia; treatment failure

INTRODUCTION

Local-regional control of squamous cell carcinoma of the head and neck (SCCHN) is attainable with definitive concurrent chemoradiotherapy (CCRT).[1–4] Despite this, treatment failure remains a concern for these patients. In 2010, approximately 11,600 deaths were expected to occur from head and neck cancer in the United States[5] and the primary cause of mortality in these patients is locoregional progression. Data demonstrate that treatment interruptions adversely affect treatment outcomes among patients receiving definitive radiation therapy alone[6–10] or definitive CCRT.[11]

Previously, we retrospectively reviewed outcomes of 78 patients with SCCHN treated with CCRT between 2004 and 2007 at Roswell Park Cancer Institute (RPCI) and showed that treatment duration was a significant independent predictor of treatment failure in a multivariate model that controlled for weight status and pretreatment hemoglobin, 2 other factors with prognostic importance relative to treatment failure.[12,13] Since that review, efforts were made at RPCI to limit prolongation of therapy. The purpose of this analysis was to quantify the effect of overall treatment time on locoregional progression and test its significance as an independent predictor of locoregional progression in an expanded and updated cohort of patients with SCCHN.

PATIENTS AND METHODS

This retrospective review of patients with head and neck cancer at RPCI was institutional review boardapproved. All patients who were definitively treated with intensity modulated radiation therapy (IMRT) and concurrent chemotherapy between 2004 and 2010 were included in this study. After a prior analysis of patients treated between August 2004 and September 2007 (cohort 1), measures were taken to limit prolongation of therapy beyond 7 weeks for patients treated between October 2007 and June 2010 (cohort 2). Comparisons of outcomes were made between these 2 cohorts of RPCI patients.

Treatment

The original cohort has been previously described in great detail.[12,13] Briefly, patients were treated with IMRT to 70 Gy in 35 daily fractions to the high-dose target volume and 56 Gy to the elective target volume. All patients received concurrent chemotherapy. The most commonly prescribed regimen was cisplatin 100 mg/m^2 on days 1, 22, and 43 of

radiotherapy or cisplatin 30 to 40 mg/m^2 weekly. For patients in cohort 2, measures taken to avoid treatment interruptions included: beginning all treatments on a Monday which reduced optimal total treatment time from 49 days to 47 days, providing twice-daily treatments up to a total of 6 fractions per week to make up for any missed treatments, early initiation of social work support to assist with transportation issues, aggressive smoking and alcohol cessation counseling, and standardizing supportive care with a preprinted sheet explaining nutritional goals and proper use of prophylactic salt/baking soda rinses and pain medications.

Upon completion of treatment, all patients underwent a complete head and neck examination including flexible laryngoscopy every 2 months for year 1, every 3 to 4 months for year 2, every 6 months for years 3 to 4, and then annually thereafter. A positron emission tomography or CT scan was used to evaluate initial response to therapy at the 8 to 12-week follow-up visit after completion of treatment.

Outcomes collected

Data were abstracted from the electronic medical record and the following patient information was collected: age at diagnosis, sex, tumor site, tumor stage, lymph node stage, duration of radiotherapy, height and weight, pretreatment hemoglobin levels, date of last follow-up, and treatment failure status. Body weight measurements were collected for the time period directly before the start of treatment (within 4 weeks) and after the end of treatment (within 4 weeks). Ideal body weight (IBW) was calculated using the Hamwi formula (IBW = 106 lbs for 5 feet tall and 6 lbs/inch for each inch over 5 feet for men and 100 lbs for 5 feet tall and 5 lbs/inch for each inch over 5 feet for women).[14]

Locoregional progression was defined as any disease in the primary disease site or neck that was not eradicated by therapy and included both persistent disease (viable disease noted within 6 months of completion of therapy) and recurrent disease (viable disease noted beyond 6 months of completion of therapy). Failure was pathologically confirmed for all cases. For cohort 1, it was only necessary to update existing information and therefore the date of last follow-up and failure status was recorded.

Statistical analysis

The Statistical Package for the Social Sciences (version 16, SPSS, Chicago, IL) was used for all statistical analyses. The chi-square or Fisher Exact test was used to examine categorical variables and the Mann–Whitney *U* test was used to examine continuous variables. Differences for these variables were compared for patients with and without locoregional progression between and within cohorts 1 and 2. Statistical assessment of observed differences in locoregional progression distribution between cohorts was done using the log-rank test.

