Time Course and Predictors for Cancer-Related Fatigue in a Series of Oropharyngeal Cancer Patients Treated with Chemoradiation Therapy

DANIEL E. SPRATT,^a MAYUKO SAKAE,^b NADEEM RIAZ,^d BENJAMIN H. LOK,^e SAMUEL ESSANDOH,^b MEIER HSU,^c ZHIGANG ZHANG,^c KAREN SCHUPAK,^a JEREMY SETTON,^a NANCY Y. LEE^a

^aDepartment of Radiation Oncology, ^bDepartment of Pain and Palliative Care, and ^cDepartment of Epidemiology-Biostatistics, ^dMemorial Sloan-Kettering Cancer Center, New York, New York, USA; ^eNew York University School of Medicine, New York, New York, USA

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Discuss the incidence of cancer-related fatigue and the impact it has on cancer patients.
2. Evaluate clinical correlates of cancer-related fatigue and describe possible interventions.
3. Explain the time course of cancer-related fatigue before, during, and post-treatment and the effect treatment has on patients for years after treatment.

CME

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ABSTRACT

Background. Cancer-related fatigue (CRF) is a highly prevalent and underestimated symptom in cancer patients. This study aims to analyze CRF solely in a cohort of oropharyngeal cancer patients who underwent treatment with radiotherapy (RT).

Methods. In January 2008 to June 2010, 87 consecutive oropharyngeal carcinoma patients underwent definitive RT. Concurrent chemotherapy was used for 94% of patients. The median prescription dose to the planning target volume of the gross or clinical tumor volume was 70 Gy for definitive cases ($n = 84$) and 66 Gy for postoperative cases ($n = 3$), both delivered over 6.5 weeks. A normalized 12-point numeric rating scale assessed CRF from patient visits before, during, and after RT.

Results. The median follow-up of living patients was 14

months. Fatigue peaked 1–2 weeks post-RT and remained higher than baseline for up to 2 years post-RT in 50% of patients. The average fatigue score at the time of completion of therapy or maximum thereafter up to 1 year post-RT was significantly worse than baseline. Patients who experienced pain had a trend toward significance with association for a higher maximum difference in fatigue from baseline. Karnofsky performance status score, weight change, and mood disorders did not correlate with CRF.

Conclusions. Fatigue was a common treatment-related symptom in this uniform cohort of patients with oropharyngeal cancer. RT was highly correlated with worsening of CRF. Pain control has the potential to help mitigate CRF in patients experiencing pain, and will need to be confirmed using larger datasets. *The Oncologist* 2012;17:569–576

Correspondence: Daniel Spratt, M.D., Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, Box 22, New York, New York 10021, USA. Telephone: 212-639-6800; Fax: 212-717-3104; e-mail: sprattdd@mskcc.org Received December 10, 2011; accepted for publication January 20, 2012; first published online in *The Oncologist Express* on March 7, 2012. ©AlphaMed Press 1083-7159/2012/\$20.00/0 <http://dx.doi.org/10.1634/theoncologist.2011-0437>

INTRODUCTION

Of the ~300 million people in the U.S., 11 million currently have or have carried a diagnosis of cancer. Almost 1.5 million people will be diagnosed with cancer annually, and >50% will live >5 years [1, 2]. Strides in extending overall survival have led to an increased focus on improving quality of life (QOL) for these patients. One of the symptoms that has become of increasing interest is fatigue or, more specifically, cancer-related fatigue (CRF) [3, 4]. CRF is experienced by these patients from the time of diagnosis and for an indeterminate number of years after treatment [3–5].

The National Comprehensive Cancer Network (NCCN) defines CRF as “a distressing persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning” [2]. Numerous reports cite CRF as one of the most common symptoms experienced by cancer patients [6–11]. However, CRF is often underreported and undertreated [2]. Studies have shown that CRF is present at the time of cancer diagnosis in 50%–75% of patients. This is prior to the intense therapies that are used to prolong patient’s overall survival. Furthermore, the prevalence of CRF can increase up to 80%–96% and 60%–93% for patients undergoing chemotherapy and radiotherapy (RT), respectively [5]. A large survey of 1,569 patients found that CRF was experienced by 80% of individuals who underwent chemotherapy and/or RT [10, 11].

