Charateristics of Chronic Pain among Head and Neck Cancer Patients Treated with Radiation Therapy: A Retrospective Study

Anusha Kallurkar,1 Shreedhar Kulkarni,2 Kristin Delfino,3 Daniel Ferraro,4 and Krishna Rao5

1Department of Anesthesiology, Louisiana State University Health Sciences Center at Shreveport, Shreveport, LA, USA
2Division of Medicine/Psychiatry, Department of Medicine, SIU School of Medicine, Springfield, IL, USA
3Department of Surgery, SIU School of Medicine, Springfield, IL, USA
4University Radiologists, Memorial Medical Center, Springfield, IL, USA
5Division of Hematology/Oncology, Simmons Cancer Institute at SIU School of Medicine, Springfield, IL, USA

Correspondence should be addressed to Shreedhar Kulkarni; shree.kulkarni82@gmail.com

Received 19 November 2018; Revised 14 March 2019; Accepted 27 March 2019; Published 6 May 2019

1. Introduction

Pain is common among patients with head and neck cancer (HNC). However, there are very limited data on chronic pain among HNC patients treated with radiation therapy (XRT). In this retrospective study, we focused on the characteristics of chronic post-XRT pain in such patients. Post-XRT pain is common among HNC patients; however, we found discrepancy between frequency of treatment and frequency of chronic pain, suggesting poor documentation of pain in the medical records. Among patients who reported to have chronic post-XRT pain, most of them described having severe pain and used descriptors of neuropathic pain. Pharynx was the commonest site of cancer as well as the commonest site of cancer-related chronic pain; squamous cell carcinoma was the most frequent histological pattern, and opioids were used most often to treat such chronic pain. There was a significant association between chronic pain and number of sites of pain, and chronic pain was also associated with use of opioids.

HNC can take up to 3 months to disappear histologically after completion of treatment, thus indicating remission of disease [5]. The follow-up visit at 3 months of completion of cancer therapy is particularly important since it helps in establishing the baseline result of treatment response and also marks the timing of the posttreatment baseline imaging [6, 7]. A negative PET-CT scan after treatment with chemoradiotherapy in HNC is associated with a high negative predictive value (>95%), and a negative scan around 3 months after completion of cancer therapy may indicate no residual disease [5, 8]. Patients who achieve a complete remission at the three-month posttreatment time point and who are still...
experiencing pain are thought to be having chronic pain. According to the International Association for the Study of Pain (IASP), “chronic pain” is defined as “the pain that has persisted beyond normal tissue healing time,” lasting for “more than 3 months” in the absence of other criteria [9].

Oral mucositis is a common cause of acute pain in HNC patients, and it typically lasts for 2–4 weeks after the end of radiation therapy (XRT) [10]. However, HNC patients can experience pain even up to 6–12 months after the radiation therapy [11]. There are very limited data on the prevalence and characteristics of chronic pain among HNC patients treated with XRT, and it is not clear which subgroup of HNC patients is more prone for chronic pain after XRT. In this retrospective observational study, we investigated the prevalence of chronic pain and the characteristics of patients in complete remission afflicted with chronic posttreatment pain.

2. Methods

2.1. Design. This retrospective study was conducted at Southern Illinois University (SIU) School of Medicine and Memorial Medical Center, Springfield, IL. All head and neck cancer patients aged 18 years and above, treated with radiotherapy from February 2011 to February 2016, were included in the study. Head and neck cancer patients treated only with chemotherapy were excluded. The chart review identified a total of 53 patients, who met the inclusion criteria. Demographic features such as age at diagnosis, gender and race, clinicopathologic features (location, histology, and staging of the cancer), cancer therapy (surgery and chemotherapy) and details pertinent to XRT (such as dose, duration, and area involved) were collected. In terms of location, data pertaining to upper aerodigestive tract sites (oral cavity, pharynx, larynx, nasal cavity, and paranasal sinuses) as well as salivary glands were collected. We focused on cancers of the oral cavity, pharynx, and larynx in this study because of their similarities in epidemiology, treatment, and prognosis; cancers of the lip, salivary gland, nose, paranasal sinuses, middle ear, nerves and bones, thyroid, nonmelanoma skin cancers, lymphoma, and sarcomas were excluded.

