Cancer Care Ontario

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Ontario Neuroendocrine Expert Panel Report 2011

Radionuclide Therapy for Patients with Neuroendocrine Tumours (NETs) in Ontario

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EXECUTIVE SUMMARY

Neuroendocrine tumours (NETs) may arise from specific endocrine glands or from diffuse neuroendocrine cells widely distributed in the body. These tumours present in many different ways and are increasing in incidence and prevalence. The treatment of NETs, particularly when advanced, often requires a multidisciplinary team of providers with highly specialized training and may involve multiple treatment modalities over time, including radionuclide (RN) therapy.

Currently, patients in Ontario may receive RN therapy at the London Health Sciences Centre or by travelling out of country. Access to the therapy has been variable due to pressures on funding and health human resources, and inconsistent referral from across the province. Furthermore, RN treatment products are only available through Health Canada's Special Access Program (SAP) and there has been no provincial consensus on which radiopharmaceuticals should be funded in Ontario. There has also been an information gap, as there is no current Province-wide collection of data on this patient population, and SAP regulations preclude the use of data for research purposes.

In recognition of the need to review these issues, Cancer Care Ontario (CCO) struck the Ontario Neuroendocrine Expert Panel to develop recommendations for the organization and delivery of RN therapy for NET patients in Ontario. The work was supported by CCO's Program in Evidence-Based Care (PEBC) division, who performed a formal search for evidence to support these guidelines, and for existing guidelines in other jurisdictions. Data sources available to CCO were also used to provide information on current patterns of care.

The fundamental principles addressed in developing the recommendations that follow, include:

1. Equitable geographic access for patients;

2. Program stability with regards to funding and human resources;

3. Adherence to the Health Canada and Canadian Nuclear Safety Commission Regulatory Framework;

4. Provincial consensus regarding the agent or agents to be utilized;

5. Rigorous standardized data collection to support provincial planning, evidence-based decision making and future funding.

RECOMMENDATIONS

1. **In Ontario, radionuclide therapy for neuroendocrine tumours should be offered in a province-wide clinical trial, under the authority of a Clinical Trial Agreement with Health Canada, with appropriate data collection and analysis of outcomes to: 1) support the securing of a Notice of Compliance from Health Canada for the therapeutic radiopharmaceutical; and, 2) enable future clinical and funding decisions.**

2. **Patients must meet specific criteria to be considered as eligible for radionuclide therapy.**
3. **Patient support specific to RN therapy must be provided by NET program teams.**
4. **Provincial service volume current state and forecasting is needed to estimate present and future demand for radionuclide therapy in Ontario.**
5. **Treatment centre facilities and multidisciplinary case conferences must meet minimum requirements as defined.**
6. **Medical facilities providing radionuclide therapy must have a radiation safety program that undergoes an annual review to confirm that the program meets the operational objectives of the facility and regulatory requirements. The program must include policies, practices and equipment to maintain radiation exposures to workers and the public as low as reasonably achievable (ALARA), with social and economic factors being taken into account.**
7. **The availability of the radiopharmaceuticals should be facilitated by partnering with an organization (or organizations) capable of bringing the radiopharmaceuticals to market in Canada through a Health Canada-approved regulatory framework, and ensuring a safe and consistent supply to any and all treatment facilities in the province.**
8. **Provincial specialized services oversight for RN therapy should be established by Cancer Care Ontario (CCO).**

RADIONUCLIDE THERAPY FOR NETS IN ONTARIO

CURRENT STATE

There are approximately 2,500 people in Ontario currently living with neuroendocrine tumours (NETs). It is not possible to get an exact count of this population because these tumours are still commonly under-reported and under-counted. The general trend found in the surveillance data from the Ontario Cancer Registry shows the incidence, prevalence, and survival of patients with NETs are all rising steadily (Tables 1–3). This trend is consistent with the international literature and the trend in the U.S. (Yao et al., 2008). The reported increase in neuroendocrine tumours over time is likely due to multiple factors, including better detection, better classification of tumours, and a true increase in incidence. In comparison with other GI neoplasms, neuroendocrine tumours are now seen to be significantly more common than esophageal cancer, gastric cancer, pancreatic cancer, and hepatobiliary cancer due to their prolonged survival (Yao et al., 2008).