Our understanding of CRF is rudimentary because for many years debilitating symptoms of pain and nausea captured oncologists attention [12]. During the past two decades, significant strides have been made in palliative pharmacologic interventions, such as greater use of effective serotonin 5-HT₃ receptor antagonist antiemetics and newer formulations of μ -opioid receptor (MOR) agonist pain medications [5]. With better control of these symptoms, CRF, a new phenomenon, arose as one of the most pronounced side effects of cancer itself as well as the therapy these patients receive [3, 4, 13, 14].

A key element in understanding CRF is that it is not relieved by rest or sleep, unlike the commonly confused term of “tiredness” [15]. Its mechanism likely is multifactorial, and cited causes of CRF are anemia, depression, a cancer-induced hypermetabolic state, pain, poor nutrition, and the cancer treatment itself [5]. More specifically, CRF is thought to be partially mediated by proinflammatory cytokines [16–18], circadian rhythm disturbances [19], endocrine dysregulation [16], vagal-afferent activation [20], and genomic disruption [21]. However, the exact mechanism remains unknown and is an area of active research.

Head and neck cancer patients who undergo definitive treatment experience some of the most dramatic acute side effects while undergoing therapy. The treatment regimens are intense and often include induction chemotherapy followed by concurrent chemoradiotherapy [22, 23]. The acute treatment effects include, but are not limited to, severe mucositis, epidermal ulceration/desquamation of the neck, xerostomia, agusia, and odynophagia. Opioid pain medications, oral analgesics, and proper oral rinses and hygiene can palliate some of these

acute side effects. CRF, when coupled with these side effects, can be debilitating and lead to improper ongoing self care, malnutrition, loss of weight, productivity, and reduced overall QOL [24, 25].

We applied a fatigue assessment form created at the Memorial Sloan-Kettering Cancer Center (MSKCC) based on the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, to help gain further information on the time course, severity, and clinical correlates of CRF in oropharyngeal head and neck cancer patients.

MATERIALS AND METHODS

Patients

This study was conducted in accordance with ethical standards at the MSKCC and was approved by the institution’s ethics committee. The approval process was completed to incorporate our fatigue assessment form to be included during routine consultation, treatment visits, and follow-up appointments. Institutional review board/privacy board approval was under waiver number WA0469–09.

From January 2008 to June 2010, 87 consecutive patients who underwent curative intent treatment at MSKCC for oropharyngeal cancer were analyzed. Ninety-seven percent were definitive cases ($n = 84$), treated to a total RT dose of 70 Gy, and 3% were postoperative cases ($n = 3$), treated to a total dose of 66 Gy. All RT plans used intensity-modulated RT with dose painting. Concurrent chemotherapy was used for 94% of patients ($n = 82$). By the American Joint Committee on Cancer *Cancer Staging Manual*, Seventh Edition, 84% of patients were stage IV. The majority of patients ($n = 65$) had cisplatin-based chemotherapy (Table 1).

Data Collection

A fatigue assessment form created at MSKCC based on the CTCAE, version 4.0, was used to capture the degree of CRF experienced by patients. Two separate physician-completed assessment forms were used to capture CRF. The main campus used a four-point fatigue scale questionnaire whereas satellite centers used a three-point scale. The scales were unified by converting to a 12-point scale. Baseline fatigue levels prior to treatment were imputed using the first observation carried backward (FOCB) method [26, 27]. The assessment was performed at the time of consultation, at weekly treatment visits, and at follow-up appointments at 6–12 weeks, and in 3-month intervals for 1 year and then 4-month intervals for year 2, and biannually thereafter. In addition, weight, Karnofsky performance status (KPS) scores, and pain scores were collected at each appointment. At the time of consultation and follow-up, comorbid conditions, including mood disorders, were evaluated using standard *Diagnostic and Statistical Manual of Mental Disorders*, version 4, definitions [28]. Comorbid diagnoses were filtered using *International Classification of Diseases*, Ninth Revision, coding to include only conditions that have been associated with CRF, including anemia, pain disorders, diabetes mellitus (I or II), hypothyroidism, Parkinson’s disease, chronic obstructive pulmonary disease, cardiovascular disease,