Data were also collected regarding the characteristics of pain: location, onset, frequency, severity, nature of pain, and information regarding use of medications including opioids, gabapentin, TCAs, and NSAIDs. Data regarding characteristics of pain up to 3 months after completion of XRT were categorized as “data related to acute pain,” and subsequent data (after 3 months of completion of XRT) were considered as “data related to chronic pain.” Pain was documented as mild, moderate, or severe based on the documentation in the charts. If pain severity was documented numerically, it was converted into mild (documented as 1–3 in the charts), moderate [4–6], and severe [7–10]. The local institutional review board approved the study, protocol number 17-021 (approval date 02/20/2017).

2.2. Statistical Analyses. Data were analyzed with the use of SAS software, version 9.4, and Zotero bibliography software was used for citing references. Descriptive statistics were computed for all study variables. Continuous variables are described with measures of central tendency (mean and median) and dispersion (range and standard deviation). Categorical variables are summarized as frequencies and percentages. Given smaller cell sizes, the following adaptations were made during statistical analyses: cancer stages were grouped into “stage 1 or 2” and “stage 3 or 4”; data for mild, moderate, and severe pain were combined into one group, and number of sites of pain were grouped into three categories such as “pain at 0 site,” “pain at 1 site,” and “pain at 2+ sites.” Statistical analysis was not performed for use of TCA’s given smaller sample size. Fisher’s exact tests were used to compare categorical variables. Independent t-tests (or nonparametric equivalent) were used to compare continuous variables. All significance was assumed at the p < 0.05 level.

3. Results

Demographic and clinicopathologic factors are described in Tables 1 (categorical variables) and 2 (continuous variables). Mean age at diagnosis was 61.23 years, and 73.6% were males. 88.7% of the patients had squamous cell carcinoma (n = 47), and other types of histology included adenocarcinoma (n = 1), high-grade neuroendocrine tumor (n = 1), solitary extramedullary plasmacytoma (n = 1), and adenoid cystic carcinoma (n = 1).

A total of 41 patients (77.4%) reported any kind of treatment for chronic pain, whereas only 32 patients (60.38%) reported any kind of chronic pain, suggesting poor documentation of pain characteristics in the charts. There was insufficient description of nature of pain; among the patients who reported any kind of chronic pain (n = 32), only 4 individuals described the nature of their pain (all of them used descriptors of neuropathic pain such as stinging or burning pain) and less than 4 individuals reported onset, frequency of chronic pain, and exacerbating features. Eleven patients died during the study period with average duration of survival of 15 months.

Pharynx (Table 3) was the most common location of cancer (39.6%), and oropharynx was the most frequent subsite of HNC (34%). Site of cancer was associated with use of medications. Specifically, laryngeal cancer (p = 0.01; supraglottic cancer, p = 0.021) was associated with higher use of gabapentin, and cancer of pharynx (p = 0.016; cancer of oropharynx, p = 0.04) was associated with lower use of gabapentin.

Pharynx (26.4%) was the commonest site of cancer-related chronic pain, followed by oral cavity (24.5%) (Table 4). Chronic neck pain was associated with use of gabapentin (p = 0.013).

