Clinical and Translational Radiation Oncology 13 (2018) 1–6

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.elsevier.com/locate/ctro

Original Research Article

Predictors of acute throat or esophageal patient reported pain during radiation therapy for head and neck cancer

Hiram A. Gay [a,*,1], Jung Hun Oh [b,1], Aditya P. Apte [b], Mackenzie D. Daly [a], Douglas R. Adkins [c,d], Jason Rich [e], Peter J. Oppelt [c], Pawel T. Dyk [f], Daniel F. Mullen [a], Laura Eschen [a], Re-I. Chin [a], Brian Nussenbaum [g], Bruce H. Haughey [h], Wade L. Thorstad [a], Joseph O. Deasy [b]

[a] Department of Radiation Oncology, Washington University School of Medicine, St. Louis, MO, United States
[b] Department of Medical Physics, Memorial Sloan Kettering Cancer Center, New York, NY, United States
[c] Division of Medical Oncology, Washington University School of Medicine, St. Louis, MO, United States
[d] Alvin J. Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO, United States
[e] Department of Otolaryngology, Washington University School of Medicine, St. Louis, MO, United States
[f] Department of Radiation Oncology, Missouri Baptist Cancer Center, St. Louis, MO, United States
[g] American Board of Otolaryngology, Houston, TX, United States
[h] Head and Neck Surgery, Florida Hospital Celebration Health, Celebration, FL, United States

ARTICLE INFO

Article history:
Received 20 April 2018
Revised 29 August 2018
Accepted 31 August 2018
Available online 4 September 2018

Keywords:
Head and neck
Pain
Radiotherapy
Esophagus
Throat

ABSTRACT

Background and purpose: Acute pain during weekly radiotherapy (RT) to the head and neck is not well characterized. We studied dose-volume metrics and clinical variables that are plausibly associated with throat or esophageal pain as measured with a weekly questionnaire during RT.

Materials and methods: We prospectively collected weekly patient-reported outcomes from 122 head and neck cancer patients during RT. The pain score for each question consisted of a four-level scale: none (0), mild (1), moderate (2), and severe (3). Univariate and multivariate ordinal logistic regression analyses were performed to investigate associations between both esophageal and throat pain and clinical as well as dosimetric variables.

Results: In multivariate analysis, age was significantly associated with both types of pain, leading to odds ratio (OR) = 0.95 (p = 0.008) and OR = 0.95 (p = 0.007) for esophageal and throat pain, respectively. For throat pain, sex (OR = 4.12; p = 0.010), with females at higher risk, and fractional organ at risk (OAR) mean dose (OR = 3.30; p = 0.014) were significantly associated with throat pain.

Conclusions: A fractional OAR mean dose of 1.1 Gy seems a reasonable cutoff for separating no or mild pain from moderate to severe esophageal and throat pain. Younger patients who received RT experienced more esophageal and throat pain. Females experienced more throat pain, but not esophageal pain.

1. Introduction

Radiotherapy (RT) to head and neck causes mucositis and pain in most patients by the end of the treatment course. Treatment-related pain results from radiation damage to the mucosal epithelium, causing thinning, atrophy, inflammation, and resulting ulceration [1]. The pain can be worsened by radiation-induced xerostomia and reduced mucosal lubrication, and in some cases superimposed candida or bacterial infection [1]. Mucositis seems to involve five biological phases: initiation, primary damage response, signal amplification, ulceration, and healing [2]. Erythema, an early sign of mucositis, presents around 4–5 days following chemotherapy or 10 Gy or more of radiation [3]. Confluent ulcers develop 7–10 days after chemotherapy or after 30 Gy of radiation given in 2 Gy fractions [3], coinciding with an increase in pain. The addition of cytotoxic chemotherapy to RT has been reported to be associated with worse oral mucositis than RT alone [4].

A qualitative study noted that all participants viewed effective pain management as a key facet of their RT treatment for head and neck cancer, previous pain experienced influenced current perceptions of pain, forewarning of potential pain did not reliably

* Corresponding author at: Department of Radiation Oncology, Washington University School of Medicine, 4921 Parkview Place, Campus Box 8224, St. Louis, MO 63110, United States.
E-mail address: hiramgay@wustl.edu (H.A. Gay).

[1] Drs. Gay and Oh are co-first authors who equally contributed to the study.

https://doi.org/10.1016/j.ctro.2018.08.004

improve pain experiences, and participants preferred and benefited from pain management by a specialist team [5].

Tumor, dental extraction, neoadjuvant chemotherapy, or head and neck surgery-related pain may be present prior to the initiation of radiation, thereby complicating the patient's pain experience during radiation. Chang et al. have found that transdermal fentanyl reduced pain during RT, but with increased nausea and vomiting [6]. In a phase III randomized trial comparing doxepin rinse versus placebo, Leenstra et al. have shown that doxepin diminished oral mucositis pain [7]. In contrast, Ling and Larsson have found that individualized pain treatment with systemic analgesics maximally exploited was insufficient to reduce pain severity [8].

Acute pain during weekly RT is not well characterized or understood, despite the resulting significant impact on quality of life. Given this knowledge gap, we studied dose-volume metrics and clinical variables that are plausibly associated with throat or esophageal pain as measured with a weekly questionnaire during RT.

