Scientific Article

Palliative Radiation Therapy for Bone Metastases in Neuroendocrine Neoplasms

Michelle Guan BS [a], **Ingrid He MD** [a], **Michael Luu MPH** [b], **John David MD** [c], **Jun Gong MD** [a], **Veronica R. Placencio-Hickok PhD** [a], **Robert S. Reznik MD** [c], **Richard Tuli MD, PhD** [c], **Andrew E. Hendifar MD** [a,*]

[a]*Division of Hematology and Oncology, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, California;* [b]*Biostatistics and Bioinformatics Research Center, Cedars-Sinai Medical Center, Los Angeles, California; and* [c]*Department of Radiation Oncology, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, California*

Abstract

Purpose: Bone metastases are reported in 10% to 12% of patients with neuroendocrine neoplasms (NENs) and can lead to pain and skeletal-related events (SREs), resulting in diminished quality of life and functional status. In other solid tumors with bone metastases, radiation therapy (RT) is an established treatment approach for SREs, yet few data are available in NENs historically considered to be radioresistant. We hypothesize that RT is effective for pain and other SREs in NENs and aimed to delineate any differences in pain palliation and time until progression of pain between different fractionation and dosing schedules of RT.

Methods and Materials: We retrospectively reviewed 686 records of patients with NENs treated at the institution between 2011 and 2018 and identified 28 (4.1%) patients treated with RT for 61 cases of SREs. The primary endpoint was change in patient reported pain scores after RT.

Results: All 28 patients experienced bone pain. Nineteen sites were treated with a single fraction (doses of 800-1800 cGy) and 42 sites with fractionated regimens (doses of 900-3750 cGy over 3-15 fractions). In 55 of 61 cases (90%), patients experienced improvement in pain after RT. The median time to recurrence or progression of pain was 3.5 months. Significant differences were found between primary site and change in performance status ($P = .024$), sex, and reported magnitude of pain score decrease after RT ($P = .025$). There were no differences in the time to the progression of pain, change in performance status, and degree of improvement in pain based on age, chemotherapy received during RT, or radiation site. Outcomes were similar for patients who received single-fraction versus fractionated regimens ($P = .545$) and between those receiving palliative versus ablative RT regimens ($P = .812$).

Conclusions: Although the majority of cases in this NEN cohort benefited from RT, additional studies on the use of RT in the treatment of painful bone metastases are warranted.

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Introduction

Neuroendocrine neoplasms (NENs) can arise from various primary sites of the diffuse endocrine system, most commonly from the gastrointestinal tract, pancreas, and lung.[1] NENs typically remain asymptomatic until the tumor has metastasized, resulting in a need for palliative care for the management of cancer-related pain. The heterogeneity of NENs results in variable clinical manifestation, prognosis, and metastatic capacity of the disease.[2] Although survival for all NENs has steadily improved over time, the incidence and prevalence of NENs continue to rise.[3]

With advances in imaging techniques, more than half of patients with NEN present with metastatic or unresectable disease on initial diagnosis, with 10% to 12% of the patients experiencing bone metastases (BM).[3,4] Metastases to the bone represent the most commonly reported reason for cancer-related pain, with 42.4% of patients with NEN with BM experiencing pain.[5] BMs can also result in skeletal-related events (SREs) other than pain, including hypercalcemia, anemia, susceptibility to infection, skeletal fractures, compression of the spinal cord, spinal instability, and decreased mobility.[4,6-8] This cancer-related bone pain and other SREs can substantially diminish quality of life, functional status, and outcomes in patients with cancer.[8] Current management of skeletal metastases include analgesia, systemic therapy, radiation therapy (RT), surgery, ablative technique, or combinations thereof.[9] However, many of these modalities may not produce satisfactory long-term pain relief.[10] Pharmacologic approaches are also still widely used to address bone pain, but both opiates and nonsteroidal anti-inflammatory drugs involve significant dose-limiting side effects.[8]

Palliative RT is an established treatment approach for reducing SREs in other cancer types and is effective in reducing cancer-related bone pain and frequency of other SREs.[11,12] Multiple studies have shown that approximately 60% to 70% of patients experience some degree of pain relief after RT, regardless of RT regimen, and that RT is effective in both restabilizing the osteolytic bone and minimizing the risk of paraplegia.[13-15] Although pain relief is a proven benefit of RT, limited data are available for use of RT to manage bone-related pain in neuroendocrine neoplasms, which have historically been considered radioresistant. Subsequently, RT is not routinely selected as the main form of BM-directed treatment for patients with NEN, with only 25% of patients with NEN with BM receiving palliative RT.[5]

The purpose of this study was to evaluate the use of RT as a primary form of BM-directed therapy for the palliation of pain in patients with NEN. We evaluated the differences in pain palliation in terms of degree and time until progression of pain between different fractionation and dosing schedules of RT selected, specifically whether there are differences in pain relief resulting from ablative or palliative intent RT.