Table 1. Patient and treatment characteristics	
Variable	n
Sex	
Male	68
Female	19
Mean age $\pm$ standard deviation (range), yrs	58 $\pm$ 11.6 (27–91)
Race	
White	72
Black	3
Other	12
Treatment facility	
Main campus	70
Satellite center	17
Tumor subsite	
Base of tongue	25
Tonsil	51
Soft palate	1
AJCC stage ^a	
I	2
II	2
III	12
IV	84
Chemotherapy	
Cisplatin based	65
Cetuximab	15
Induction	5
Concurrent with radiotherapy	82
Intent of radiotherapy	
Definitive (70 Gy)	84
Postoperative (66 Gy)	3
Mucositis ^b	
Grade 0	11
Grade 1	8
Grade 2	46
Grade 3	22
Grade 4	0
Dysphagia ^b	
Grade 0	1
Grade 1	23
Grade 2	46
Grade 3	17
Grade 4	0
Xerostomia ^b	
Grade 0	5
Grade 1	51

(continued)

Table 1. (Continued)	
Variable	n
Grade 2	31
Grade 3	0
Grade 4	0
Trismus ^b	
Grade 0	75
Grade 1	9
Grade 2	3

^aAccording to the American Joint Committee on Cancer (AJCC) *Cancer Staging Manual*, Seventh Edition.
^bGrade based on the Common Terminology Criteria for Adverse Events, version 4.0.

pulmonary hypertension, renal failure, chronic liver disease and cirrhosis, and nutritional deficiencies. Also, the number of and type of CRF-inducing medications were recorded. This was limited to opioids, antihistamines, benzodiazepines, anxiolytics, antipsychotics, antidepressants, and antiepileptics.

Statistical Analysis

As seen in Table 2, for missing fatigue assessment scores at baseline, prior to any treatment, the FOCB method was used to replace the missing value with the first valid score during RT. This correction factor can alter the baseline pre-RT fatigue scores toward a higher mean than the original data. The resulting effect is to dampen the calculated effect of RT on fatigue.

The mean effect of RT on fatigue was evaluated by calculating the net difference between the maximum fatigue score over the entire RT period through 1 year post-RT and the baseline score. The Wilcoxon signed rank test was used to assess the statistical significance of this difference. To investigate the association between this maximum difference in fatigue and potential fatigue level predictors, nominal categorical variables were evaluated using the Wilcoxon rank sum or Kruskal-Wallis test for two or multiple groups, respectively, and ordinal or continuous variables were evaluated using the test of nonzero Spearman's rank correlation coefficient. *p*-values $< .05$ were considered statistically significant. Because of the nature of this retrospective study, and it being the first of its type to the best of our knowledge to look at a cohort of head and neck subsite cancer patients, we did not perform any multiple testing adjustments. We choose to report and comment on all the *p*-values directly. We caution here that an enhanced overall (family-wise) type 1 error rate is present.

RESULTS

Time Course of Fatigue

With a median follow-up of 14 months for living patients (range, 6–24 months), the entire 87-patient cohort was able to be evaluated with near uniform completion rates of fatigue assessment at each visit. On average, less than one fatigue score per course of follow-up was not captured per patient. All pa-

Table 2. Time course of CRF

	Before RT		During RT							After RT								Maximum (B)
	Imputed (A)	Original data	1	2	3	4	5	6	7	1-2 wks	3-4 wks	5-8 wks	3-4 mos	5-8 mos	11-15 mos	16-19 mos	20-30 mos	
<i>n</i>	87	75	75	80	81	75	76	79	75	76	66	61	65	67	63	24	10	87
Mean	0.76	0.71	1.68	2.86	3.23	3.72	4.08	4.80	5.19	5.39	4.02	4.16	3.69	2.12	2.11	2.00	2.50	6.89
Standard deviation	1.36	1.32	2.15	2.18	2.39	2.20	2.60	2.48	2.42	2.73	2.18	2.56	2.46	2.51	2.29	2.84	3.72	2.44
Standard error	0.15	0.15	0.25	0.24	0.27	0.25	0.30	0.28	0.28	0.31	0.27	0.33	0.31	0.31	0.29	0.58	1.18	0.26
Median	0	0	0	3	3	3	3	4	4	6	3	3	3	3	3	0	1.5	6
Range	0-4	0-4	0-9	0-8	0-9	0-9	0-9	0-12	3-12	0-12	0-9	0-12	0-9	0-12	0-12	0-12	0-12	3-12

(A) is based on imputation by first observation carried backward. (B) is based on actual fatigue values from all patients within 12 months post-RT.

