

## RADIOTHERAPY FOR PANCREATIC NEUROENDOCRINE TUMORS

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**Purpose:** Pancreatic neuroendocrine tumors (PNTs) are rare malignant neoplasms considered to be resistant to radiotherapy (RT), although data on efficacy are scarce. We reviewed our institutional experience to further delineate the role of RT for patients with PNTs.

**Methods and Materials:** Between 1986 and 2006, 36 patients with PNTs were treated with RT to 49 sites. Of these 36 patients, 23 had radiographic follow-up data, which were used to determine the tumor response rate and freedom from local progression. Long-term toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events.

**Results:** The overall response rate to RT was 39% (13% complete response, 26% partial response, 56% stable disease, and 4% progressive disease). A significant difference in the freedom from local progression between the groups receiving either greater than or less than the median 2 Gy/fraction biologically equivalent dose of 49.6 Gy was found, with all radiographic progression occurring in patients who had received  $\leq 32$  Gy. The actuarial 3-year local freedom from progression rate was 49%. Palliation was achieved in 90% of patients, with either improvement or resolution of symptoms after RT. Of 35 patients, 33 had metastatic disease at their referral for RT, and the median overall survival for this patient population was 2 years. Three long-term Grade 3 or greater toxicities were recorded.

**Conclusion:** RT is an effective modality for achieving local control in patients with PNTs. RT produces high rates of symptomatic palliation and freedom from local progression. Prospective trials of radiotherapy for PNTs are warranted. © 2009 Elsevier Inc.

### INTRODUCTION

Pancreatic neuroendocrine tumors (PNTs) are relatively rare neoplasms, occurring with an incidence of approximately 5 cases per million persons. This tumor type is heterogeneous and includes functional tumors that produce peptide hormones, as well as those that are nonfunctional. Regardless of histologic subtype, definitive therapy for nonmetastatic PNTs involves surgical resection, which is the only potentially curative modality for this disease. For metastatic disease, responses to systemic chemotherapy have been demonstrated (1, 2), and these patients are typically treated with either a strategy of combination chemotherapy or observation. Additionally, for functional tumors, octreotide therapy is used to suppress peptide hormone secretion.

There are several therapeutic options that attempt to reduce tumor burden and provide palliation for patients with neuroendocrine tumors; however, because of the low incidence of this tumor type few studies have limited their analysis to only PNTs. For example, radiofrequency ablation has been shown

to produce symptomatic improvement in the palliative setting (3). Hepatic chemoembolization of PNTs has also been shown to produce both radiographic and clinical responses in patients with unresectable liver metastases (4), and symptomatic palliation with radionuclide therapy continues to be an active area of investigation for PNTs in the metastatic setting (5).

The role of external beam radiotherapy (EBRT) in the management of PNTs is largely unknown and limited to anecdotal experiences. It is, therefore, somewhat surprising that PNTs are commonly considered to be radioresistant. In contrast, the data from published case reports suggest that PNTs may be responsive to RT and chemoradiotherapy (6–10). Furthermore, PNTs often present as unresectable tumors, making EBRT an attractive therapeutic modality for the management of this disease.

Because few data regarding the efficacy of RT for PNT exist, we undertook a review of our institutional experience in treating this subtype of pancreatic tumor with EBRT. We

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investigated patient outcomes after RT with respect to local control, radiographic response, and survival. We now report the largest case series of PNTs treated with EBRT, and demonstrate that RT is an effective treatment modality to provide symptomatic palliation and local control of this disease.

## METHODS AND MATERIALS

We completed an institutional review board-approved retrospective analysis of all patients with neuroendocrine tumors of the pancreas treated with RT at the University of Michigan between January 1986 and January 2006. The patient charts were reviewed to collect individual patient data for age, gender, race, date of diagnosis, tumor histologic type, and history of multiple endocrine neoplasia. Previous surgical resection, receipt of cytotoxic chemotherapy, or participation in clinical trials was also recorded. Because patients in this group had undergone multiple therapeutic interventions before referral for RT, the indication for RT was also determined.