The treatment of neuroendocrine tumours with radiopharmaceuticals began nearly 30 years ago with the use of ^{131}I-metaiodobenzylguanidine (mIBG) (Grunwald & Ezziddin, 2010), followed by the introduction of peptide receptor radionuclide therapy (PRRT) in the late 1980s (Pool et al., 2010). Over the last 20 years, a number of different PRRT agents and regimens have been developed. Although there is broad clinical agreement that PRRT is beneficial, the literature supporting its use is relatively modest. Furthermore, there are no published randomized controlled trials conducted on either mIBG or PRRT in NET patients (Gulenchyn, Yao, Asa, Singh, & Law, 2011). To date all published studies have reported on patients with inoperable residual or metastatic disease that was measureable on anatomical imaging and detectable with ^{111}In-octreotide (Octreoscan[TM]).

Radionuclide (RN) therapy services for Ontarians with neuroendocrine tumours are currently provided at the London Health Sciences Centre (LHSC) and via the Out-of-Country program of the Ministry of Health and Long-Term Care (Tables 4, 5). Since 1996, the Neuroendocrine Cancer Program at London Health Sciences Centre has treated 379 patients (primarily after 2000) with one of three agents: ^{131}I-Lipiodol, ^{131}I-mIBG, or ^{111}In-Octreoscan™ (high-dose custom preparation). Those patients who have been referred to hospitals in the UK and Europe due to disease recurrence have received one of two agents: ^{177}Lutetium or ^{90}Yttrium chelated to somatostatin receptor binding agents. There has not been consensus in the province, around which radiopharmaceuticals should be funded for the management of NETs, or on which patients should be eligible for this treatment modality.

None of the radiopharmaceuticals indicated for the treatment of NETs have received a Notice of Compliance from Health Canada, nor have these drugs been administered under the authority of a Clinical Trials Agreement (CTA). The drugs currently being used at LHSC are approved on a case-by-case basis through Health Canada's Special Access Program (SAP), the regulations of which preclude the publication of patient outcomes, with the exception of reporting adverse events. The drugs are being manufactured on-site in London.

The LHSC program was reviewed by Deloitte Consulting in 2007, and the final report was issued January 30, 2008. The report noted that the number of patients being treated in London was growing with a compounded annual growth rate of approximately 9%, a growth rate slightly greater than that of other programs reviewed. Note was made of the disproportionate number of patients seen from the South West Local Health Integration Network and the current review of more recent data (Table 4) indicates that this disparity has persisted. The conclusion was drawn that there was disparity of access across the province, due largely to inconsistent referral of patients, and that the workloads at that time were likely underestimates of the full numbers of patients eligible for therapy in the province.

Based on the incidence and prevalence data extracted from the Ontario Cancer Registry (Tables 1,3), and the usual eligibility criteria defined in the current literature on PRRT, the Ontario NET Expert Panel estimates that there are between 120 and 150 NET patients in Ontario (per year) who would be newly eligible for radionuclide therapy.

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Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, Abdalla EK, Fleming JB, Vauthey J, Rashid A, Evans DB. (2008). One Hundred Years After "Carcinoid": Epidemiology of and Prognostic Factors for Neuroendocrine Tumors in 35,825 Cases in the United States. *Journal of Clinical Oncology*, 26 (18): 3063-3072.