RT effect: Wilcoxon signed rank test on (B) - (A): $p < .0001$.

Abbreviations: CRF, cancer-related fatigue; RT, radiotherapy.

tients were evaluated at least once per week while on treatment, unless complications arose, in which case they were evaluated more frequently.

Figure 1 and Table 2 show the trends in fatigue scores over time. The mean baseline fatigue score for the entire cohort was 0.76 (SD, 1.36). The average fatigue score at the time of completion of therapy or maximum thereafter up to 1 year after treatment was 6.89 (SD, 2.44). The difference between these values was statistically significant ($p < .0001$). Fatigue peaked at week 8-9 from the initiation of RT (post-RT week 1-2), with a mean fatigue score of 5.39 (SD, 2.73).

Clinical Correlates of CRF

The mean fatigue impairment caused by RT (Table 2) was quantified as 6.13 points ($p < .0001$). Table 3 shows the results from the univariate analysis of the association between clinical factors and the maximum change in fatigue from baseline. These variables included the KPS score, percent weight change at the end of treatment compared with baseline and at 1 month post-treatment compared with baseline, other comorbid diagnoses that were previously reported to worsen CRF, the number of unique fatigue-inducing prescription medications, the experience of pain, and mood disorders (anxiety, depressive disorders, and the combination of anxiety and depressive disorders).

All patients had KPS scores >70 , and performance scores had a mild trend toward predicting CRF ($p = .12$). Thirty patients had weight loss $>10\%$ at 1 month into treatment, with a fatigue score at baseline versus a maximum post-RT minus baseline score of 0.83 ± 1.43 versus 6.31 ± 2.64 . Overall both weight change from baseline at the end of treatment and at 1 month post-treatment were not significant predictors of CRF ($p = .65$ and $p = .82$, respectively).

The most common comorbid conditions were cardiovascular disease (22%), chronic obstructive pulmonary disease (14%), endocrine dysfunction combining hypothyroidism and diabetes mellitus (12%), and anemia (10%), with the remaining conditions having an incidence of $<4\%$ each. Patients with two comorbid diagnoses had a fatigue score at baseline of 0 and a maximum post-RT minus baseline score of $7.75 \pm$

(3.88). Overall, other comorbid diagnoses were not significant as predictors for fatigue ($p = .52$). Patients with a depressive or dysthymic disorder without an anxiety disorder had a baseline fatigue score of 0 and a maximum post-RT minus baseline score of 6.4 ± 0.89 . Mood disorders overall were not predictive of CRF ($p = .43$).

The most common fatigue-inducing medications used by patients were opioids (93%), anxiolytics and antidepressants (36%), and benzodiazepines (28%), with the remaining medications each with an incidence $<7\%$. Patients taking two fatigue-inducing medications had a fatigue score at baseline of 0.90 and a maximum post-RT minus baseline score of 6.40 ± 1.65 . The number of fatigue-inducing medications did not reach significance ($p = .84$).

Forty patients experienced significant pain, necessitating MOR-agonist pain medications or an increase in the pain medication management regimen. Pain reached a strong trend toward significance for correlation with CRF, with a baseline fatigue score of 0.93 ± 1.44 in patients experiencing pain, compared with a baseline score of 0.6 ± 1.25 in patients without pain. The maximum post-RT minus baseline score for patients with pain was 6.63 ± 2.61 , compared with 5.68 ± 2.64 for patients who did not experience pain ($p = .06$).