Methods and Materials

With institutional review board approval, a retrospective analysis of patients with NENs treated at a single institution from 2011 to 2018 was conducted. Patients with histologic diagnosis of stage IV NEN, development of BM, resulting pain from the BM, and receipt of RT were identified.

Clinical variables and SRE incidents from clinical notes and radiology reports were recorded for each patient. Data included sex, age, treatment history, primary tumor location, histologic grade, radiation site location, RT dosing and fractionation schedules, pain scores, performance statuses, and time until progression of pain.

Patient characteristics and treatment history were abstracted by medical record review, characterized using descriptive statistics, and expressed as frequencies and percentages. Time to event analysis was performed only for patients with known follow-up by fitting a univariate Cox proportional hazard model assessing time until the progression of pain. For the purposes of statistical analysis, patient age was stratified into 3 groups (<50, 50-70, >70 years), chemotherapy was stratified into 3 groups (somatostatin analog only, targeted therapies, and other), primary site was stratified into 3 groups (nonpancreatic gastrointestinal NENs, lung NENs, other), radiation site was stratified into 3 groups (axial skeleton, appendicular skeleton, both), and radiation schedules were stratified into 2 groups (ablative dosing, palliative dosing).

A subset univariate analysis was performed among patients with documented change in pain score and change in performance status. Analysis of change in pain and Eastern Cooperative Oncology Group performance scores was performed using 1-way analysis of variance, Welch t test, or Pearson χ^2 test as appropriate among age, sex, primary site, stereotactic radiation type, radiation site,

Table 1   Patient with NEN demographic characteristics

Characteristic	No. (%)
Sex (n = 28)	
Female	15 (53.6)
Male	13 (46.4)
Primary Site (n = 29)*	
Pancreas	7 (24.1)
Nonpancreatic GI cancers	5 (17.2)
Lung	9 (31.0)
Other	6 (20.7)
NR	2 (6.9)
Grade—GI NENs (n = 17)*	
G1	8 (27.6)
G2	8 (27.6)
G3	1 (3.4)
Grade—lung NENs (n = 12)*	
Typical	7 (24.1)
Atypical	2 (6.9)
Large cell	1 (3.4)
Small cell	1 (3.4)
Unspecified	1 (3.4)

Abbreviations: GI = gastrointestinal; NEN = neuroendocrine neoplasm; NR = not reported or unavailable.
  * Two separate NENs were diagnosed in 1 patient.

Table 2   Treatment of SREs

Characteristic	No. (%)
Site of radiation (n = 61)	
Axial skeleton	48 (77.4)
Appendicular skeleton	9 (14.5)
Both	4 (6.5)
Type of radiation therapy (n = 61)	
Single fraction	19 (31.1)
Fractionated	42 (68.9)
Radiation dose (n = 61)	
Definitive dose*	19 (31.1)
Palliative dose*	40 (65.6)
Incomplete[†]	2 (3.3)
Response to radiation (n = 61)	
Improvement	55 (90.2)
No response	3 (4.9)
NR*	2 (3.3)
Did not complete treatment	1 (1.6)
Time to recurrence (n = 61)	
No recurrence	20 (32.8)
≤2 mo	17 (27.9)
>2 mo	19 (31.1)
NR*	5 (8.2)
Systemic therapy received (n = 28)	
1 line	7 (25)
2 lines	19 (67.9)
No systemic therapy	2 (7.1)
Other SREs (n = 62)[‡]	
Neurologic compromise	7 (11.3)
Impending or compression fracture	9 (14.5)
No other SREs	46 (74.2)
Other treatments for SRE (n = 61)	
None	18 (29.5)
Surgery	4 (6.6)
Zoledronic acid	1 (1.6)
Denosomab	3 (4.9)
Surgery and zoledronic acid	1 (1.6)
Surgery and denosomab	1 (1.6)
NR*	33 (54.1)