There was a significant association between chronic pain and number of pain sites (p < 0.0001), and chronic pain was also associated with use of opioids (p = 0.006) (Table 5). There was no significant association between site of cancer and site of cancer-related chronic pain. Surgery was not associated with chronic pain or use of pain medications (details of statistical analyses for surgery, chemotherapy, XRT dose, and duration have been listed as separate tables, which can be found in Tables 6–9, respectively). Similarly,
Table 1: Demographic and clinicopathologic factors (categorical variables) (frequency and percentage of demographic factors including age, gender, and race and clinicopathologic factors such as histology, cancer staging, severity of pain, and pain treatment).

| Variable          | n   | %    |
|-------------------|-----|------|
| Categorical variables |    |      |
| Gender            |     |      |
| Female            | 14  | 26.4 |
| Male              | 39  | 73.6 |
| Race              |     |      |
| White             | 46  | 86.8 |
| AA                | 5   | 9.4  |
| Histology         |     |      |
| Squamous          | 47  | 88.7 |
| Staging           |     |      |
| 1                 | 4   | 7.6  |
| 2                 | 4   | 7.6  |
| 3                 | 5   | 9.4  |
| 4                 | 21  | 39.6 |
| Surgery           |     |      |
| No                | 32  | 60.4 |
| Yes               | 21  | 39.6 |
| Chemo             |     |      |
| No                | 21  | 39.6 |
| Yes               | 32  | 60.4 |
| Severity of chronic pain |     |      |
| No pain           | 35  | 66.0 |
| Mild              | 1   | 1.9  |
| Moderate          | 4   | 7.5  |
| Severe            | 13  | 24.5 |
| Medication        |     |      |
| Use of opioids    |     |      |
| No                | 20  | 37.7 |
| Yes               | 33  | 62.3 |
| Use of gabapentin |     |      |
| No                | 45  | 84.9 |
| Yes               | 8   | 15.1 |
| Use of TCAs for chronic pain |     |      |
| No                | 47  | 88.7 |
| Yes               | 6   | 11.3 |
| Use of NSAIDs     |     |      |
| No                | 39  | 73.6 |
| Yes               | 14  | 26.4 |

Chronic pain lasts for more than 3 months. Based on our clinical experience in managing post-XRT patients with HNC, we observed that chronic pain is commonly encountered; however, there are very limited data in the literature on the characteristics of chronic pain among HNC patients treated with XRT. Kuo and Williams listed 14 studies investigating pain in HNC patients, in which 3 studies reported persistence of pain up to 6–24 months, and prevalence of pain varied from 15% to 46% [16]. Only one study focused on post-XRT pain in HNC patients [11]. Recently, Srivastava et al. reported 54.7% patients reporting chronic post-XRT pain [17]. In our study, the sample size is larger, and we found almost two-thirds of patients to have some characteristics of chronic pain. The higher rate of prevalence of chronic pain in our study could be due to methodological differences as we included any documentation pertaining to chronic pain (location, nature, frequency of pain, etc.) in the study analysis.

We found discrepancy between frequency of treatment and frequency of chronic pain suggesting poor documentation of pain in the medical records, and less than 4 individuals reported onset (n = 1), frequency (n = 3), and exacerbating factors (n = 2) of chronic pain. It is difficult to generalize these data, given small proportion of patients receiving appropriate documentation. Nevertheless, this phenomenon of inadequate pain documentation is not limited to patients with HNC. Fink [18] reported poor documentation of acute and chronic noncancer pain. However, appropriate cancer pain documentation is one of the key elements of the American Society of Clinical Oncology (ASCO) Quality Oncology Practice Initiative (QOPI), and Rampura et al. showed improvement in documentation of pain among cancer patients with orientation and education of healthcare providers [19].

Mean age at diagnosis in our group was 61.23 years [20], and almost three-fourths of the patients were males (n = 39), which is comparable to other studies in the literature [21]. However, we found that most of our patients were Caucasians (n = 46, 86.8%) although historically, HNC is more common in African American individuals; this statistic probably reflects local demographics of Central Illinois. According to a population survey in 2013 [22], average Caucasian population in this area is 90.45%. Also, HPV-positive cases of HNC are more common in Caucasians, and we did not assess for HPV status in our study.