The radiation doses, fractionation schedules, treatment dates, and RT techniques were documented. For comparison, all doses were converted to a 2 Gy/fraction biologically equivalent dose (BED<sub>2Gy</sub>). All patients were treated with megavoltage equipment. The clinical responses to RT were determined from physician assessments at the follow-up evaluations. Radiographic follow-up data were available for 26 patients. Computed tomography scans and written reports were both reviewed to determine the pre- and post-RT tumor sizes, and the objective radiographic response was scored according to the Response Evaluation Criteria in Solid Tumors (11). Long-term toxicity was evaluated by review of the patient's departmental chart and the University of Michigan centralized, multidisciplinary electronic medical records. Long-term toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

The goal of RT in this patient population was to provide either local disease control in the pancreas or to palliate symptomatic distant metastasis. Therefore, for analysis, the patients were divided into two groups: those who had undergone RT to the primary pancreatic site and those who had undergone RT to a metastatic site. Patients with R1 or R2 resections treated to the pancreatic resection bed were included in the primary pancreatic site group.

The probability of overall survival was estimated using the product-limit Kaplan-Meier method. The follow-up time for local progression was calculated from the initiation of RT and continued until documented local progression or the last known radiographic assessment without evidence of progression.

## RESULTS

### *Patient and treatment characteristics*

A total of 36 patients, treated to 49 sites, were identified for this review. RT records were available for 35 of these patients. A pathologic diagnosis of neuroendocrine carcinoma was established in each case by tissue biopsy. The tumors were classified as one of the four following histologic categories: islet cell carcinoma, gastrinoma, vasoactive intestinal peptide producing carcinoma, or neuroendocrine carcinoma not otherwise specified. No patient had a history of multiple endocrine neoplasia. Additional patient characteristics are listed in Table 1.

Of the 35 patients, 14 were treated with RT to the primary tumor or tumor resection bed. Of these 14 patients, 8 had had

Table 1. Patient characteristics

Characteristic	Value
Gender ( <i>n</i> )	
Male	15
Female	21
Race ( <i>n</i> )	
White	33
Black	3
Age at diagnosis (y)	
Range	19–77
Median	51
Histologic type ( <i>n</i> )	
Islet cell	18
Gastrinoma	5
VIPoma	2
Neuroendocrine (NOS)	11
History of MEN ( <i>n</i> )	0
Sites treated ( <i>n</i> )	49
Total patients ( <i>n</i> )	36

*Abbreviations:* VIPoma = vasoactive intestinal peptide producing carcinoma; NOS = not otherwise specified; MEN = multiple endocrine neoplasia.

surgically unresectable disease, and 6 had undergone resection with either gross residual disease left behind/positive margin (*n* = 3) or multiple positive lymph nodes (*n* = 3). The remaining 21 patients were treated solely to sites of distant metastasis, predominantly to the liver or bone. Of the 14 patients treated to the primary site, 13 were chemotherapy naive, and 20 of the 21 patients treated to metastatic sites had undergone at least one course of cytotoxic chemotherapy before RT. The median dose delivered to the primary and metastatic sites was 58.4 and 24.6 Gy, respectively. Of the 35 patients included in this report, 32 were treated for symptoms or because of progressive disease. Additional treatment characteristics are listed in Table 2.

### *Radiographic response and time to radiographic progression*

For 23 patients treated to 26 sites, follow-up computed tomography scans were performed to evaluate the disease

Table 2. Treatment with surgery, radiotherapy, and chemotherapy

Treatment	RT site	
	Pancreas	Metastasis
First site treated with RT	14	21
Previous surgical resection	4	9
Previous chemotherapy	1	20
Metastasis at RT	12	21
Total dose delivered (Gy)		
Range	50.4–63	20–72.6
Median	59.4	24.2
Concurrent chemotherapy		
Yes	4	15
No	10	6

*Abbreviation:* RT = radiotherapy.

Data presented as numbers, unless otherwise noted.