SURVEILLANCE DATA

Source: Cancer Care Ontario (Ontario Cancer Registry, 2010)
Data prepared by: Surveillance, Population Studies and Surveillance

Table 1: Number of Neuroendocrine Incident Cases in Ontario by Histology, 2002–2007, by year and sex, age 15+

	Histology code	2002	2003	2004	2005	2006	2007	2002–2007
Large cell neuroendocrine carcinoma	8013	7	17	22	17	13	30	106
Carcinoid tumour, NOS	8240	161	168	216	248	234	253	1,280
Neuroendocrine carcinoma	8246	104	132	147	144	202	215	944
Other neuroendocrine	*	33	26	26	25	37	39	186
Paragangliomas	8680, 8693	†	†	†	†	†	†	17
Pheochromocytoma, malignant	8700	†	†	5	†	†	†	21
Neuroblastomas	9500, 9522	†	14	†	10	†	8	42
All "neuroendocrine"	‡	314	361	420	452	495	554	2,596

*Other neuroendocrine histologies: 8150–8156, 8241, 8244–8245, 8249, 9091
† Number of incident cases less than 5 are suppressed
‡All neuroendocrine histologies: 8013, 8150–8156, 8240–8241, 8244–8246, 8249, 8680, 8693, 8700, 9091, 9500, 9522

Table 2: Neuroendocrine 5-Year Relative Survival Estimates for Ontario*

Years	Number	Survival	Confidence Interval
1988–92	771	62.4	(58.4, 66.2)
1993–97	1,000	61.3	(57.7, 64.7)
1998–02	1,360	64.9	(61.9, 67.7)
2003–07**	1,953	71.2	(68.6, 73.7)

*combined 8240 (Carcinoid tumour, NOS) and 8246 (neuroendocrine carcinoma), age 15+
** The survival estimate for this interval was calculated using the period method, which allows a more accurate estimate of the survival being experienced by patients diagnosed in the most recent years of diagnosis. For the three earlier time periods, the usual cohort method was used.

Table 3: Neuroendocrine 10-Year Prevalence Estimates for Ontario*

Date	Cases Still Alive
Jan 1, 1997	986
Jan 1, 2002	1,368
Jan 1, 2007	1,939

*combined 8240 (carcinoid tumour, NOS) and 8246 (neuroendocrine carcinoma), age 15+

Radionuclide Therapy in Ontario

Table 4: Number of RN Therapy Treatments* at the Nuclear Medicine Program, London Health Sciences Centre

Year	Patient Residence			Total
	Ontario – South West LHIN	Ontario – Other	Out of Province	
2004	37	117	3	157
2005	49	126	12	187
2006	23	140	20	183
2007	17	129	17	163
2008	22	109	34	165
2009	25	92	30	147
2010	41	106	19	166

Source: London Health Sciences Centre, London Regional Cancer Program – Nuclear Medicine Database

*including: 131I mIBG, In-111 octreotide and 131I Lipiodil.

Table 5: Out of Country Requests, April 1, 2007 to March 1, 2011

Outcome	Requests for Treatment*
Approved and Funded	48
Approved but never paid/cancelled	15
Denied	0
Total requested treatments	**63**

Source: Health Services Branch, Ministry of Health and Long-Term Care

*Represents number of treatments, not number of patients. Requests were for either ^{90}Yttrium or ^{177}Lutetium.

RECOMMENDATIONS

1 In Ontario, radionuclide therapy for neuroendocrine tumours should be offered in a province-wide clinical trial, under the authority of a Clinical Trial Agreement (CTA) with Health Canada, with appropriate data collection and analysis of outcomes to: 1) support the securing of a Notice of Compliance from Health Canada for the therapeutic radiopharmaceutical; and, 2) enable future clinical and funding decisions.