Among 53 patients in our study, pharynx was the most common site (39.6%), followed by larynx (32.1%), and among subsites of larynx, supraglottic carcinoma (17%) was the most common site that is consistent with the previous literature [23, 24]. In our study, laryngeal cancer (supraglottic cancer in particular) was associated with higher use of gabapentin. Supraglottic cancers usually have worse prognosis, given high frequency of cervical lymph node involvement, recurrences, and visceral metastases, likely explaining the increased use of analgesics.

Site of chronic pain was also associated with use of medications; chronic neck pain was associated with higher use of gabapentin. HNC patients treated with XRT are found to have neuropathic pain [25], and gabapentin is well
**Table 3: Site of cancer: frequency and percentage of prevalence of cancer by site and subsites and association between site of cancer and use of medications*.**

| Site of cancer | Total | Use of opioids | Use of NSAIDs | Use of gabapentin |
|----------------|-------|----------------|---------------|-------------------|
|                | n     | %              | % yes         | p                 |
| 1. Oral cavity |       |                |               |                   |
| No             | 53    | 88.7           | 61.7          | 1                 |
| Yes            | 6     | 11.3           | 66.7          | 1                 |
| 1A. Lip        |       |                |               |                   |
| No             | 53    | 100            | 62.3          | —                 |
| Yes            | 0     | 0              | 0             | —                 |
| 1B. Buccal mucosa |     |                |               |                   |
| No             | 53    | 100            | 62.3          | —                 |
| Yes            | 0     | 0              | 0             | —                 |
| 1C. Alveolar ridge, retromolar trigone | | | | |
| No             | 50    | 94.3           | 62.0          | 1                 |
| Yes            | 3     | 5.7            | 66.7          | 1                 |
| 1D. Floor of mouth |     |                |               |                   |
| No             | 50    | 94.3           | 60.0          | 0.282             |
| Yes            | 3     | 5.7            | 100.0         | 1                 |
| 1E. Hard palate |     |                |               |                   |
| No             | 52    | 98.1           | 63.5          | 0.377             |
| Yes            | 1     | 1.9            | 0             | 0.0               |
| 1F. Oral tongue |     |                |               |                   |
| No             | 51    | 96.2           | 60.8          | 0.521             |
| Yes            | 2     | 3.8            | 100.0         | 1                 |
| 2. Pharynx     |       |                |               |                   |
| No             | 32    | 60.4           | 62.5          | 1                 |
| Yes            | 21    | 39.6           | 61.9          | 1                 |
| 2A. Nasopharynx |     |                |               |                   |
| No             | 52    | 98.1           | 63.5          | 0.377             |
| Yes            | 1     | 1.9            | 0             | 0.0               |
| 2B. Oropharynx |     |                |               |                   |
| No             | 44    | 92.5           | 63.3          | 0.715             |
| Yes            | 9     | 7.5            | 50.0          | 0.627             |
| 2C. Oropharynx: base of tongue | | | | |
| No             | 49    | 95.9           | 63.3          | 0.715             |
| Yes            | 4     | 4.1            | 50.0          | 0.627             |
| 2D. Soft palate |     |                |               |                   |
| No             | 43    | 81.1           | 58.1          | 0.286             |
| Yes            | 10    | 18.9           | 80.0          | 1                 |
| 2E. Tonsillar fossa pillar | | | | |
| No             | 46    | 86.8           | 65.2          | 0.405             |
| Yes            | 7     | 13.2           | 42.9          | 0.0               |
| 3. Larynx      |       |                |               |                   |
| No             | 36    | 67.9           | 55.6          | 0.225             |
| Yes            | 17    | 32.1           | 76.5          | 0.225             |
| 3A. Supraglottis |   |                |               |                   |
| No             | 44    | 83             | 56.8          | 0.129             |
| Yes            | 9     | 17             | 88.9          | 0.129             |
| 3B. Glottis    |       |                |               |                   |
| No             | 46    | 86.8           | 60.9          | 0.697             |
| Yes            | 7     | 13.2           | 71.4          | 0.697             |
| 3C. Subglottis |     |                |               |                   |
| No             | 50    | 94.3           | 60.0          | 0.282             |
| Yes            | 3     | 5.7            | 100.0         | 1                 |
| 4. Nasal cavity |     |                |               |                   |
| No             | 50    | 94.3           | 62.0          | 1                 |
| Yes            | 3     | 5.7            | 66.7          | 1                 |
| 5. Paranasal sinuses | | | | |
| No             | 53    | 100            | 62.3          | —                 |
| Yes            | 0     | 0              | 0             | —                 |
| 6. Others      |       |                |               |                   |
| No             | 50    | 94.3           | 64.0          | 0.549             |
| Yes            | 3     | 5.7            | 33.3          | 0.549             |
| 7. Salivary gland |     |                |               |                   |
| No             | 50    | 94.3           | 66.0          | 0.049             |
| Yes            | 3     | 5.7            | 0.0           | 0.049             |