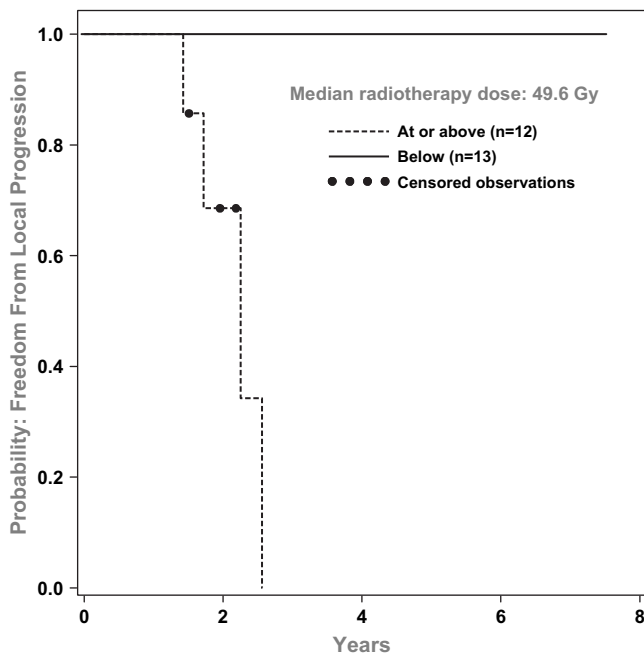


Fig. 1. Freedom from local progression.

status (Fig. 2). Of these 26 sites, 10 were treated to the primary site and 16 were treated to sites of metastasis, with 14 of this latter group receiving palliative RT to the liver. An analysis of the response rates demonstrated 13% complete response, 26% partial response, 56% stable disease, and 4% progressive disease.

The interval to radiographic disease progression was also determined for patients receiving either greater than or less than the median  $BED_{2Gy}$  of 49.6 (Fig. 1). A significant difference was observed between these groups ( $p < .01$ ), and all cases of radiographic progression occurred in patients who had received  $\leq 32$   $BED_{2Gy}$ . This dose–response relationship could not be separated from the potential effect of treatment site, because each patient with tumor progression was treated for a hepatic metastasis. An additional analysis of only those 14 patients treated to the liver was therefore performed, but no significant differences were found in the median dose between the patients with and without progression (27.8 and 34.9 Gy, respectively;  $p = .24$ ). The radiographic response

rate was also evaluated as a predictor of local tumor control. Differences between responders (complete or partial) and non-responders were not significant, with a freedom from local progression time of 2.6 and 2.3 years, respectively ( $p = .36$ ).

#### Palliation

Follow-up data describing the symptomatic response to therapy was available for 20 patients treated to 31 sites. The patients were typically treated to the pancreas ( $n = 8$ ) or liver ( $n = 8$ ) to palliate symptoms of pain, nausea, vomiting, or obstructive jaundice. RT was also prescribed for brain metastases ( $n = 1$ ) or painful metastases to bone ( $n = 12$ ) or other sites ( $n = 2$ ). Overall, the symptoms were substantially improved or resolved in 28 (90%) of 31 patients, and 22 of 28 sites had documented improvement by the 1-month follow-up appointment.

#### Toxicity

Two acute and three late Grade 3 or greater toxicities developed among the 33 patients who completed RT (Table 3). All toxicities occurred in patients who had undergone both an open surgical procedure (open biopsy, tumor “debulking,” or distal pancreatectomy) and RT to the primary site. All patients experiencing toxicity had received  $>50.4$  Gy. Both acute toxicities were considered to be possibly related to the delivered RT course or chemoradiotherapy. In both patients, surgical exploration and repair were required for either gastric perforation or what was described as large bowel inflammation leading to sepsis. Both of these patients had been treated for unresectable primary tumors  $>5$  cm in size. Late effects of RT were identified in 3 patients. Two Grade 3 toxicities (duodenal stricture, gastrointestinal bleeding requiring hospitalization and transfusion) were identified at 10 and 14 months after treatment to unresectable primary tumors. A third patient developed Grade 5 toxicity secondary to a duodenal perforation 21 months after completing therapy. This patient had been treated for positive margins and multiple positive lymph nodes after distal pancreatectomy.

