Radiotherapy in the Management of Pancreatic Neuroendocrine Tumors (PNET): Experience at Three Institutions

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Abstract. *Aim: Advanced pancreatic neuroendocrine tumor (PNET) presents a therapeutic challenge as many are unresectable and relatively resistant to systemic therapy with a high malignant potential. We share our experience using concurrent capecitabine or infusional 5-fluorouracil with radiation for patients with resected and locally advanced PNET. Patients and Methods: Six patients (two females, four males) with PNET were treated with capecitabine or infusional 5-FU and concurrent radiation. Results: The median age was 52 years (range: 38 to 63 years), with ECOG Performance Status (PS) 0-1, grade 0-1 weight loss, and grade 0-1 pain. One patient underwent resection with negative margins, two with positive margins, and three had unresectable locally advanced disease. All six patients demonstrated partial radiographic response and sustained local control. The treatment was tolerable with only grade 2 hand-foot syndrome and grade 1 mucositis observed. Conclusion: Prospective studies to further investigate the role of chemoradiation in this setting are warranted.*

Pancreatic neuroendocrine tumors (PNETs) represent a heterogenous group of tumors with varying tumor biology and prognosis (1). The incidence of PNET has increased over the past two decades to approximately 5/1,000,000 persons (2). Advanced PNET remains a difficult therapeutic challenge because of its high malignant potential and resistance to conventional chemotherapy. As a result, there are limited effective treatment options for patients with advanced disease. There have been recent new developments with promising results for the use of novel molecular-targeted agents for the treatment of this disease, such as evirolimus and sutent (3-5). Traditional conventional chemotherapy agents included regimens based on etoposide, platinum agents, anthracyclines, streptozocin, and 5-Fluorouracil (5-FU)-based agents (6). Combined modality chemoradiation is not widely used in the management of local PNET. We present our experience in treating patients with PNET with chemoradiation.

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Patients and Methods

Patients with biopsy-proven, previously-untreated PNET were treated with capecitabine (median dose 600 mg/m^2 *po bid*; range=600-800 mg/m^2) or infusional 5-FU (175 mg/m^2/day) and concurrent radiation. Radiotherapy began on the first day of week 1 of capecitabine or 5-FU. The target volume received external-beam radiation at 180 cGy/day delivered Monday through Friday to a total dose of 50.4 Gy using 3-D conformal radiotherapy or Intensity-modulated Radiation Therapy (IMRT). The treatment volume consisted of the gross tumor volume (GTV), defined by pancreatic and locoregional radiographic abnormalities identified by contrast-enhanced computed tomography (CT); the clinical target volume (CTV). defined as the area at risk for subclinical microscopic disease; and the planning target volume (PTV), typically consisting of a 0.5 cm margin outside of the CTV (Figure 1) (7).

Results

Six patients (two females: four males), median age of 52 years (range: 38 to 63 years), with ECOG PS 0-1, grade 0-1 weight loss, and grade 0-1 pain were included in this series (Table I). Three patients underwent attempted resection, one with negative margins, two with positive margins, and three patients had unresectable locally advanced disease. All patients completed the intended course of therapy.

The treatment was tolerable with two cases showing grade-2 hand-foot syndrome (one requiring capecitabine dose reduction), one case of grade-3 diarrhea (5-FU held for three days), and two cases of grade-1 mucositis. Local control was

Table I. *Demographic characteristics and outcome data*

PT	Age	Gender	Race	Tumor location	Resection	Capecitabine or 5-FU	Outcome	Survival
1	38	F	W	head	Resected; Pos margins	Capecitabine	LR and DM @ 27 mo	DOD @ 9 yrs
2	52	M	W	head	Locally advanced; Biopsy only	5-FU	Stable DS; Symptoms improved	Lost to FU @ 3 yrs
3	59	M	A	head	Locally advanced; Biopsy only	Capecitabine	Stable DS; Symptoms improved	Alive
4	48	F	W	head	Resected; Neg margins; High grade; 3 LN pos	Capecitabine	NED	Lost to FU @ 3 yrs
5	63	M	W	head	Locally advanced; Biopsy only	Capecitabine	Stable DS then NEB Liver mets @ 13 mo	DS controlled on Sandostatin @ 4.5 yrs
6	54	M	W	head	Resected; Pos margins Int grade; 7 LN pos	Capecitabine	LN and liver mets @ 12 mo	DOD @ 2.5 yrs

DS: Disease; LR: local recurrence; DM: distant metastasis; NED: no evidence of disease; LN: lymph node.

achieved in five patients. All three patients with locally advanced disease demonstrated sustained partial radiographic response and improved symptoms. Three distant recurrences occurred from 12 to 27 months following treatment. Progressive disease was observed in two patients with positive margins (one associated with local recurrence), and one with unresected disease. Two of these patients succumbed to PNET and one is alive at 4.5 years with disease controlled on Sandostatin-LAR®. Two patients remain alive without recurrence, one remains alive with controlled metastatic disease, two patients died of progressive disease at 2.5 and 9 years, and two patients, without evidence of recurrence, were lost to follow-up at three years.

