

Procedure guideline for the use of ^{177}Lu -DOTATATE for Neuroendocrine Tumours

Effective Date: July, 2021



Background

Neuroendocrine tumours (NETs) are a family of tumours, occurring with an incidence of about 5.25 cases per 100,000¹. The incidence of NETs is increasing over the last 3 decades. NETs can arise in several organs; the most common sites are the ileum and pancreas, followed by other sites within the GI tract, the lungs, thyroid, parathyroid, adrenal glands, and pituitary gland. However, NETS can occur anywhere in the body^{2,3}. NETs are often classified as functioning or nonfunctioning tumours, the latter of which do not present with hormone hypersecretion, and are often found as a bulky tumours with metastatic disease. The five-year survival rate for patients with NETs depends largely upon the location of the primary tumour and the extent of disease. Patients with localized disease can expect five-year survival rates ranging from 65% for ileal tumours to 84% for lung tumours and 90% for rectal tumours⁴. As expected, patients with distant disease carry a worse prognosis with five-year survival rates ranging from 24% in the rectum and 27% in the lungs to 54% in the ileum⁵.

Few curative options are available for patients with unresectable, progressive, or metastatic NETs. Peptide receptor radionuclide therapy (PRRT) has been studied in the clinical trial setting since about the year 2000. Several agents are potentially available, including 90Y-DOTAOC⁶, 111In-DTPAOC⁷, 177Lu-DOTATATE⁸, which are radionuclides bound to the somatostatin analog octreotide. These agents work by binding to the tumour receptors and emitting radiation to the tumour. The Health Canada approved product (Lutathera, 177Lu-DOTATATE) is administered with a dose of 200mCi every 8 weeks for a total of four cycles. Dosing and timing may differ based on a centre's specific clinical research trial protocol. The most common side effects of treatment are nausea /vomiting, fatigue and decreased blood counts. Rare severe toxicities include myelodysplasia, acute leukemia, renal failure and hormonal crisis (if the tumour is secretory). The full listing of adverse events can be viewed further in the Lutathera product monograph and/or the centre's trial protocol. The purpose of this guideline is to provide evidence-based recommendations on the use of PRRT for NETs and to define which patients are candidates for this treatment. This guideline will focus on the role of 177Lu-DOTATATE^{9,10} in the treatment of NETs.

Guideline Questions

1. What are the indications for use of 177Lu-DOTATATE for peptide receptor radionuclide therapy (PRRT)?
2. What work up (i.e., diagnostic imaging, blood work) is required prior to the initiation of treatment with PRRT?
3. In which patients is PRRT contraindicated?

Search Strategy

The National Guidelines Clearinghouse and individual cancer agencies' websites were searched for guidelines on the use of peptide receptor radionuclide therapy. Among the guidelines identified, Cancer Care Ontario's document, *Radionuclide Therapy for Neuroendocrine Malignancies* (August

15, 2011), was deemed appropriate by the working group for adaptation. The search strategy employed by Cancer Care Ontario was current to 2010¹¹. In order to make the guideline adaptation current to 2018, the MEDLINE and EMBASE database was searched (2010 through 2021) using the same search strategy.

The search initially resulted in 1530 citations after duplicates were removed. Studies that did not report response rates or survival rates were excluded, as well as prospective studies that included 30 or fewer patients or retrospective studies that included 100 or fewer patients. A total of 60 publications were deemed relevant. Evidence is summarized in the table in Appendix A.

Target Population

The recommendations in this guideline apply to patients diagnosed with unresectable, progressive, or metastatic neuroendocrine tumours.