#### Overall survival

At the time of this analysis, 30 of 35 patients were known to have died, with a median overall survival of 2.0 years (95%

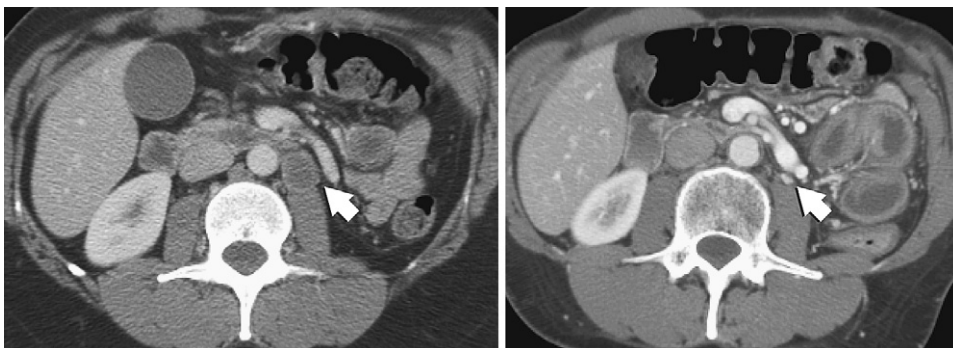


Fig. 2. Abdominal computed tomography scans of 44-year-old woman with pancreatic gastrinoma initially treated with surgical resection, sandostatin, and adjuvant chemotherapy (cisplatin, carboplatin, irinotecan) with disease progression. Arrows identify para-aortic disease before (Left) and 3 months after (Right) a course of chemoradiotherapy.

Table 3. Acute and long-term toxicity

Toxicity	Grade	Radiation dose (Gy)	Previous surgery	Chemoradiotherapy	Onset (mo)	Outcome
Acute						
Gastric perforation	4	63	Open biopsy	No	1	Surgical repair
Septic colitis	4	60	Open biopsy	Yes	<1	Surgical repair
Late						
GI bleed	3	59.4	Open biopsy	No	14	Transfusion
Duodenal stricture	3	50.4	Tumor “debulking”	No	10	Weight loss
Duodenal perforation	5	50.4	Pancreatectomy	No	21	Death

Abbreviation: GI = gastrointestinal.

confidence interval, 1.4–3.2; Fig. 3). No significant differences were found when patients were divided into groups treated to the primary or metastatic site, although patients treated to the primary site had a trend for an improved 1-year survival rate (86% vs. 62%). Patients treated to the primary site had a median overall survival of 2.1 years (95% confidence interval, 1.7–5.4), and patients treated to a metastatic site had a median overall survival of 1.5 years (95% CI, 0.7–2.7), but these differences were not statistically significant ( $p = .11$ ). This finding is consistent with the fact that 12 of 14 patients treated to the primary site also had metastatic disease.

## DISCUSSION

The results of this study have demonstrated that RT is an effective treatment modality to achieve local control in patients with PNTs. In patients with progressive disease, RT produces high rates of symptomatic palliation for both intra-abdominal and distant sites of disease, yielding an approximate 90% clinical response rate. In this heavily pretreated population of patients, RT produced a 39% radiographic response rate,

comparable to responses produced by traditional chemotherapy regimens (1, 2). Additionally, our analysis suggested the possibility of a radiation dose response for neuroendocrine tumors, with no observed local failures at a dose >32 BED<sub>2Gy</sub>. However, our analysis might have been confounded by treatment site, because all radiographic progressions occurred within the liver. Taken together, these data provide strong evidence for the use of EBRT in the symptomatic management PNTs. Furthermore, our results have challenged the belief that PNTs are radioresistant and have actually demonstrated that this tumor type is relatively sensitive to RT.

Although surgical resection is the only potentially curative therapy for PNTs, most tumors are not surgically resected. An analysis of practice patterns using the National Cancer Data Base identified 9,821 patients, of whom 5,960 (61%) did not undergo resection (12). In our series, a similar percentage of patients (63%) had not undergone surgical resection of their primary disease, but almost one-half of these patients (11 of 23) required RT for control of symptomatic disease at the primary site. In the National Cancer Data Base study, only 8.2% of patients with nonresected PNTs received RT (K. Bilimoria, personal communication, May 30, 2008), while 33% received chemotherapy. Because neuroendocrine tumors have been considered to be radioresistant, it is not surprising that RT has been an underused modality for the treatment of these tumors. Although our case series was retrospective in design, it is the largest published experience of RT for PNTs, and our findings suggest that RT is a reasonable option for symptomatic, unresectable, primary neuroendocrine tumors.