* Several cell sizes are very small and have been excluded from final statistical analyses. The ones that are included in the interpretation of final results are described in bold text.
established to be effective in treating neuropathic pain and seems to be promising in reducing the need for higher doses of opioids [26]. Gabapentin and opioids are commonly prescribed for pain, the likelihood of coprescription is high, and gabapentin appears to potentiate the effect of opioids [27].

| Site of pain | Total | Use of opioids | Use of NSAIDs | Use of gabapentin |
|-------------|-------|----------------|---------------|-------------------|
|             | n     | %              | % yes | p     | % yes | p     | % yes | p     |
| 1. Oral cavity |       |                |        |       |       |       |       |       |
| No          | 40    | 75.5           | 55.0  | 0.098 | 27.5  | 1     | 15.0  | 1     |
| Yes         | 13    | 24.5           | 84.6  | 23.1  | 1     | 15.4  | 1     |
| 2. Pharynx  |       |                |        |       |       |       |       |       |
| No          | 39    | 73.6           | 56.4  | 0.203 | 28.2  | 0.735 | 17.9  | 0.665 |
| Yes         | 14    | 26.4           | 78.6  | 21.4  | 7.1   |       |       |       |
| 3. Eyes     |       |                |        |       |       |       |       |       |
| No          | 52    | 98.1           | 61.5  | 1     | 26.9  | 1     | 15.4  | 1     |
| Yes         | 1     | 1.9            | 100.0 | 1     | 0.0   | 1     | 0.0   | 1     |
| 4. Nasal cavity, paranasal sinuses |       |                |        |       |       |       |       |       |
| No          | 52    | 98.1           | 61.5  | 1     | 26.9  | 1     | 15.4  | 1     |
| Yes         | 1     | 1.9            | 100.0 | 1     | 0.0   | 1     | 0.0   | 1     |
| 5. Odynophagia |     |                |        |       |       |       |       |       |
| No          | 44    | 83             | 59.1  | 0.456 | 25.0  | 0.684 | 13.6  | 0.611 |
| Yes         | 9     | 17             | 77.8  | 22.2  |       |       |       |       |
| 6. Headache |       |                |        |       |       |       |       |       |
| No          | 50    | 94.3           | 60.0  | 0.282 | 24.0  | 0.167 | 14.0  | 0.394 |
| Yes         | 3     | 5.7            | 100.0 | 33.3  |       |       |       |       |
| 7. Face     |       |                |        |       |       |       |       |       |
| No          | 48    | 90.6           | 58.3  | 0.144 | 27.1  | 1     | 14.6  | 0.574 |
| Yes         | 5     | 9.4            | 100.0 | 20.0  | 1     | 20.0  |       |       |
| 8. Ear      |       |                |        |       |       |       |       |       |
| No          | 45    | 84.9           | 57.8  | 0.234 | 24.4  | 0.422 | 13.3  | 0.59  |
| Yes         | 8     | 15.1           | 87.5  | 25.0  |       |       |       |       |
| 9. Neck     |       |                |        |       |       |       |       |       |
| No          | 45    | 84.9           | 60.0  | 0.695 | 22.2  | 0.186 | 8.9   | 0.013 |
| Yes         | 8     | 15.1           | 75.0  | 50.0  | 50.0  |       |       |       |

