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Gallium-68 PET Imaging in Neuroendocrine Tumours

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Gallium-68 PET Imaging in Neuroendocrine Tumours

Section 1: Recommendations and Key Evidence

OBJECTIVES

To provide a summary of evidence surrounding the clinical utility of Gallium-68 (^{68}Ga) positron emission tomography (PET) imaging in patients with neuroendocrine tumours (NETs) and recommendations for their use in Ontario.

TARGET POPULATION

Adult and pediatric patients with suspected or diagnosed well-differentiated NETs.

INTENDED USERS

This recommendation report is intended to guide the Ontario PET Steering Committee with respect to the development of indications in the context of the patient management pathway. This recommendation report may also be useful to inform clinicians who are involved in the care of patients with NETs.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

Recommendation 1
^{68}Ga-DOTA-TATE/-TOC/-NOC PET or PET/computed tomography (CT) is recommended for the initial diagnosis of adult patients with clinical (e.g., signs, symptoms) and biochemical (e.g., markers) suspicion of NETs but for whom conventional imaging is negative or equivocal or for whom biopsy is not easily obtained.
Qualifying Statements for Recommendation 1
• PET or PET/CT functions as a supplement to and does not replace biopsy for establishing a definite diagnosis. • It is unknown whether pediatric patients would benefit from PET or PET/CT since there is a lack of evidence to support making any recommendation for this specific population.
Key Evidence for Recommendation 1
• Six studies assessed the sensitivity and specificity of PET or PET/CT for the initial diagnosis of NETs [1-6]. The sensitivity and specificity on a per-patient based analysis ranged from 81% to 100%, and 85% to 100%, respectively, with a summarized sensitivity of 91% (95% confidence interval [CI], 85% to 94%) and specificity of 94% (95% CI, 86% to 98%).
Interpretation of Evidence for Recommendation 1
The meta-analysis of six studies showed that PET or PET/CT is highly sensitive and specific for evaluating patients with a suspicion of NETs at initial diagnosis. PET or PET/CT does not negate the need for a biopsy as biopsy remains the gold standard for preventing unnecessary additional tests or procedures due to the potential for false-positive scans. In addition, other disease-specific information (e.g., ki-67, differentiation) can be obtained from a tissue biopsy that is not determinable from PET or PET/CT. Poorly differentiated NETs often have reduced expression of somatostatin receptors that may lead to false-negative scans; even so, downstream testing would not be considered without other corroborating data. Overall, study quality was limited by the uncertainties surrounding the blinded interpretation of the index test (PET or PET/CT) and reference standard (histology and/or follow-up). Unclear risk may be a consequence of incomplete reporting; however, it is unknown whether this would have an impact on the results or conclusions of the study.

Recommendation 2

^{68}Ga-DOTA-TATE/-TOC/-NOC PET or PET/CT is recommended for the staging of adult patients with localized primary NETs and/or limited metastasis where definitive surgery is planned.

^{68}Ga-DOTA-TATE/-TOC/-NOC PET or PET/CT is recommended for determining somatostatin receptor status and suitability for peptide receptor radionuclide therapy.

^{68}Ga-DOTA-TATE/-TOC/-NOC PET or PET/CT is recommended for the staging of adult patients with NETs where detection of occult disease will alter the treatment options and decision making.

Qualifying Statements for Recommendation 2

- PET or PET/CT may be superior to octreoscan for all the stated indications.
- It is unknown whether pediatric patients would benefit from PET or PET/CT since there is a lack of evidence to support making any recommendation for this specific population.