Recommendations

1. Peptide receptor radionuclide therapy (PRRT) is an appropriate treatment option for patients with unresectable or metastatic; progressive or symptomatic, NETs. Consideration for treatment is to be determined at a multidisciplinary neuroendocrine tumour board.
2. Required work up
 - Confirm diagnosis and staging of NET with histopathology and biochemical assays. The tumour differentiation must be present on the pathology report: Grade 1 (ki-67 < 3%) Grade 2 (ki-67 3% -20%), and selected Grade 3 (>20%) tumours¹².
 - Images should be reviewed to assess for receptor heterogeneity. If there is discordance between imaging modalities with presence of lesions that are suspected to be dedifferentiated based on absence of uptake on somatostatin receptor imaging or if they exhibit a rapid progression pattern on anatomic imaging, an FDG PET-CT should be performed to exclude aggressive or dedifferentiated disease that would not be amenable to PRRT and for prognostic purposes.
 - Baseline tumor markers should be obtained prior to initiating therapy, depending on origin and hormonal secretion status (secreting or not, ex: CgA and 5-HIAA, Insulinemia, etc).
 - Somatostatin receptor imaging (SRI) using PET or SPECT, such as Ga68 DOTA PET, octreotide scan or other available SRI imaging, to determine if tumour is somatostatin receptor positive. Sufficient tumour uptake is defined as higher than normal liver uptake.
 - For Higher grade tumors: ki67 >10%, it is recommended that Diagnostic imaging (CT and MRI), should be less than 3 months old.
 - If PRRT is received within a clinical trial, additional work up may be required based on the study protocol.

- Conduct an appropriate laboratory assessment at baseline and before each cycle (directed at known side effects of treatment)
 - hematologic: CBCD (complete blood count and differential)
 - kidney function: electrolytes, creatinine and eGFR
 - liver function: bilirubin, albumin, INR, ALT
 - metabolic: fasting glucose
 - Perform cross sectional imaging (CT and/or MRI) at baseline (within 6 months of therapy initiation or less in case of suspected significant interval changes: significant elevation in tumor markers, clinical deterioration or other imaging showing significant progression) and at follow-up to assess tumour response. If PRRT is offered within a clinical trial, additional imaging may be required for tumour response assessment as per the trial protocol.
3. Additional recommended work-up: Echocardiogram for assessment of cardiac function in the context of serotonin-producing primary tumour.
4. The use of long acting somatostatin analogue prior and during PRRT will be individually assessed based on the PRRT therapy protocol used. This may be either offered under the Health Canada approved and provincially funded indication if applicable or under a clinical research trial protocol.
5. Contraindications to PRRT
- Absolute:
 - Absence of somatostatin receptors in progressing tumors.
 - Any conditions which may warrant surgery or other intervention in the immediate future (ex: spinal fusion for unstable pathological fracture or cord compression)
 - Pregnancy and/or breast feeding
 - Relative:
 - Impaired hematological function
 - Severe cardiac impairment
 - Chemotherapy within 8 weeks prior to the start of treatment
 - Prothrombin time increased, excluding achieved therapy targets with anti-coagulation.
 - Severe or acute concomitant illnesses, uncontrolled with treatment. This includes diabetes mellitus as assessed by a hemoglobin A1c >10%
 - Severe psychiatric or mental disorders
 - Severe renal impairment <30ml/min or as specified by the clinical trial protocol
 - Severe hepatic impairment >3xULN
 - Recent surgery within 12 weeks, individually assessed based on the type of surgery (e.g cataract surgery or removal of superficial skin lesions are permitted)
 - A minimum 4 weeks after liver-directed therapy , caution is advised to allow for longer delays in case of sequelae or with isotope liver-directed therapy

- o ECOG>2 and inability for self-care
- o Inability to follow radiation safety guidelines as per protocol

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Development and Revision History

This guideline was reviewed and endorsed by the Alberta Provincial Endocrine Tumour Team. Members include [surgical oncologists, radiation oncologists, medical oncologists, dermatologists, nurses, pathologists, and pharmacists]. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Endocrine Tumour Team, external participants identified by the Working Group Lead, and a methodologist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the [Guideline Resource Unit Handbook](#).

This guideline was originally developed in 2021.

Maintenance

A formal review of the guideline will be conducted in 2023. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

CBCD, Complete Blood Count and Differential; CT, Computed Tomography; DOTATATE, DOTA-DPhe1Tyr3-octreotate; FDG, F-fluorodeoxyglucose; ECOG, Eastern Cooperative Oncology Group; NET, Neuroendocrine tumours; PRRT, Peptide receptor radionuclide therapy; PET, Positron emission tomography, SRI, Somatostatin receptor imaging;

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial Endocrine Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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Conflict of Interest Statements

Dr. Stella Koumna: has nothing to disclose

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