*Several cell sizes are very small and have been excluded from final statistical analyses. The ones that are included in the interpretation of final results are described in bold text.

| Table 5: Characteristics of chronic pain. |
|-----------------------------------------|
| Variable                  | No | Yes | Chronic pain | % no | % yes | Fisher’s p value |
|---------------------------|----|-----|--------------|------|-------|-----------------|
| Gender                    |    |     |              |      |       |                 |
| Female                    | 10 | 4   | 14           | 71.4 | 28.6  | 0.748          |
| Male                      | 25 | 14  | 39           | 64.1 | 35.9  |               |
| Staging                   |    |     |              |      |       |                 |
| Stage 1 or 2              | 4  | 4   | 8            | 50.0 | 50.0  | 0.679          |
| Stage 3 or 4              | 17 | 9   | 26           | 65.4 | 34.6  |               |
| Surgery                   |    |     |              |      |       |                 |
| No                        | 22 | 10  | 32           | 68.8 | 31.3  | 0.768          |
| Yes                       | 13 | 8   | 24           | 54.2 | 45.8  |               |
| Chemo                     |    |     |              |      |       |                 |
| No                        | 16 | 5   | 21           | 76.2 | 23.8  | 0.247          |
| Yes                       | 19 | 13  | 32           | 59.4 | 40.6  |               |
| Opioids                   |    |     |              |      |       |                 |
| No                        | 18 | 2   | 20           | 90.0 | 10.0  | 0.006          |
| Yes                       | 17 | 16  | 33           | 51.5 | 48.5  |               |
| Gabapentin                |    |     |              |      |       |                 |
| No                        | 33 | 12  | 45           | 73.3 | 26.7  | 0.014          |
| Yes                       | 2  | 6   | 8            | 25.0 | 75.0  |               |
| TCA                       |    |     |              |      |       |                 |
| No                        | 32 | 15  | 47           | 68.1 | 31.9  | 0.397          |
| Yes                       | 3  | 3   | 6            | 50.0 | 50.0  |               |
| NSAID                     |    |     |              |      |       |                 |
| No                        | 28 | 11  | 39           | 71.8 | 28.2  | 0.191          |
| Yes                       | 7  | 7   | 14           | 50.0 | 50.0  |               |
| Number of sites of pain   |    |     |              |      |       |                |
| 0                         | 20 | 1   | 21           | 95.2 | 4.8   |                |
| 1                         | 11 | 4   | 15           | 73.3 | 26.7  |                |
| 2+                        | 4  | 13  | 17           | 23.5 | 76.5  |                |
| Variable                  | Chronic pain | N | Mean | Std. dev. | Std. error | t-test | p-value |
| Age                       | Pain = no     | 35 | 62.23 | 13.831 | 2.338 | 0.425 |
|                           | Pain = yes    | 18 | 59.28 | 9.916  | 2.337 |       |
| Dose                      | Pain = no     | 35 | 5854 | 1562.68 | 264.14 | 0.149 |
|                           | Pain = yes    | 18 | 6470 | 1191.5 | 280.84 |       |
| Duration                  | Pain = no     | 35 | 42.37 | 14.534 | 2.457 | 0.604 |
|                           | Pain = yes    | 18 | 44.33 | 8.957  | 2.111 |       |
There was a significant association between chronic pain and number of pain sites, and individuals with chronic pain were more likely to be treated with opioids. Murphy et al. found increased pain in HNC population to be associated with increased use of opioids [28]. Epstein et al. showed HNC patients treated with XRT to have both nociceptive and neuropathic pain despite ongoing pain management during XRT [25]. Chronic pain has been attributed to radiation therapy among patients with other cancers such as cervical cancer and breast cancer [29–31]. Several explanations are possible, explaining the chronic nature of pain among HNC patients treated with XRT. It could be related to chronic neuropathic pain or secondary to radiation-induced fibrosis as well as due to effects of XRT on the lymphatic system. Peuckmann et al. found almost half of the patients with chronic pain breast cancer patients to have paresthesia of the skin corresponding to the areas of surgery and XRT [31]. Allodynia was associated with XRT only. Another mechanism could be that the irradiated tissue developing increased vascular permeability which in turn leads to fibrin deposition, subsequent collagen formation, and fibrosis. Such radiation-induced fibrosis could damage peripheral nerves which could lead to chronic neuropathic pain [32–34]. Thus, it is possible that such neuropathic pain secondary to XRT might be contributing to chronic pain among HNC patients treated with XRT. XRT could cause somatic pain related to osteonecrosis of bone, and it could also disrupt lymphatics, causing lymphedema and chronic swelling and likely inflammatory pain [35]. However, further research is needed in this field with prospective studies evaluating nature of chronic pain and risk factors among HNC patients treated with XRT.