Duration of radiation therapy was examined in terms of days from initiation of therapy to the end of therapy. CCRT duration was dichotomized based on the results of McCloskey et al[13] and Rades et al.[11] Interruption of radiation therapy dichotomized as ≤56 days or ≥57 days was a significant predictor of locoregional progression in both of these studies. Additionally, Nangia et al[15] reported a similar outcome. Treatment duration for this analysis was therefore dichotomized into clinically relevant categories of ≤56 days or ≥57 days.

In a previous report, we showed that both pretreatment weight status and pretreatment hemoglobin were prognostic markers of locoregional progression. For this analysis, pretreatment percentage of IBW was categorized into normal and below normal based on clinical significance as follows: ≥90% IBW (normal body weight) and <90% IBW (below normal body weight) for both men and women.[16] Pretreatment hemoglobin values were categorized into normal and below normal based on a cutoff of 12 g/dL for both men and women. Our previous article and others have used this cutoff as a relevant marker of anemia.[11,13,17]

Odds ratios (ORs) were calculated and 95% confidence intervals (CIs) were estimated with unconditional logistic regression for the main effect of treatment duration on treatment failure status. Potential confounders that met the inclusion level of $p = .10$ were examined for inclusion in the multivariate model. All tests were 2-sided with a p value < .05 considered statistically significant.

RESULTS

From 2004 to 2010, 140 patients were definitively treated with CCRT at RPCI. The original cohort, cohort 1, included 78 patients and cohort 2 included 62 patients. The median age of both cohorts combined was 59.50 years (range, 37–82 years) and the median duration of therapy was 50 days (range, 38–83 days). Median follow-up for those still alive in the entire cohort ($n = 104$) was 35 months. A total of 92 patients (66%) had nodal-positive disease and 97 patients (69%) had a primary tumor staged at 3 or 4. Eighteen of the 140 patients (13%) experienced locoregional progression. These included: 9 primary site failures, 4 regional neck failures, and 5 failures in both the primary site and regional lymph nodes. Of the 18 patients with locoregional progression, 4 were recurrent disease and 13 were persistent disease.

A comparison of patient characteristics by cohort is provided in Table 1. The only statistically significant differences between the cohorts were related to radiation therapy duration and to locoregional progression. The median duration of radiation therapy was 51 days for cohort 1 and 46 days for cohort 2 ($p < .01$). As noted previously, measures were taken to limit treatment prolongation for cohort 2 and, as a result, 94% of this cohort were without treatment interruption (treatment duration ≤56 days) versus 82% of cohort 1 ($p = .04$). The rate of locoregional progression in cohorts 1 and 2 was 19% and 5%, respectively ($p = .01$).

Patient characteristics were compared stratified by locoregional progression for both cohorts combined (Table 2). Based on age, sex, lymph node or tumor stage, and disease site, there were no statistically significant differences between patients who experienced locoregional progression and those who did not. Differences were statistically significant between the 2 groups for the duration of therapy, pretreatment hemoglobin, and pretreatment IBW status.

Median duration of therapy was 53 and 50 days for those with and without treatment failure, respectively ($p < .01$). Based on treatment duration categorized into ≤56 days versus ≥57 days, 39% of the patients with locoregional progression compared to 9% of those who did

not experience progression were in the ≥57 days category ($p < .01$). The locoregional progression distributions were statistically significantly different between the cohorts based on the log-rank test ($p = .01$).

Median pretreatment hemoglobin was 12.45 for those in the failure group versus 13.90 for those who did not experience locoregional progression ($p = .02$). Comparing pretreatment hemoglobin with the dichotomous variable categorized by the cutoff of 12 g/dL was not statistically significant.

The median pretreatment weight was 80.55 kilograms (kg) for patients who did not experience locoregional progression and was 74.50 kg for those who did. This difference did not reach statistical significance; however, when categorized into clinically relevant terms in relation to nutritional status, the difference was statistically significantly different. For those who experienced locoregional progression, 33% were ≤90% IBW as compared with 11% of patients in the no progression group ($p = .01$).