DISCUSSION

To our knowledge, the present study is the first report, and with the longest follow-up, describing, in detail, the time course of CRF and predictive factors for CRF in a uniform cohort of patients undergoing treatment for oropharyngeal cancer. CRF is experienced by the vast majority of cancer patients undergoing treatment [5, 13, 27]. Hickok et al. [29] found that patients undergoing treatment for head and neck, gastrointestinal, and lung cancer experienced some of the greatest levels of CRF. Fatigue was experienced by the entire 87-patient cohort in our study, and RT was significantly associated with worsening of CRF (Table 2). Worsening of CRF throughout treatment is consistent with other series, and at 2 years, 50% of the patients continued to have clinically significant levels of CRF.

Two of the largest studies on CRF stem from national sur-

Table 3. Predictors of CRF

Variable	Before RT ^a		Difference (maximum post-RT minus pre-RT score)	
	<i>n</i>	Mean ± SD	Mean ± SD	<i>p</i> -value
Overall	87	0.75 ± 1.34	6.11 ± 2.7	
Karnofsky performance status score				.12 ^b
70	2	1.50 ± 2.12	6 ± 4.24	
80	14	0.69 ± 1.32	5.31 ± 3.28	
90	59	0.77 ± 1.38	6.04 ± 2.43	
100	12	0.50 ± 1.17	7.17 ± 2.95	
% Weight change at end of treatment				.65 ^b
<5% weight loss	18	1.00 ± 1.46	6.11 ± 3.20	
5%–10% weight loss	34	0.74 ± 1.36	6.38 ± 2.67	
>10% weight loss	30	0.63 ± 1.30	6.33 ± 2.07	
% Weight change at 1 mo				.82 ^b
<5% weight loss	10	0.90 ± 1.45	5.80 ± 2.53	
5%–10% weight loss	23	0.65 ± 1.27	6.91 ± 2.41	
>10% weight loss	42	0.83 ± 1.43	6.31 ± 2.64	
<i>n</i> of other diagnoses				.52 ^b
0	6	0.67 ± 1.63	4.50 ± 2.07	
1	7	0.43 ± 1.13	5.14 ± 1.86	
2	8	0.00 ± 0.00	7.75 ± 3.88	
3	8	1.25 ± 1.75	6.00 ± 3.07	
4	15	0.6 ± 1.24	6.40 ± 2.67	
5	43	0.91 ± 1.39	6.12 ± 2.42	
<i>n</i> of medications				.84 ^b
0	25	0.40 ± 1.12	6.68 ± 3.20	
1	16	1.31 ± 1.54	5.44 ± 2.50	
2	10	0.90 ± 1.45	6.40 ± 1.65	
3	13	1.00 ± 1.58	5.23 ± 2.05	
4	11	0.55 ± 1.21	6.82 ± 1.94	
5	11	0.55 ± 1.21	6.18 ± 3.34	
6	1	0 ± .	3.00 ± .	
Pain				.06 ^c
No	47	0.60 ± 1.25	5.68 ± 2.64	
Yes	40	0.93 ± 1.44	6.63 ± 2.61	
Mood disorder				.43 ^c
None	58	0.71 ± 1.34	6.41 ± 2.55	
Anxiety state	23	0.91 ± 1.41	5.43 ± 3.04	
Depressive disorder/dysthymic disorder	5	0.00 ± 0.00	6.40 ± 0.89	
Anxiety and depressive disorder	1	3.0 ± .	3.00 ± .	

^aBaseline fatigue values are presented in this table for ease of visualization; however, *p*-values are based on the maximum post-RT minus baseline scores compared with the entire cohort.

^b*p*-value calculated from test of nonzero Spearman's correlation coefficient.

^c*p*-value from Wilcoxon or Kruskal-Wallis test for two groups or multiple groups, respectively.

Abbreviations: SD, standard deviation; RT, radiotherapy.