Abbreviations: NR = not reported or unavailable; SRE = skeletal-related event.
  * Definitive: doses of 1600 to 2500 cGy over 1 to 5 fractions; palliative: doses of 800 to 3750 cGy over 1 to 15 fractions.
  [†] Incomplete; patients did not complete regimen.
  [‡] More than 1 other SRE was found in 1 patient.

and type of systemic therapy.[16] All statistical analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria, version 3.5.1) with a 2-sided test and significance level of .05.[17]

Results

Study population

From 2011 to 2018, of the 686 patients with NEN reviewed, we identified a total of 28 who were treated with RT for 61 cases of BM-related pain, including 1 patient diagnosed with 2 different NENs (Table 1). There were 13 male (46%) and 15 female (54%) patients between the ages of 35 and 88 years. The majority of patients had lung NENs (37.9%) and included 7 typical carcinoids (24.1%), 2 atypical carcinoids (6.9%), 1 large cell (3.4%), and 1 small cell (3.4%) NEN. Eighteen nonlung NENs were also found; this includes 7 pancreatic (24.1%), 5 nonpancreatic gastrointestinal (17.2%), 6 other (20.7%), and 2 undocumented primary (6.9%) NENs. The tumor grades of these nonlung NENs included 8 low- (27.6%), 8 intermediate- (27.6%), and 1 high-grade (3.4%) NEN (Table 1).

The treatment and radiation details of the patients are summarized in Table 2. Of all the identified patients with NEN who underwent radiation treatment for their BM, 48 lesions involved the axial skeleton (77.4%), 9 were appendicular skeleton related (14.5%), and 4 cases (6.5%) involved both. A total of 19 sites (31.1%) were treated

with single-fraction (SF) doses of 800 to 1800 cGy and 42 sites (68.9%) with fractionated regimens that included doses of 900 to 3750 cGy given over 3 to 15 fractions. Of these documented radiation regimens, 19 (31.1%) were classified as ablative (doses of 1600-2500 cGy over 1 to 5 fractions), 40 (65.6%) as palliative (doses of 800-3750 cGy over 1 to 15 fractions), and 2 (3.3%) as incomplete doses. Seven patients (25%) received 1 line of systemic therapy, 19 patients (67.9%) received ≥2 lines, and 2 patients (7.1%) received no systemic therapy. Other treatments received for the BM-related pain include 4 with surgery (6.6%), 1 with zoledronic acid (1.6%), 3

Table 3   Univariate analysis for analysis of variance for decrease in pain score

Characteristic	Means (SD)	P value*
Age, y		.674
<50	5.33 (2.08)	
50-70	5.75 (1.66)	
>70	4.90 (2.01)	
Primary site		.646
Pancreas	5.75 (0.96)	
Nonpancreatic gastrointestinal	6.00 (2.00)	
Lung	5.50 (2.17)	
Other	4.38 (2.06)	
Stereotactic radiation		.392
Definitive	6.00 (0.89)	
Palliative	5.25 (1.99)	
Sex		.025
Male	6.17 (1.34)	
Female	4.44 (1.84)	
Radiation site		.537
Appendicular	6.50 (0.71)	
Axial	5.50 (1.78)	
Both	4.67 (2.08)	
Systemic therapy		.853
Chemotherapy	4.50 (2.12)	
Somatostatin analog only	5.45 (1.61)	
Targeted therapy	5.67 (2.25)	
Other	6.00 (1.41)	

* A significant P value indicates a significant linear correlation.

Table 4   Univariate analysis for time to progression of pain

Progression of Pain	Hazard ratio (95% CI)	P value
Age (vs < 50 y)		
50-70	0.863 (0.368-2.022)	.734
>70	0.533 (0.187-1.525)	.241
Systemic therapy (vs chemotherapy)		
Somatostatin analog only	2.030 (0.600-6.870)	.255
Targeted therapy	2.534 (0.706-9.098)	.154
Other	2.068 (0.417-10.252)	.374
Primary site (vs pancreatic)		
Lung	1.302 (0.531-3.192)	.565
Nonpancreatic GI	1.302 (0.486-3.485)	.599
Other	0.594 (0.206-1.715)	.336
Radiation site (vs appendicular)		
Axial	1.132 (0.438-2.929)	.798
Both	0.849 (0.164-4.386)	.845

Abbreviations: CI = confidence interval; GI = gastrointestinal.

with denosumab (4.9%), 1 with surgery and zoledronic acid (1.6%), and 1 with surgery and denosumab (1.6%).