Key Evidence for Recommendation 2

- In the 10 direct-comparison studies, the sensitivity of PET or PET/CT for detecting primary and/or metastatic lesions ranged from 78.3% to 100%, whereas the specificity ranged from 50% to 100% [2,7-15].
- Naswa et al [11] demonstrated that ^{68}Ga-DOTA-NOC PET/CT was better than conventional imaging (contrast-enhanced CT [CeCT], magnetic resonance imaging, ultrasound) in detecting both the primary tumour (sensitivity, 78.3% versus 63.8%, $p<0.001$) and metastases (sensitivity, 97.4% versus 81.8%, $p<0.001$), while maintaining high specificities.
- Albanus et al [14] reported ^{68}Ga-DOTA-TATE PET/CT to be more sensitive and more specific than CeCT in detecting lymph node metastases (sensitivity, 92% versus 64%, $p=0.0156$; specificity, 83% versus 59%, $p=0.0386$) and bone metastases (sensitivity, 100% versus 47%, $p=0.0039$; specificity, 89% versus 49%, $p=0.0004$). ^{68}Ga-DOTA-NOC PET/CT was also more specific than CeCT for the detection of pulmonary metastases (95% versus 82%, $p=0.0313$), with equal sensitivity.
- Overall, change in management occurred in 45% (95% CI, 36% to 55%) of cases, with the majority of the changes involving surgical planning and patient selection for peptide receptor radionuclide therapy [7,10,11,13,16-20].

Interpretation of Evidence for Recommendation 2

Due to the heterogeneity of the studies in terms of diagnostic performance measure for which PET or PET/CT was indicated, the Working Group members considered a change or impact in decisions in patient management to be the most appropriate outcome. There remains the possibility that PET or PET/CT may demonstrate false-positive results that would lead to inappropriate changes in management. Nonetheless, PET or PET/CT provides superior evaluation of disease when conventional imaging is equivocal. This is particularly true in instances where a biopsy is not easily obtained.

Recommendation 3

There is no recommendation regarding the use of ^{68}Ga-DOTA-TATE/-TOC/-NOC PET or PET/CT in the assessment of treatment response for NETs.

Qualifying Statements for Recommendation 3

- PET or PET/CT may be a good early predictor of disease progression by identifying new metastases that developed during therapy.

Key Evidence for Recommendation 3

- In one study, 46 patients with advanced NETs were investigated before and after two to

seven cycles of ^{90}Y-DOTA-TOC or ^{177}Lu-DOTA-TATE. According to visual response criteria, ^{68}Ga-DOTA-TOC PET showed no advantage over CT for assessing response to therapy (accuracy, 91.3% versus 78.3%, respectively, p=0.27) [22].
Interpretation of Evidence for Recommendation 3
Only one study evaluated the role of PET or PET/CT in the assessment of response after therapy; therefore, the evidence is currently insufficient to support the use of PET or PET/CT in this setting. Since the study utilized a dedicated PET scanner without a CT component, it is uncertain whether the integration of PET with low-dose CT (PET/CT) would significantly impact the diagnostic yield of the test.
Recommendation 4
There is no recommendation regarding the use of ^{68}Ga-DOTA-TATE/-TOC/-NOC PET or PET/CT in the routine surveillance of NETs.
Qualifying Statements for Recommendation 4
• PET or PET/CT should not be used in place of conventional imaging for routine monitoring of asymptomatic patients with no evidence of neuroendocrine activity.
Key Evidence for Recommendation 4
• There were no studies identified that met the study selection criteria examining PET or PET/CT in the routine surveillance of NETs.
Interpretation of Evidence for Recommendation 4
The evidence is currently insufficient to support the use of PET or PET/CT in this setting.

IMPLEMENTATION CONSIDERATIONS

The Working Group members considered these recommendations to be aligned with current practices and patterns of care as well as the desire of the patient community for extended access to ^{68}Ga-DOTA-TATE/-TOC/-NOC PET/CT. Requests from physicians for the provision of this imaging modality for patients will be streamlined in a registry setting. As per all PET scanning services in Ontario, requests for a PET scan for clinical scenarios outside of the recommended indications can be made through the PET Access Program. Each referral is assessed on a case-by-case basis by a panel of experts.

FUTURE RESEARCH

There currently are insufficient data displaying improved outcomes in the routine use of ^{68}Ga-DOTA-TATE/-TOC/-NOC PET/CT in surveillance and to assess treatment response. These indications should be reviewed as new data become available in the future.