Pancreatic neuroendocrine tumors have a relatively long natural history and superior prognosis compared with adenocarcinomas of the pancreas. It is for this reason that aggressive therapeutic interventions are considered for patients with these tumors; for example, up to one-fourth of patients who undergo surgical resection are known to have metastatic disease (12). This approach remains controversial, and the potential morbidity of aggressive surgical procedures in the metastatic setting has been noted (13). Similarly, the use of EBRT should also be weighed against the risk of complication. The toxicities observed in our study have demonstrated the potential for adverse outcomes with RT. It is, therefore, our recommendation that sophisticated planning techniques, as well as appropriate dose fractionation regimens, should be used. In our series, all patients who experienced a Grade

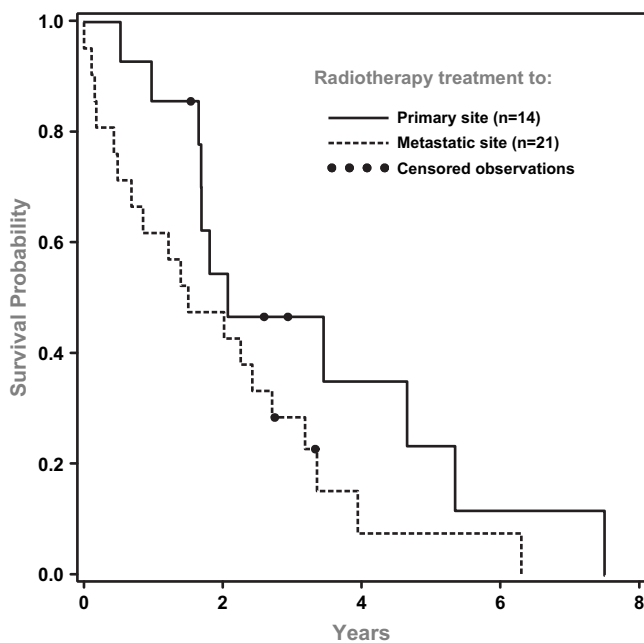


Fig. 3. Overall survival.

3 or greater toxicity had undergone an open surgical procedure followed by RT, consistent with the increase in long-term complications known to occur at other anatomic sites when surgery and RT are combined. Because our patients were treated during a time period that experienced great improvements in abdominal imaging, it is likely that the current ability to determine resectability before surgical exploration would substantially reduce the number of complications.

Recently, several investigations of novel systemic therapies have been reported for patients with metastatic neuroendocrine tumors. In a Phase II trial of combined temozolomide and thalidomide for neuroendocrine tumors, a radiographic response rate of 25% was found for all tumors, and 5 of the 11 patients with PNTs had a response to therapy (14). Based upon the rationale that PNTs are highly vascular, trials of agents with anti-angiogenic properties such as endostatin and sunitinib have also been conducted (15, 16). Sunitinib resulted in a 17% response rate in the 66 patients with PNT, suggesting that novel targeted therapies might be effective in the treatment of this disease. Because RT is known to block the growth of tumor vasculature, a combination of targeted agents and EBRT is an avenue for future investigations.

Our study had some limitations. The analysis was retrospective, the patients were treated during an extended period

(1986–2006), and any bias introduced by referral patterns for RT was unknown. Furthermore, although questions exist regarding the reliability and reproducibility of the World Health Organization grading system (17), we were unable to determine the pathologic grade of the tumors in our series, because most had been diagnosed before the revised 2000 World Health Organization guidelines. Despite these limitations, this report has provided convincing data that RT produces radiographic responses, reduces local progression, and provides a palliative benefit for patients with PNTs.

The findings from this study have also raised a question for the role of RT in the adjuvant setting. For patients with PNT who undergo surgical resection with curative intent, 50% will develop a recurrence within 5 years (13), and positive surgical margins are known to be a poor prognostic factor (18). Because one-half of patients with surgically resectable disease will have a recurrence, prospective investigations of adjuvant therapy in this patient population should also be considered. In the present study, we identified RT as an effective tool for treating patients with PNTs in the palliative setting, and, on the basis of these findings, we suggest that RT should be considered as a part of multimodality therapy for this disease and in the design of future clinical trials.

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