The multivariate logistic regression model that was developed to examine treatment duration (≤56 days vs ≥57 days of CCRT) as an independent predictor of locoregional progression in the combined cohort included the following confounders: pretreatment hemoglobin as a continuous variable, and pretreatment weight categorized by IBW status and age. The cutoff for inclusion of confounders was set at $p = .10$. Because the statistical significance of tumor stage on univariate analysis was $p = .11$, this variable was tested in the model.

Both the crude and adjusted estimates are shown in Table 3. Compared with patients whose treatment duration was not prolonged, patients with prolonged treatment duration (≥57 days) had an 8-fold increased risk of locoregional progression in the adjusted model. When tumor stage was entered into the model as an additional confounder, the estimate remained relatively stable. In this experience, a median difference of 5 days in treatment duration between the original cohort and the new cohort resulted in a 14% increase in locoregional progression.

DISCUSSION

In this updated cohort of patients with SCCHN who received definitive CCRT treatment, duration of treatment remained a significant independent predictor of locoregional progression. Previously, using the original cohort ($n = 78$) and a similarly adjusted multivariate model, we showed that risk of locoregional progression was 8 times higher in those who experienced treatment interruption.[12] After an addition of 62 patients, this estimate remains stable. Efforts were made to minimize treatment time in this second cohort of patients treated between 2007 and 2010 enabling us to investigate the effect of treatment time.

This is the first manuscript to quantify the impact of optimizing treatment time in 2 consecutive cohorts of patients treated with CCRT and IMRT. It has long been known that total treatment time significantly impacts local control after radiation therapy alone for SCCHN. This fact is supported by a strong radiobiological rationale.[18–24] Additionally, there is robust clinical support for this effect.[6,9,25–27]

Recent clinical data confirms that treatment time remains a significant predictor of local control in patients treated with CCRT and IMRT.[11,13,28] Estimates of the detrimental effect of treatment interruption during CCRT with IMRT for SCCHN on survival and local control vary between 1% to 5% per day.[11,13,15] The findings from our comparative analysis of cohorts 1 and 2 are consistent with the literature. In this experience, there were only 3 cases of locoregional progression in the group (cohort 2) for which steps were taken to minimize treatment interruption as opposed to 15 cases of locoregional progression in cohort 1. Follow-up time for cohort 2 was a median of 26 months; in our experience, all cases of locoregional progression were known or suspected by imaging within 12 months of completion of treatment (data not shown). Human papillomavirus (HPV) status was not performed routinely enough to allow comparison between the groups, and this certainly is a confounding factor. Oropharyngeal cancers are known to be more likely associated with HPV infection[29] and there was an increased percentage of oropharyngeal cancer in the more recent cohort, but the difference between cohorts was not statistically significantly different.

The median difference of 5 days in treatment duration between cohorts 1 and 2 did result in a 14% increase in locoregional progression. Additionally, our data demonstrates that virtually all patients can complete concurrent chemoradiation therapy with careful monitoring, adequate pain management, intensive supportive care, and a general determination to complete therapy on time. This can be managed without frequent inpatient admissions. In fact, only 1 patient in the second cohort ($n = 62$) was hospitalized (for pneumonia) during therapy.

It is true that acute side effects will be higher in a patient who completes therapy on time as opposed to a patient who is given a break during therapy. Certainly, the enhanced local control associated with completing treatment on time merits this increase in acute toxicity.

CONCLUSION

Treatment duration is a significant predictor of locoregional progression for patients with SCCHN receiving CCRT. Whereas increased toxicity to treatment may occur when patients are not given a break from treatment, minimizing the risk of locoregional progression should outweigh this possibility. Referring and treating physicians must be educated to understand that this increased acute toxicity (which reliably resolves by 4 weeks) is a vital part of the therapy and not simply a result of suboptimal management during radiation.

Acknowledgments

Contract grant sponsor: This work was funded in part by the National Institutes of Health grant number R25CA114101.

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TABLE 1

Descriptive characteristics of cohort 1 (original) and cohort 2 (new).