Higher doses of XRT are known to have a positive correlation with chronic pain among HNC patients, possibly related to radiation-induced fibroatrophic processes [36]. However, we did not find any significant association of XRT dose or XRT duration with chronic pain or with use of pain medications (Tables 8 and 9). This could be due to the lower than average XRT dose used in our study. The average XRT dose in our study was 6063.34cGy, which is lower as compared to the standard regimen of 7000cGy. The lower dose may be due to refusal of further XRT by patients due to side effects of treatment and overall poor quality of life.

In our study group, surgery was not associated with chronic pain or use of pain medications (Table 6). Similarly, chemotherapy had no effect on chronic pain or use of analgesics (Table 7). We did not have any data on use of botulinum toxin injection in HNC patients. Type-A botulinum toxin is an analgesic and a muscle relaxant and has been used to treat pain related to neck muscle spasm and contracture in post-XRT HNC patients. Along with conventional analgesics, future studies should explore Botulinum toxin injection and other therapies as therapeutic options to treat chronic pain in post-XRT HNC patients [37, 38].

Limitations of our study include the fact that it is a retrospective single center study. Comorbid chronic medical conditions were also not adjusted during the statistical analysis.

### Table 6: Surgery and medications.

| Surgery | No | Yes | Total | Fisher’s p value |
|---------|----|-----|-------|------------------|
| **Use of opioids** | | | | |
| No | 14 | 18 | 32 | 0.3859 |
| Yes | 6 | 15 | 21 | |
| **Use of gabapentin** | | | | |
| No | 29 | 3 | 32 | 0.2403 |
| Yes | 16 | 5 | 21 | |
| **Use of TCA** | | | | |
| No | 28 | 4 | 32 | 1 |
| Yes | 19 | 2 | 21 | |
| **Use of NSAIDs** | | | | |
| No | 23 | 9 | 32 | 1 |
| Yes | 16 | 5 | 21 | |

### Table 7: Chemotherapy and medications.

| Chemo | No | Yes | Total | Fisher’s p value |
|-------|----|-----|-------|------------------|
| **Use of opioids** | | | | |
| No | 9 | 12 | 21 | 0.5733 |
| Yes | 11 | 21 | 32 | |
| **Use of gabapentin** | | | | |
| No | 15 | 5 | 21 | 0.2403 |
| Yes | 29 | 3 | 32 | |
| **Use of TCA** | | | | |
| No | 18 | 3 | 21 | 0.6711 |
| Yes | 29 | 3 | 32 | |
| **Use of NSAIDs** | | | | |
| No | 13 | 8 | 21 | 0.2017 |
| Yes | 26 | 6 | 32 | |

