Peptide Receptor Radionuclide Therapy for Advanced Neuroendocrine Tumors

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KEYWORDS

• Bone marrow • Bronchopulmonary • Carcinoid • Gastroenteropancreatic neuroendocrine tumor • Hepatic neuroendocrine metastasis • Peptide receptor radionuclide therapy • PRRT • Renal toxicity

KEY POINTS

- Peptide receptor radionuclide therapy (PRRT) with either ^{90}Y-octreotide or ^{177}Lu-octreotate is an efficient and relatively safe treatment of unresectable or metastatic neuroendocrine tumors.
- Over 2 decades, PRRT has been demonstrated to provide effective tumor response, symptom relief, and quality-of-life improvement, biomarker reduction, and, ultimately, a positive impact on survival.
- PRRT is generally well tolerated. Chronic and permanent effects on target organs, particularly the kidneys and the bone marrow, are generally mild if appropriate precautions are undertaken.

INTRODUCTION

Neuroendocrine neoplasms are variously referred to as "carcinoids," neuroendocrine tumors (NETs), or gastroenteropancreatic (GEP) neuroendocrine (NE) neoplasms (GEP-NENs).[1] Most NETs are located in the gastroenteropancreatic tract and in the lung (**Fig. 1**).[1] In general, they are slow-growing tumors but in some instances may behave in a highly aggressive fashion (neuroendocrine carcinoma; NEC).[2] Due to their diverse and protean symptoms (sweating, flushing, diarrhea, bronchospasm, and anxiety), diagnosis is often significantly delayed and lesions therefore are only identified when metastatic spread has occurred. Metastasis can occur locally, in the mesentery, in adjacent lymph nodes, and by hematogenous spread. In most, the liver is the dominant site of metastatic spread, but lung, bone, and brain may also be affected.[3] As a consequence of the substantial percentage of individuals with metastatic disease, most therapeutic strategies are directed at the management of hepatic secondaries or local recurrence.[4]

Given the different organ distribution of the primaries and their widely different biologic behavior,

The authors have nothing to disclose.

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Thorac Surg Clin ■ (2014) ■–■

http://dx.doi.org/10.1016/j.thorsurg.2014.04.005

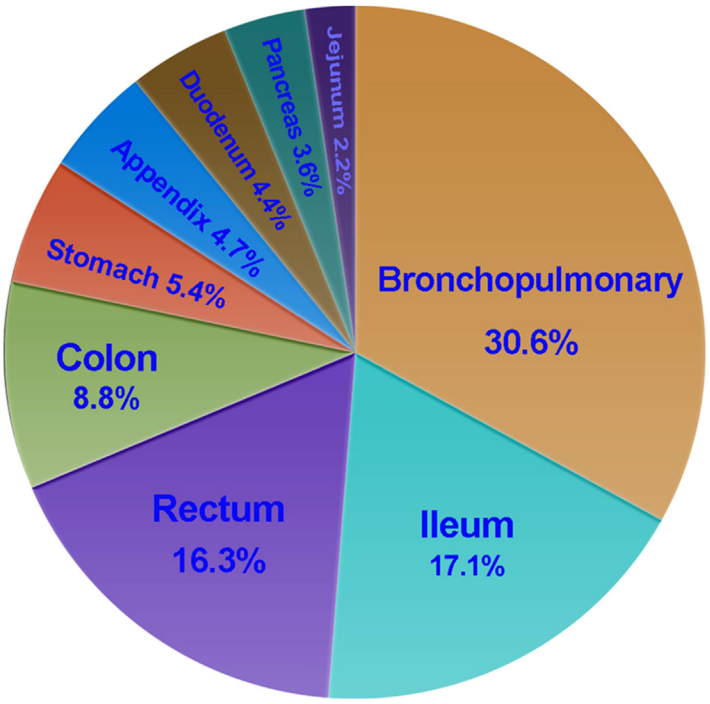

Fig. 1. Incidence of different types of NETs. Most are located in the gastroenteropancreatic tract and the lung.

treatment of NETs is typically multidisciplinary and is individualized according to the tumor type, extent of the disease, and level of symptoms. GEP-NENs were previously considered rare, but in fact, not only are increasing in incidence (3.65/100,000), but also occur as frequently as testicular tumors, Hodgkin disease, gliomas, and multiple myeloma.[1] They represent a significant clinical issue for 2 reasons. First, at diagnosis, 40% to 95% are metastatic (depending on the primary site) and, second, there is a paucity of evidence-based best practice strategies.[1] A key management issue is that at diagnosis, 65% to 95% of GEP-NENs (excluding appendiceal and gastric NETs) have metastasized to the liver.[5,6] Therapeutic endeavors are therefore in most instances focused on the management of metastatic disease, and neuroendocrine liver metastases (NE LMs) represent one of the most significant prognostic factors irrespective of the primary tumor site. Thus, the 5-year survival in historical series is 13% to 54% compared with 75% to 99% in individuals without hepatic metastases.[7,8]

Recent experience from some specialized centers documents improved 5-year overall survival rates of 56% to 83% for metastasized intestinal NENs and 40% to 60% for pancreatic NENs.[9] Although these data have been used to suggest that NET management should only be undertaken at specialized centers, such proposals may not be realistic in the current medical economic climate. Despite the use of a diverse variety of complex management strategies for NE LMs, surgery remains the only treatment option with the potential to cure.[9] For unresectable tumors, optimal selection of palliative treatment options (timing and modality) is of paramount importance to maintain or improve quality of life (QoL) and prolong overall survival.

OVERVIEW

Unlike many well-studied neoplastic diseases such as breast or colon cancer, NETs represent relatively recent clinicopathologic entities. As a consequence, their management has evolved over the last decade based on increased understanding of their tumor biology and molecular regulation. Given the diverse appreciation of the disease complexity, a variety of different sequences of diagnostic and therapeutic procedures has being proposed and debated in individual medical centers.[10] Key issues involved in the development of an optimal management strategy include the precise type of the tumor, the grade and stage of the lesion, and the overall patient's general condition. Ideally, removal of the primary tumor should be initially undertaken and, thereafter, appropriate strategies should be developed for the management of residual disease. It is the latter issue that often evokes controversial discussion because there exists a paucity of rigorous