Figure 1. Fatigue scores before, during, and after radiotherapy (RT). Data are shown as mean plus standard deviation of the original scores after the scales were unified before any data imputation. The dashed line represents the completion of treatment.

veys from The Fatigue Coalition, a multidisciplinary team whose goal is to gain an understanding of fatigue in cancer patients specifically [3, 4]. The Fatigue-1 study included 419 cancer patients, 59% of whom had been treated with chemotherapy and 63% of whom had been treated with RT. Survey results from that study found that 78% of patients suffered from fatigue during their treatment; the most common malignancy included in that study was breast cancer [4]. The Fatigue-2 study included 379 cancer patients and found results similar to those of the Fatigue-1 study, with 76% of patients being affected by CRF at least monthly while on treatment, and 30% suffering with fatigue daily [3]. When the two studies' data were combined with other reports, it was estimated that 50% of cancer patients suffer from CRF at the time of diagnosis, and this is greater, at 75%, if they have bone metastasis. While on chemotherapy and RT, 93% and 96% of patients, respectively, experience fatigue [30]. In our study, ~92% of patients were treated with concurrent chemoradiotherapy, and 6% were treated with induction chemotherapy followed by concurrent chemoradiotherapy. The combination of these differences likely explains the greater incidence of CRF in our cohort.

The peak in CRF in our study occurred 1–2 weeks after RT was completed. This phenomenon mimics the common complaint of worsening mucositis and dysphagia in the weeks after completing RT. It is known that the side effects of RT accumulate through therapy secondary to the DNA-damaging nature of the treatment. Whether it is the accumulation of acute

side effects that is the cause for the worsening of CRF during treatment or RT itself innately worsens CRF, the causality is difficult to isolate. Other disease sites show a similar worsening trend in CRF, whereby fatigue rapidly peaks while on treatment and is slow to return to baseline [1, 7, 26, 31]. In our study, even at 100 weeks after treatment patients still had not returned to baseline levels of fatigue. The only other report in the literature specifically dedicated to head and neck cancer patients, a study that analyzed numerous subsites of the head and neck, found that the peak in CRF occurred at 6 weeks into RT, decreased slightly at week 7, and had a second peak at 2 weeks post-RT [1]. Our study did not exhibit this effect, and CRF continued to climb every week from the initiation of treatment until 2 weeks post-RT.

A unique aspect of our study, unlike most series, is that we analyzed a specific head and neck subsite (oropharynx). The importance of this fact is that the RT fields and the relatively similar anatomic primary tumor site among all 87 patients allowed fewer confounding variables to interfere with the associated factors of CRF. Therefore, the organs at risk for receiving high bystander doses of radiation are comparable. This would not be true if one was comparing subglottic larynx or nasopharyngeal cancer, let alone including breast or prostate tumor sites. In addition, the dose prescribed to the primary tumor and involved lymph nodes was uniformly 70 Gy, unless it was postoperative (three patients), in which case the dose was lower at 66 Gy. Other series often have more widely varied

treatment approaches [14, 26, 29]. There is conflicting reports on whether or not CRF correlates with tumor-related factors or RT parameters (dose, duration of treatment, and volume) [1, 29, 32–35]. Our study did not analyze these factors because of the homogeneity of the treatment groups, which is a strength of our study in identifying correlates of CRF.

Numerous studies have correlated physiologic findings with RT-related fatigue. These include weight change, concurrent symptoms (nausea, mucositis), use of analgesics, interleukin levels, and anemia [1, 31, 36, 37]. The NCCN identifies several factors believed to be paramount in CRF—pain, malnutrition, and other comorbidities, including other medical conditions [2]. Our study did not find a significant difference in CRF based on weight change, fatigue-associated comorbid diagnoses, or the number of medications with a known side effect of fatigue or somnolence. The fact that nearly everyone loses weight during the treatment of oropharyngeal cancer likely explains why our cohort did not show a difference in CRF related to weight loss. An additional study to help further elucidate this could measure percent lean body mass change rather than gross total body weight loss.

The correlation between psychological disorders and CRF has also been studied by many. Our study did not find a correlation between CRF and mood disorders. Reports from others are conflicting, and it appears that there is a complex interplay among CRF, pain, and mood disorders such as depression [1, 5, 26].

The number of medications a patient uses can be a marker of not only comorbid conditions, such as hypertension or diabetes, but also symptoms of treatment. A prospective study by Jerezek-Fossa et al. [27] analyzing CRF found that patients who needed cortisone during treatment had higher levels of CRF. They concluded that the need for medications to palliate RT-induced side effects may be a marker for RT-induced toxicity. In our cohort, we did not find a correlation between RT-induced toxicities and CRF. The correlation between medication use and its mechanism of association with CRF remains to be fully understood.