Characteristics	No. (%) or median		*p* value*
	Cohort 1 (*n* = 78)	Cohort 2 (*n* = 62)	
Median age at diagnosis (range), y	62 (37–81)	59 (38–82)	.15
Follow-up time (range), mo	54 (1–85)	26 (5–54)	<.01
Sex: male/female	56 (72)/22 (28)	51 (82)/11 (18)	.15
Lymph node stage treated (*n* = 129) N0/N+	25 (32)/53 (68)	12 (24)/39 (76)	.30
Primary tumor stage (*n* = 135) 1 or 2/3 or 4	38 (49)/40 (51)	31 (54)/26 (46)	.52
Disease site condensed (*n* = 134)			
Oral cavity	4 (5)	0 (0)	
Oropharynx	42 (54)	37 (66)	
Hypopharynx	4 (5)	5 (9)	
Larynx	28 (36)	14 (25)	.13
Median RT duration, d	51 (39–83)	46 (38–67)	<.01
RT duration			
≤56 d	64 (82)	58 (94)	
≥57 d	14 (18)	4 (6)	.04
Median pretreatment Hgb, (range) g/dL	13.50 (9–17.10)	14 (8.6–19.40)	.17
Pretreatment Hgb, g/dL			
<12	18 (23)	9 (15)	
≥12	60 (77)	53 (85)	.20
Median pretreatment weight, (range) kg	79.75 (46.80–141)	81.75 (42.60–125.50)	.39
Pretreatment weight status			
<90% IBW	14 (18)	6 (10)	
≥90% IBW	64 (82)	56 (90)	.23
Locoregional progression: no/yes	63 (81)/15 (19)	59 (95)/3 (5)	.01
Locoregional failure type, recurrent/persistent	4/10	0/3	.03

Abbreviations: RT, radiation therapy; Hgb, hemoglobin; g/dL, grams per deciliter; kg, kilograms; IBW, ideal body weight.

*Chi-square (2-tailed) was used to examine differences for categorical variables and Mann–Whitney U test (2-tailed) was used to examine differences for continuous variables.

TABLE 2

Descriptive characteristics of cohorts 1 and 2 combined by locoregional progression.

Characteristics	Patients Locoregional progression, No. (%) or median		
	No (n = 122)	Yes (n = 18)	p value*
Median age at diagnosis (range), y	59 (37–82)	63 (47–81)	.17
Sex: male/female	92 (75)/30 (25)	3 (17)/15 (83)	.46
Lymph node stage treated (n = 129) N0/N+	30 (27)/81 (73)	7 (39)/11 (61)	.30
Primary tumor stage (n = 135) 1 or 2/3 or 4	63 (54)/54 (46)	6 (33)/12 (67)	.11
Disease site condensed (n = 134)			
Oral cavity	3 (3)	1 (6)	
Oropharynx	72 (61)	7 (41)	
Hypopharynx	8 (7)	1 (6)	
Larynx	34 (29)	8 (47)	.37
Median RT duration (range), d	50 (38–79)	53 (49–83)	<.01
RT duration			
≤56 d	111 (91)	11 (61)	
≥57 d	11 (9)	7 (39)	<.01
Median pretreatment Hgb, (range) g/dL	13.9 (8.60–19.40)	12.45 (9.50–15.50)	.02
Pretreatment Hgb, g/dL			
<12	20 (16)	7 (39)	
≥12	102 (84)	11 (61)	.11
Median pretreatment weight, (range) kg	80.55 (42.60–140.50)	74.50 (46.80–141)	.26
Pretreatment weight status			
<90% IBW	14 (11)	6 (33)	
≥90% IBW	108 (89)	12 (67)	.01

Abbreviations: RT, radiation therapy; Hgb, hemoglobin; g/dL, grams per deciliter; kg, kilograms; IBW, ideal body weight.

*Fisher Exact Test or chi-square (2-tailed) was used to examine differences for categorical variables and Mann–Whitney U test (2-tailed) was used to examine differences for continuous variables.

TABLE 3

Risk of locoregional progression estimated by duration of therapy.

Exposure	Locoregional progression no/yes	Crude OR (95% CI)	*Adjusted OR (95% CI)	†Adjusted OR (95% CI)
RT duration				
≤56 d (reference)	111/11	1	1	1
		6.42	8.1	7.67
≥57 d	11/7	(2.07–9.92)	(2.13–30.85)	(2.01–29.22)
		$p < .01$	$p < .01$	$p < .01$

Abbreviations: OR, odds ratio; CI, confidence interval; RT, radiation therapy.

*OR was adjusted by age, pretreatment hemoglobin, and pretreatment percentage of ideal body weight.

†OR was adjusted by age, pretreatment hemoglobin, pretreatment percentage of IBW, and stage of disease.