Outcomes analyses in all patients

Out of all the identified patients with NEN who underwent radiation treatment for their BM, all 28 patients experienced bone pain; 7 patients (25%) experienced neurologic compromise, and 9 patients (32.1%) had documented impending or pathologic fractures (Table 2). Fifty-five of the BM-related pain events (90.2%) responded positively to radiation, 3 had no response (4.9%), 2 had undocumented response to radiation (3.3%), and 1 did not complete treatment (1.6%). Outcomes were similar for patients who received SF versus fractionated regimens (P = .545) in this cohort. Twenty-one (38.2%) of the 55 BM-related pain events with palliation of pain had documented quantitative pain scores using a 10-point scale before and after RT, with a median decrease in pain score of 6. Of the 32 BM-related pain events with documented performance status before and after RT, there were 4 with improved (12.5%), 26 with unchanged (81.5%), and 2 with worsened Eastern Cooperative Oncology Group or Karnofsky scores after RT (6.3%).

Among all patients with NEN, there were no significant correlations between changes in performance status after RT and the variables of age (P = .408), sex (P = .145), radiation site (P = 1.000), stereotactic radiation (P = .474), and systemic therapy (P = 1.000). There was a significant difference between different primary sites and change in performance status (P = .024). Only 4 lung NENs had improved performance status (40%). A majority reported unchanged performance status (n = 23), including 4 pancreatic (100%), 5 nonpancreatic gastrointestinal cancers (71.4%), 6 lung (60%), and 8 other NENs (100%). Two nonpancreatic gastrointestinal cancers (28.6%) had documented worsening of performance status after RT.

Furthermore, there were no significant correlations between the decrease in pain score after RT and age (P = .674), primary site (P = .646), radiation site (P = .537), stereotactic radiation (P = .392), and systemic therapy (P = .853, Table 3). A significant correlation was observed between the variables of sex and the magnitude of decrease in reported pain score after RT (P = .025), with more males reporting a greater decrease in numerical pain score. Mean values and standard deviations for the magnitude changes in pain scores after RT are summarized in Table 3.

Time to progression analyses

Median time to recurrence or progression of pain was 3.5 months, which includes 20 (32.8%) BM-related pain cases with no recurrence, 17 SRE cases (27.9%) with ≤2 months until recurrence, and 19 BM-related pain events (31.1%) with >2 months until recurrence of pain

(Table 2). There was no significant difference in the time to progression of pain based on primary site (non-pancreatic gastrointestinal 1.30 [95% confidence interval {CI}, 0.5-3.5; P = .599], lung 1.30 [95% CI, 0.5-3.2; P = .565], other 0.59 [95% CI, 0.2-1.7; P = .336], vs pancreatic; Table 4). There was also no significant difference in time to progression of pain based on treatment differences such as systemic therapy received during RT (somatostatin analog only 2.03 [95% CI, 0.6-6.9; P = .255]), targeted therapy (2.53; 95% CI, 0.7-9.1; P = .154), other (2.07; 95% CI, 0.4-10.3; P = .374, vs chemotherapy only), radiation site (axial 1.13; 95% CI, 0.4-2.9; P = .798), both (0.85; 95% CI, 0.2-4.4; P = .845, vs appendicular), or radiation regimen (palliative dose 1.09; 95% CI, 0.5-2.2; P = .812, vs ablative dose).

Discussion

Metastases to the bone currently represent the most common cause of cancer-related pain, reported in all the patients with NEN with BMs selected for this study. Although RT is the most frequent nonsurgical approach prescribed to manage pain from osteolytic bone lesions for patients with cancer, few studies have evaluated the use of palliative RT specifically in NEN patients with BMs and the long-term palliative results of these treatments. To the best of our knowledge, this is the first study that reports the impact of RT on the outcomes of patients with NEN based on an ablative or palliative approach.