Other than RT itself, pain was also associated with fatigue in our study, with borderline significance ($p = .06$). This was an interesting observation because >90% of the patients in this study required opioid pain medications, and of these an additional 70% required escalation of their pain medication regimen during or after treatment. It is difficult to accurately capture morphine-equivalent dosing because most patients are prescribed opioid medications on an as-needed basis. The approximate mean level of oral morphine-equivalent dose during the first 3 weeks of treatment for patients on opioid medications was 15 mg/day. This increased by the end of treatment to a mean value of 37.5 mg/day. The maximum morphine-equivalent oral dose at the end of treatment was 90 mg/day.

Pain in and of itself is debilitating; however, the side effects from opioid use are also significant. Common side effects of MOR-agonist medications include constipation, nausea, vomiting, hypotension, histamine release, and lethargy or lack of energy [38–40]. It would appear from this study, as well as others, that pain plays an important role in contributing to CRF [3]. Furthermore, there are data to also suggest that patients with greater

levels of CRF have greater symptoms of pain [5, 7, 41, 42]. Interestingly, data from The Fatigue Coalition studies found that oncologists perceive pain to be more debilitating to cancer patients than CRF; however, patients felt just the opposite, with CRF negatively affecting their daily lives more than pain [4].

Interestingly, it appears from our study that, despite the sedative effects of analgesic use, fatigue is lower in patients whose pain is controlled. Pain management in cancer patients is another challenge that is highly prevalent [43–45]. Oxycodone, a semisynthetic opioid, has been in use for >90 years and is one of the mainstays in treating the pain head and neck cancer patients experience [46]. Numerous other MOR-agonist-based formulations have been created and are well studied for cancer-related pain [44–48]. Heiskanen et al. [46] performed a trial looking at opioid pain medications in 45 patients with chronic cancer pain. The study began with an open-label, randomized titration phase to achieve stable pain control for at least 48 hours, followed by a double-blind, randomized, crossover phase. During the titration period, seven patients withdrew off the medication secondary to nausea, vomiting, sweating, or dry mouth. Only one patient withdrew as a result of sedation complaints, and, furthermore, patients also reported nausea, dizziness, and headaches as reasons they withdrew from the study. This highlights that, by controlling cancer-related pain, it appears that CRF mitigation may offset the sedative nature of this class of medications.

In conclusion, our study presents a detailed depiction of the time course of CRF with a median follow-up >1 year post-treatment specifically for a uniform cohort of patients with oropharyngeal squamous cell cancer. Numerous previously reported variables, including change in weight, comorbid conditions, number of medications, KPS score, and mood disorders, failed to predict with statistical significance which patients suffered from worse CRF in our patient population. Correlation between CRF and the experience of pain appeared to strongly trend toward significance, and this highlights a potential therapeutic target to not only help increase the QOL of these patients, by reducing their symptom of pain, but also to potentially reduce the deleterious effects of CRF. Further studies aimed at addressing not only specific contributors of CRF for each tumor subsite but also methods to quantifiably reduce CRF would be of tremendous value for future research.

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Daniel E. Spratt and Mayuko Sakae contributed equally to the manuscript.

AUTHOR CONTRIBUTIONS

Conception/Design: Mayuko Sakae, Meier Hsu, Karen Schupak, Nancy Y. Lee

Provision of study material or patients: Samuel Essandoh, Karen Schupak, Jeremy Setton, Nancy Y. Lee

Collection and/or assembly of data: Daniel E. Spratt, Mayuko Sakae, Benjamin H. Lok, Jeremy Setton

Data analysis and interpretation: Daniel E. Spratt, Nadeem Riaz, Benjamin H. Lok, Samuel Essandoh, Meier Hsu, Zhigang Zhang, Nancy Y. Lee

Manuscript writing: Daniel E. Spratt, Mayuko Sakae, Benjamin H. Lok, Zhigang Zhang, Nancy Y. Lee

Final approval of manuscript: Daniel E. Spratt, Mayuko Sakae, Nadeem Riaz, Benjamin H. Lok, Samuel Essandoh, Meier Hsu, Zhigang Zhang, Karen Schupak, Jeremy Setton, Nancy Y. Lee

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