LETTER TO THE EDITOR
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Are PNETs radiotherapy resistant?

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Pancreatic neuroendocrine tumors (PNETs) are a heterogeneous group of tumors with highly variable biological behaviors and clinical course. Despite being rare, its incidence is steadily increasing over time. In recent years, advances have been made in the treatment of these tumors in parallel to the increase in the incidence of PNETs. Although a multidisciplinary approach is required for the clinical management of PNETs, resection remains to be the single curative treatment in early disease. In retrospective studies, it has been reported that surgical resection alone provides better outcomes than other treatment modalities; however, patients eligible for resection comprise only 39% of the patients (1-3). Chemotherapy, radiofrequency ablation, transarterial chemoembolization, biotherapy, polypeptide radionuclide receptor therapy, anti-angiogenic treatment and selective internal radiotherapy alone can be used in advanced PNETs. However, studies have failed to demonstrate long-term survival benefit in these alternative approaches. Today, there is no effective treatment modality for locally advanced PNETs due to high malignancy potential and resistance to conventional chemotherapy. However, it has been attempted to use targeted therapies such as Everolimus or Sutent, radiotherapy and chemotherapy in combination strategies (1-5).

Although there are several studies attempting to define the role and importance of radiotherapy in PNETs in the literature, many uncertainties are present regarding these tumors. Role of external beam radiation therapy (EBRT) is largely unknown in the management of PNETs, and data are limited to anecdotal reports. In general, it is thought that PNETs are resistant to radiotherapy. However, in recent years, there have been studies indicating that PNETs respond to both radiotherapy and chemotherapy. In a study by Saif et al., radiotherapy (50.4 Gy/1.8 Gy fractions) plus capecitabine or infusional 5'-flurouracyl has been given to patients uundergoing surgery due to locally advanced PNET. Authors have reported that chemoradiotherapy was tolerable and provided good local control in the treatment of PNET (1). In a study by Contessa et al., 36 patients with PNET have been treated by external beam radiation therapy. Authors have reported that no local failure was observed at doses > 32 BED (2 Gy) (2). In a study on patients with pancreatic PNET, Zagar et al. have stratified patients into two groups as patients treated with surgical resection alone and those received combined chemoradiotherapy following surgery. In the combination group, patients received radiotherapy (50.4 Gy/1.8 Gy fraction) plus fluoropyrimidine-based chemotherapy. Authors have reported that there was no significant difference in disease-free survival and overall survival between the groups (4). Another study has compared patients undergoing surgery alone with those that received adjuvant radiotherapy among PNET cases with positive surgical margins. Authors have reported that recurrence rate was comparable between the groups and that radiotherapy could be helpful in achieving local control (5). It has been emphasized that radio-

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therapy is a good palliative modality in patients with unresectable tumor and symptomatic findings (2). In another study, it has been suggested that local radiotherapy can achieve debulking in unresectable or locally advanced tumors (6).

Despite being rare, PNETs are treatable tumors increasingly diagnosed by advancing imaging modalities. They have highly variable clinical course with life expectancy varying from months to years. Several modalities have been used in the management of PNET. Due to lack of prospective, randomized studies, it is unknown which criteria should be used to select treatment modality. In the last decade, significant advances have been achieved in the treatment of PNETs by radiotherapy and chemoradiotherapy. In inoperable or locally advanced PNETs, local control, decrease in tumor burden, regression in clinical symptoms, decelerated disease progression and prolonged progression-free survival can be achieved by radiotherapy and chemoradiotherapy. It will be possible to determine the role of radiotherapy by multicenter, prospective studies with larger sample size, providing relatively uniform analysis and specific assessment of tumor groups. The selection of eligible patients, well-constructed treatment plan, and well-planned clinical and radiological follow-up should be the mainstay of studies in this field.

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