   1.0   The recommendations for the clinical trial are:

      1.0.1   The PRRT agent recommended for clinical trial is ^{177}Lu-DOTATATE.

      1.0.2   A single-arm Phase II trial should be conducted.

      1.0.3   There must be a companion trial of the related diagnostic radiopharmaceutical ^{68}Ga-DOTATATE.

      1.0.4 ^{131}I-mIBG therapy should be maintained as an option to be used only if: a) The patient's tumour does not show concentration of the PRRT-related diagnostic radiopharmaceutical and does show uptake of diagnostic doses of ^{123}I-mIBG or ^{131}I-mIBG; or b) the patient's disease has progressed following PRRT and the tumour shows uptake of diagnostic doses of ^{123}I-mIBG or ^{131}I-mIBG; or c) the patient's renal function does not allow treatment with PRRT and the tumour shows uptake of diagnostic doses of ^{123}I-mIBG or ^{131}I-mIBG. These patients should be entered into a registry under the authority of a CTA with ongoing formal data collection regarding patient outcome.

   1.1   Final proposed CTAs should be subjected to external peer review by acknowledged experts in PRRT.

   1.2   Collaboration with other Canadian NET treatment centres should be explored.

2 Patients must meet specific criteria to be considered as eligible for radionuclide therapy.

   2.0   Patients meeting all of the following inclusion criteria may be eligible for consideration for radionuclide therapy:

      2.0.1 Adults (18+) with a diagnosis of advanced well or moderately differentiated neuroendocrine carcinoma who are inoperable, or have progressive residual disease following surgery or other ablative therapy.

      2.0.2 The patient has had a diagnostic radionuclide scan demonstrating adequate uptake of somatostatin.

2.0.3 The patient has been discussed at a neuroendocrine tumour multidisciplinary case conference (MCC) and is a candidate for radionuclide therapy by consensus opinion.

2.0.4 The patient has adequate renal, hepatic, cardiac and hematologic function.

2.0.5 All medical options have been discussed with the patient.

2.0.6 The patient is aware of toxicity and the level of evidence for the use of RN therapy, and has signed their consent to the therapy.

2.1 The following exclusion criteria are recommended:

2.1.1 Patients who are pregnant or lactating

2.1.2 Patients with poorly differentiated tumours or ki-67>20%

3   Patient support specific to RN therapy must be provided by the NET program team

3.0 Instructions to patients regarding radiation protection and safety should be given prior to any planned hospital admission or out-patient therapy administration in order to ensure that any questions from the patients can be addressed.

3.1 The NET program team should include an Advanced Practice Nurse or a Nurse Navigator to ensure co-ordination of care.

4   Provincial service volume current state and forecasting is needed to estimate present and future demand for radionuclide therapy in Ontario.

4.0 By fiscal year 2012/13, the province should be prepared to deliver radionuclide therapy to 120–150 Ontario patients annually. This forecast is based on an Ontario current state analysis, which uses incidence, prevalence, and treatment course data to estimate current and future demand.

4.1 By the second year of operation, treatment centres should each be doing a minimum volume of 40 new cases per year in order to maintain competence.

4.2 Projected treatment volumes should be re-evaluated after 12 months of program initiation.

4.3 Ontario should be prepared to receive additional patients from out of province, as capacity allows.

5 Treatment centre facilities and multidisciplinary case conferences must meet minimum requirements as defined.

5.0 Radionuclide therapy should be administered in a facility with the capacity to offer both in- and out-patient therapy.

5.1 Radionuclide therapy should be administered in a facility where there is a multidisciplinary NET treatment program team. The facility should have, at a minimum, the following human resources (with a focused practice and specific expertise in the treatment of neuroendocrine neoplasms):

5.1.1 Physicians with Royal College Certification (or equivalent) in the specialties of Medical Oncology, Surgery, Radiation Oncology, Nuclear Medicine, Endocrinology, Pathology, and Diagnostic Radiology.

5.1.2 Diagnostic Radiology and/or Nuclear Medicine physician(s) must have additional training in cross-sectional imaging as applied to oncology.

5.1.3 An interventional radiologist.

5.1.4 Nuclear Energy Workers (NEWs) who have received specific training in the use of ionizing radiation as well as specific handling of therapeutic radiopharmaceuticals.