Although various dosing regimens were used in our cohort of patients with NEN identified in this retrospective study, no differences on the basis of dose used have been found in patients with cancer achieving complete or partial pain relief from RT.[18-20] Furthermore, no significant differences have been found in quality of life, time until improvement of pain, time until complete pain relief, time until pain progression, nausea, vomiting, or spinal cord compression on the basis of RT dosing, results that we validated in our cohort.[18-20] Similar to our findings, other studies have shown that primary tumor site is also not predictive of initial pain relief or quality of life from palliative RT.[21]

The findings from this study and those from many other clinical trials have also demonstrated no differences in outcomes or pain relief from BM in patients treated with SF versus multifraction (MF) RT.[22,23] In a meta-analysis from Canada, randomized trials of localized RT on BMs were analyzed and no dose-response relationship was detected between SF and MF palliative RT for pain relief from BMs.[23] A recent systematic review of the outcomes of palliative RT for BMs also produced results consistent with previous meta-analyses showing similar rates of overall response and complete response between SF and MF RT for palliation of BMs.[24]

Our findings are similar to those reported in these clinical trials and meta-analyses in that we did not observe any significant differences in outcomes in patients with NEN who received SF versus MF regimens. SF- and MF-treated patients experienced differences in toxicity, with 17% of patients receiving MF RT having experienced grade 2 to 4 acute toxicity, whereas only 10% of the patients receiving SF reported toxicity (P = .002).[25] Previous data on differences in pathologic fractures between those receiving SF and MF regimens has been inconsistent. Although a Dutch study reported that more patients in the MF arm (4%) experienced pathologic fractures compared with the SF arm (2%; P = .05), in nearly all other randomized trials, there are no significant differences in the rate of pathologic fracture between the 2 fractionation regimens.[25,26] Despite the clinical effectiveness, increased quality of life, convenience, and cost efficiency of SF RT, surveys on the patterns of practice of palliative radiation oncologists worldwide reveal that SF regimens of RT continue to be underused for palliative care of cancer-related pain.[27,28]

Several modalities of RT are available for patients with BMs, including external beam RT, stereotactic body RT, and radiopharmaceutical therapy. Notably, the radio-labeled somatostatin analog lutetium-177-Dotatate (^{177}Lu-Dotatate; Lutathera) was approved by the Food and Drug Administration in 2018 for the treatment of gastroenteropancreatic neuroendocrine tumors. The phase 3 NETTER-1 trial demonstrated that ^{177}Lu-Dotatate provided markedly increased progression-free survival, response rates, and time until the deterioration of quality of life measures compared with octreotide LAR alone.[29,30] Additional quality of life findings from the trial include significantly lengthened time until the progression of muscle and bone pain (95% CI, 0.38-0.95; P = .027) with this radiopharmaceutical therapy, which is consistent with our findings that RT is an effective form of palliative treatment in neuroendocrine tumors.[30] To select the most appropriate modality of RT for each patient, various elements must be considered, including prognosis, tumor histology, location, extent of metastases, and association with cord compression, which are factors that need to be studied more comprehensively in patients with NEN.[31]

Combination therapies with RT and ablative approaches, including radiofrequency ablation, high-intensity focused ultrasound, and cryoablation, have also been proposed to control painful BMs.[32,33] An Italian prospective study comparing outcomes in pain relief from cryoablation, RT, or a combination of both concluded that the addition of cryoablation to RT resulted in the highest proportion of improved perceived pain in their cohort of patients with painful BMs.[32] Although some studies have reported that pain relief after RT is temporary and only 15% to 18% of patients report complete responses, a combination approach with ionizing radiation and radiofrequency ablation resulted in effective long-term

management of painful BMs with complete responses (45%) up to 12 weeks after treatment.[34] Current clinical studies include combining thermal ablation and spine stereotactic radiosurgery to control cancer that has spread to the spine.[33] Although these studies do present promising data, more clinical trials need to be done to determine the optimal combinations of RT and various ablative approaches for the most effective pain management of BM and best improvement in quality of life, especially in patients with NEN.

Conclusions

It should be noted that this study is limited by its retrospective design, low number of patients, and heterogeneity across patient characteristics. Nevertheless, we demonstrated that RT effectively led to improvements in pain in a large majority of the patients with NEN reporting pain from BM and that RT reduced pain regardless of age, systemic therapy, primary site, radiation site, or regimen of stereotactic radiation. Because palliative RT has typically demonstrated high local control rates and minimal toxicity to the treated skeletal area, we propose the integration of RT into the standard guidelines for the clinical care of BM from NENs.[31,35] More comprehensive studies need to be done in NENs to understand the role of RT in palliation of pain from BMs and to determine both the optimal modality and schedule of RT for each patient, quality of life changes after RT, cost-effectiveness, and reirradiation rates.

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