2. Materials and methods

We prospectively collected weekly patient-reported outcomes (PROs) from 122 consecutive head and neck cancer patients during RT who were treated at Washington University School of Medicine in St. Louis between 2010 and 2012. The study was approved by institutional review board. After removing patients who received multiple RT and who did not have target RT structures analyzed in this current study, 96 patients were evaluable. The majority of patients (N = 94) were treated with intensity-modulated RT (IMRT); only two patients were treated with 3D conformal RT (3DCRT). The questionnaire was designed to measure the degree of pain in 16 anatomical structures: gums/gingiva, lip, lymph node(s), ear, eye, face, food pipe/esophagus, mouth, neck, scalp, sinus, skin, throat, tongue, tooth/teeth, and voice box/larynx. Patients were asked: "Do you have pain in the:". The pain score for each question consisted of a four-level scale: none (0), mild (1), moderate (2), and severe (3). The current study focused on 2 of the 16 anatomical locations: the "food pipe/esophagus" and the "throat". The organ at risk (OAR) contouring was standardized. The esophagus was contoured inferiorly from the level of the sternal notch to its superior extent. The throat was contoured inferiorly from the inferior border of the mandible superiorly to the hard palate and encompassed the oral cavity.

Patients were treated in the supine position while immobilized using a thermoplastic mask. Fusion of PET/CT and/or MRI scans to the planning CT helped define the clinical tumor volumes (CTVs) as well as clinical and pathologic information. Up to two CTVs (CTV1, CTV2) were defined. In general, for surgical patients, the CTV1 encompassed the high-risk volume which consisted of the preoperative primary gross tumor volume (GTV) with a 0.5–1 cm margin and any involved lymph node levels. For non-surgical patients, the CTV1 encompassed the primary GTV with a 1–1.5 cm margin and involved lymph nodes plus a 0.5 cm margin. For both types of patients, the CTV2 corresponded to electively treated lymph node levels. Planning target volumes (PTVs) were defined by adding 0.5 cm to the corresponding CTVs and subtracting 3 mm from the skin. Depending on the treatment, CTV1 and CTV2 received 70 and 56 Gy (non-surgical), 66 and 54 Gy (surgical p16-), or 60 and 52 Gy (surgical p16+), respectively. Patients receiving chemotherapy received: either induction or concurrent chemotherapy. Concurrent chemotherapy consisted of either cisplatin, carboplatin, or cetuximab. Induction chemotherapy included TPF (docetaxel, cisplatin, and 5-FU), ACCF (Abraxane, Cetuximab, Cisplatin, and 5 –FU), or carboplatin and etoposide. In general, pain medications were prescribed as needed starting with "magic mouthwash" (aluminum hydroxide and magnesium hydroxide, diphenhydramine elixir, viscous lidocaine, and nystatin in equal parts swish and swallow), followed by an opioid prescribed on an as-needed basis, and finally, a combination of a fentanyl patch for baseline pain and oxycodone or morphine as needed for breakthrough pain.

2.1. Statistical analysis

Univariate and multivariate ordinal logistic regression analyses were performed to investigate associations between both esophagus and throat pain and clinical as well as dosimetric variables. Dosimetry data was extracted from the esophagus and oral cavity planning volumes using CERR (computational environment for radiological research) [9]. Because peak pain levels are typically reached well before the end of treatment, we tested "fractional" OAR dose-volume metrics obtained by dividing dose-volume histogram metrics by the number of fractions. The endpoint was the maximum pain score derived from the weekly PROs.

3. Results

Weekly completion rates of PROs were 79%, 82%, 83%, 80%, 81%, 79%, and 64% for esophageal pain and 81%, 84%, 88%, 82%, 80%, 77%, and 70% for throat pain. Table 1 shows patient characteristics. Regarding sex, out of 96 patients, 75 were male and 21 were female. At the time of RT consultation, 21 were smokers. There were 26 heavy drinkers and 57 patients with $\geq$20 pack-year smoking history. Forty-seven patients received chemotherapy and 47 patients underwent surgery. Most patients (N = 63) received RT to both sides of the neck and 20 patients were treated on one side of the neck whereas 13 patients received no neck RT; for those patients, only the primary PTV was irradiated without intentional neck radiation. Forty-six patients required a feeding tube at any time and 31 of those patients still had one at the last follow-up. The most common primary tumor sites were oropharynx and larynx with 33 and 20 patients, respectively. The T stage of most patients (N = 57) was T3 or T4. The N stage of most patients (N = 52) was N2.

For this cohort, maximum pain scores were averaged for each treatment week as shown in Fig. 1. For both types of pain, the pain score reached its peak, on average, in the 5th week, with an average pain score of 2.5 (standard error (SE): 0.19) for esophageal pain and 2.5 (SE: 0.22) for throat pain, respectively. Fig. 2 shows the fractional mean dose in the esophagus for esophageal pain and the oral cavity for throat pain as a function of maximum pain scores. Overall, a trend was observed where pain scores increase as fractional OAR mean doses increase with Spearman correlation coefficients of 0.26 ($p = 0.014$) and 0.50 ($p < 0.001$) for esophageal and throat pain, respectively. Using Fisher's exact test, the best cutoff in fractional OAR mean dose that separates those patients who had an esophageal pain score of 0 or 1 from those with 2 or 3 was 1.09 Gy ($p = 0.001$) whereas it was 1.06 Gy ($p < 0.001$) for throat pain (Fig. 3). For simplicity, we summarize this using 1.1 Gy as the fractional OAR mean dose cutoff for both pain endpoints.

In univariate ordinal logistic regression using Dx (minimum dose to the x% highest dose volume), mean dose, and maximum dose in esophagus, mean dose showed the highest odds ratio (OR) associated with esophagus pain: OR = 2.40 ($p = 0.027$) (see Table 2). For throat pain, maximum dose in the oral cavity showed the highest OR of 19.55 ($p = 0.006$) followed by mean dose with an OR of 6.64 ($p < 0.001$). In univariate analysis, significant clinical variables were found to be associated with both types of pain, including age, side of neck treated, alcohol, chemotherapy, and surgery (see Table 3). Sex was significantly associated with throat pain