### Table 8: XRT dose and medications.

| | n | Mean | Std. dev. | Std. error | p value | Test |
|---|---|------|-----------|------------|---------|------|
| Opioids | No | 20 | 5398.00 | 1910.38 | 427.17 | 0.05 | Mann–Whitney |
| | Yes | 33 | 6466.58 | 937.33 | 163.17 | |
| Gabapentin | No | 45 | 5981.80 | 1561.94 | 232.84 | 0.342 | t-test |
| | Yes | 8 | 6522.00 | 579.23 | 204.79 | |
| TCA | No | 47 | 6101.21 | 1422.24 | 207.45 | 0.603 | t-test |
| | Yes | 6 | 5766.67 | 1899.12 | 775.31 | |
| NSAID | No | 39 | 5922.69 | 1618.93 | 259.24 | 0.247 | t-test |
| | Yes | 14 | 6455.14 | 839.43 | 224.35 | |

### Table 9: XRT duration and medications.

| | n | Mean | Std. dev. | Std. error | p value | Test |
|---|---|------|-----------|------------|---------|------|
| Opioids | No | 20 | 38.20 | 16.13 | 3.61 | 0.277 | Mann–Whitney |
| | Yes | 33 | 45.97 | 9.51 | 1.66 | |
| Gabapentin | No | 45 | 41.89 | 13.36 | 1.99 | 0.124 | t-test |
| | Yes | 8 | 49.50 | 6.97 | 2.46 | |
| TCA | No | 47 | 42.81 | 11.92 | 1.74 | 0.72 | t-test |
| | Yes | 6 | 44.83 | 20.19 | 8.24 | |
| NSAID | No | 39 | 42.56 | 13.42 | 2.15 | 0.659 | t-test |
| | Yes | 14 | 44.36 | 11.47 | 3.07 | |
analysis. The overall sample size in our study is small, and particularly, very small cell sizes \( n < 8 \) should be interpreted with caution.

5. Conclusions

In summary, post-XRT pain among HNC patients is common not only during the acute period but also in the chronic period lasting well beyond three months after completion of XRT. We found discrepancy between frequency of treatment and frequency of chronic pain, suggesting poor documentation of pain in the medical records. Among patients who reported having chronic post-XRT pain, most of them described having severe pain and used descriptors of neuropathic pain. Pharynx was the commonest site of cancer as well as the commonest site of cancer-related chronic pain; squamous cell carcinoma was the most frequent histological pattern, and opioids were used most often to treat such chronic pain. There was a significant association between chronic pain and number of pain sites, and chronic pain was associated with use of opioids. Surgery was not associated with chronic pain or use of pain medications. Similarly, chemotherapy had no effect on chronic pain or use of analgesics. XRT dose had no effect on chronic pain or use of pain medications. Likewise, XRT duration was not associated with chronic pain or use of pain medications. There was no difference in rates of survival among patients with chronic pain as compared to those without pain. Site of cancer and site of cancer-related chronic pain were associated with use of pain medications. However, these results have to be carefully interpreted, given small sample size. Further research using prospective studies with larger samples is needed to explore the characteristics of chronic pain among HNC patients treated with XRT and parse the roles of chemotherapy and radiation.

Data Availability

The clinical data used to support the findings of the study are restricted by the Springfield Committee for Research in Human Subjects (SCRIHS) in order to protect patient privacy. Data are available from Krishna Rao for researchers who meet the criteria for access to confidential data.

Disclosure

This is an unfunded investigator-initiated project. All authors, except Dr. Kallurkar, worked for SIU School of Medicine at the time of data collection.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Acknowledgments

The authors gratefully acknowledge the role of Kissindra Moore, who greatly assisted us in manuscript preparation.

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