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Original Article

# External Beam Radiotherapy in the Treatment of Gastroenteropancreatic Neuroendocrine Tumours: A Systematic Review

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## Abstract

*Aims:* External beam radiotherapy (EBRT) is infrequently used to treat gastroenteropancreatic neuroendocrine tumours (GEPNETS), with little published data to date. We carried out a systematic review to assess the activity of EBRT for GEPNETS.

*Materials and methods:* Major databases were searched for papers including at least five patients treated with contemporary EBRT techniques. Eligible studies underwent dual independent review. The primary end points were response rate for lesions treated with definitive intent and recurrence-free survival for primary lesions treated with neoadjuvant or adjuvant intent.

*Results:* Of 11 included studies (all retrospective), seven investigated pancreatic neuroendocrine tumours (PNETs, 100 patients, 14% grade 3) and four studies investigated extra-pancreatic neuroendocrine tumours (84 patients, 14% grade 3). Trials investigating PNETs administered a median of 50.4 Gy via three-dimensional conformal radiotherapy and intensity-modulated radiotherapy. EBRT was given with neoadjuvant or adjuvant intent in 56 patients, with a recurrence rate of 15%. For the 44 patients not undergoing surgery, the radiological response rate was 46%. Grade 3 + toxicity rates were 11% (acute) and 4% (late). Twelve patients with anorectal neuroendocrine carcinoma received 58 Gy to the primary tumour. Seventy-two patients were treated to sites of metastatic disease (34 bone, 27 brain, 11 soft tissue). Local and distant control were poorly reported. Overall survival ranged from 9 to 19 months. No studies in this group reported toxicity outcomes.

*Conclusions:* There are limited, retrospective data on the overall activity and safety of EBRT in GEPNETS. EBRT generally seems to be well tolerated in selected PNET patients with encouraging activity. Well-designed prospective studies in clearly defined populations are required to clarify the role of EBRT in neuroendocrine tumours.



*Key words:* EBRT; neuroendocrine tumour; radiotherapy; review

## Introduction

Gastroenteropancreatic neuroendocrine tumours (GEP-NETs) are increasing in incidence and are now the second most common upper gastrointestinal cancer after pancreatic adenocarcinoma. They vary greatly in terms of anatomical origin, histology and clinical aggressiveness. High-grade tumours may cause death within weeks, whereas low-grade tumours may remain indolent for years on surveillance alone. The histological classification of neuroendocrine tumours (NETs) has evolved over the past three decades, culminating in the publication of the World Health Organization (WHO) 2010 grading system [1], which classifies them into histological grades by the mitotic and Ki-67 proliferation indices.

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The standard of care for resectable NETs is surgery. However, some patients may not be candidates for surgical resection due to their medical comorbidities; in addition, 50% of tumours may be unresectable (either locally advanced or metastatic) at presentation [2]. For these tumours, systemic therapy is often the primary treatment modality, with the choice of therapy dependent on histology and grade. Unfortunately, systemic therapies such as somatostatin analogues and targeted therapies have a limited duration of effect. Tumour progression at the primary site or metastatic disease can cause significant morbidity, including pain, neurological compromise, small bowel obstruction or hormonal symptoms. In many cases, non-surgical local ablative therapies, such as radiofrequency ablation or external beam radiotherapy (EBRT), may prevent or palliate such morbidity and may improve survival rates.

EBRT has a well-established role in the treatment of carcinomas of the gastrointestinal tract, used either alone or in combination with other modalities such as surgery or chemotherapeutic agents. It may be delivered over several weeks in small daily fractions of 1.8–2 Gy, referred to as conventional fractionation, or as a single or few high-dose, spatially focused highly conformal therapies, referred to as stereotactic radiosurgery (SRS) or stereotactic body radiotherapy (SBRT), respectively. In general, EBRT may be used as the primary treatment modality for a patient with a localised and non-metastatic malignancy or to palliate symptoms or maximise local control of the primary tumour or metastases. Although there is a significant body of data regarding the efficacy and role of EBRT in other solid tumours, there is a paucity of data for EBRT in GEPNETS.

We carried out a systematic review to assess the current literature regarding the benefits and harms of EBRT in the treatment of GEPNETs.

## Materials and Methods

### *Eligibility Criteria*

Eligible studies included all clinical studies, whether retrospective or prospective, and case series investigating the use of EBRT in humans with histologically confirmed GEPNETs of any histological grade. Studies or reports with less than five patients with GEPNETs treated with radiotherapy were excluded. Radiotherapy could consist of any dose, fractionation and technique of EBRT, including SBRT or SRS. Studies utilising whole abdominal radiotherapy were excluded as this modality is now largely obsolete. Studies that did not report on any of the end points listed below were excluded from qualitative analysis.

### *Search Strategy*

We carried out a literature search of MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic reviews, ACP Journal Club and DARE on 14 July 2016. A manual search of the proceedings of ASCO, ASCO GI and ENETs from 2013 to 2016 was carried out on 17 October 2016. The reference lists of relevant review articles were also scrutinised for potentially eligible studies. The search strategy is described in the Appendix.

### *Study End Points*

For studies investigating radiotherapy to primary lesions, either with neoadjuvant or definitive intent, the primary end point was response rate. For studies investigating radiotherapy to the primary lesion in the adjuvant setting, the response rate was not measureable and recurrence-free survival was instead adopted as the primary end point. For studies investigating radiotherapy to metastatic lesions, the response rate was the primary end point.

Secondary end points included disease control rate (a composite of complete response, partial response and stable disease), biochemical response, progression-free survival, overall survival and toxicity. Studies that did not report on any primary or secondary end points were excluded.

Studies were classified according to their type (retrospective or prospective) and the site of radiation (primary or metastatic). Where studies investigated radiation of both the primary and metastatic sites, they were classified under the metastatic category.

### *Study Selection and Data Extraction*

The methods of potentially eligible studies were assessed independently by two reviewers (DC, ML), with disagreements resolved by consensus with a third reviewer (SM). Information extracted from studies included study identifiers, inclusion/exclusion criteria, baseline information regarding the participants, radiotherapy details of the interventional arm and control arm (if available), length of follow-up and risk of bias assessment. Risk of bias assessments were to be carried out using the GRADE criteria [3] for prospective studies and the Newcastle–Ottawa Scale for retrospective cohort studies. We aimed to summarise the above end points without performing a meta-analysis, given the anticipated clinical heterogeneity in the identified trials.

## Results

### *Study Selection*

The results of the search are detailed in the CONSORT diagram (Figure 1). In total, 4445 records were identified using the electronic search strategy; 180 records were evaluated in full-text form, with 156 being excluded on further review. This left 24 study records (11 studies after de-duplication) for analysis [4–14].

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