Discussion

Chemoradiation for PNET is tolerable and results in excellent local control. Our results are in agreement with a recent report by the University of Maryland School of Medicine, Baltimore, MD and Johns Hopkins University School of Medicine, Baltimore, MD (8). In that series, 11 patients with histologically-confirmed PNET (T3-T4) received external beam radiation therapy to the primary tumor or resection bed to a median dose of 50.4 Gy. Out of these 11 patients, seven received concurrent capecitabine (1,000 mg/m^2 *bid*). Among nine patients with locally advanced disease, two were able to undergo surgical resection. At a median follow-up of 30.4 months, three patients were dead with progressive disease, two had died without progressive disease, three were alive with metastases, and three were alive without metastases (one stable, one partial response, one complete response). Only two grade 3 toxicities were noted. The authors concluded that local radiation therapy may convert initially unresectable, locally advanced tumors to disease amenable to surgical resection, which would theoretically improve local control. In another series by Strosberg *et al*., six patients who were treated with induction chemotherapy followed by concurrent chemoradiation with infusional 5-FU or capecitabine. These studies in addition to ours underline the rationale for administering chemoradiation in patients with PNET. The regimen resulted in 80% objective radiographic response rate and was well-tolerated (9). Prospective studies to further investigate the role of chemoradiation in this setting are warranted. In addition, tumor marker response (chromogranin-A) and symptomatic response should also be studied.

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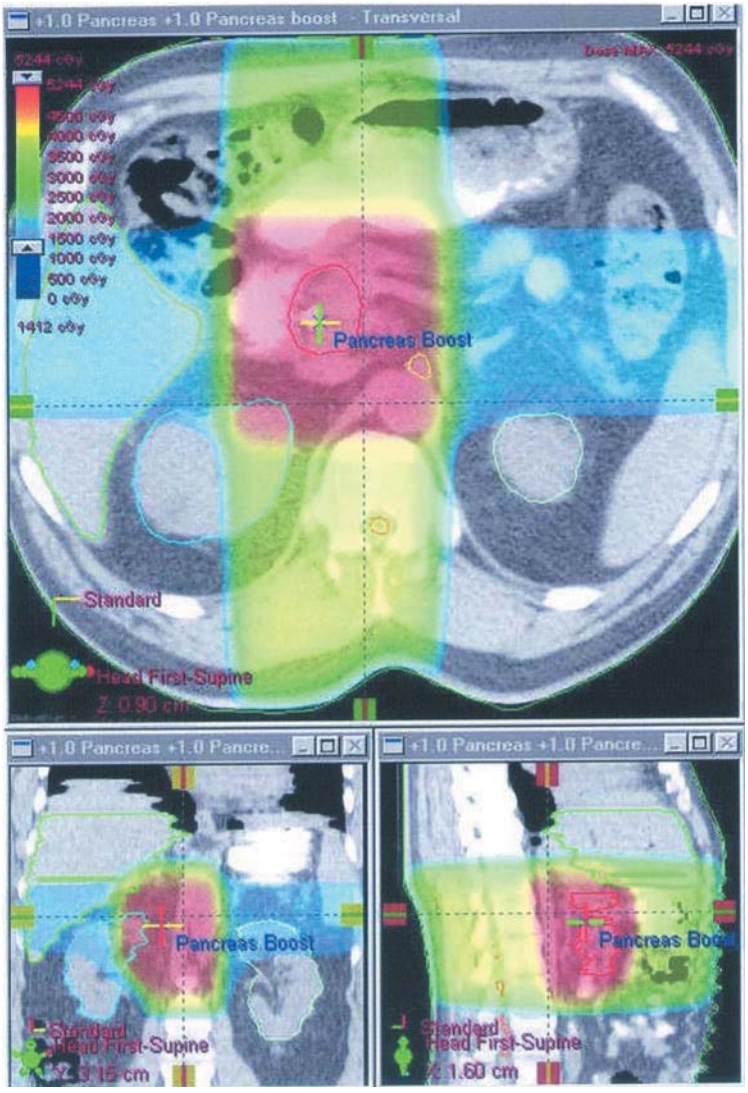

Figure 1. *Three-dimensional treatment plan with color wash dose distributions identifying the dose of tumor delivered to the tumor volume and surrounding normal anatomical structures*.

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