5.1.5 The NET program team should include an Advanced Practice Nurse or a Nurse Navigator (see recommendation 3.2).

5.2 Each treatment centre should hold regular neuroendocrine tumour Multidisciplinary Cancer Conferences (MCC) to discuss NET patients regionally.

5.2.1 The neuroendocrine tumour MCCs should include, at a minimum, the expertise listed in 5.1.1 – 5.1.3.

5.2.2 MCC regions should be defined following the identification of treatment centres. MCCs would have the option to bring forward cases for review at the provincial level (see recommendation 8.1).

5.3 Each treatment centre is encouraged to have in place a Multidisciplinary Reference Centre (MRC) to support the co-ordination of care for NET patients by facilitating multiple consultations into a single patient visit.

6   Medical facilities providing radionuclide therapy must have a radiation safety program that undergoes an annual review to confirm that the program meets the operational objectives of the facility and regulatory requirements. The program must include policies, practices and equipment to maintain radiation exposures to workers and the public as low as reasonably achievable (ALARA), with social and economic factors being taken into account.

6.0   Treatment centres must secure and maintain a licence from the Canadian Nuclear Safety Commission (CNSC) for the possession and use of appropriate amounts of the therapeutic and diagnostic nuclear substances.

6.1   Patients requiring isolation (due to emissions from gamma radionuclides), must be placed in an approved private hospital room with a private toilet and sink. The *CNSC Design Guide for Nuclear Substance Laboratories and Nuclear Medicine Rooms (GD-52)* should be consulted for the specific radionuclide therapy design requirements.

6.2   At a minimum, the facility must have policies and procedures in place that address the following:

6.2.1   Determination as to whether therapy will be administered on an in-patient or out-patient basis.

6.2.2   Use of therapeutic radionuclides on an out-patient basis.

6.2.3   Release criteria for patients treated on an in-patient basis.

7   The availability of the radiopharmaceuticals should be facilitated by partnering with an organization (or organizations) capable of bringing the radiopharmaceuticals to market in Canada through a Health Canada-approved regulatory framework, and ensuring a safe and consistent supply to any and all treatment facilities in the province.

7.0   Criteria for the evaluation of partner organizations to provide radiopharmaceuticals for the NET program should include:

7.0.1   Defined approach to secure the intellectual property for the production of agents for localization and treatment of NETs.

7.0.2   In good standing with Health Canada's Drug Inspectorate surrounding quality issues, preferably demonstrated by holding a Health Canada Drug Establishment Licence.

7.0.3   Appropriate infrastructure, facilities and equipment to manufacture the agents.

7.0.4   Qualified personnel in regulatory affairs, quality assurance and manufacturing.

7.0.5   Ability to distribute agents to multiple centres.

8   Provincial specialized services oversight for RN therapy should be established by Cancer Care Ontario (CCO)

8.0   The CCO oversight body should include representation from all NET program treatment centres and the mandate should include:

8.0.1 Oversee funding for radionuclide therapy services for NET patients in Ontario, including the allocation of provincial funds to treatment centres.

8.0.2 Establish reporting mechanisms to enable monitoring and performance management.

8.0.3 Review service volume forecasts and allocations.

8.0.4 Assess cost effectiveness of radionuclide therapy for NETs.

8.0.5 Develop strategies to promote awareness of the program to patients, providers, and referring physicians.

8.0.6 Monitor access to services for NET patients throughout the province.

8.0.7 Monitor the development of new treatment options for introduction or clinical trial in Ontario.

8.1   A provincial endocrine oncology disease site group (DSG) should be established for ongoing clinical guidance in the form of provincial guideline development.

8.2   A provincial Multidisciplinary Cancer Conference (MCC) should be established to conduct case review at the request of local MCCs.

APPENDICES

APPENDIX A: EXPERT PANEL TERMS OF REFERENCE, September 2010 – September 2011

The Ontario Neuroendocrine Expert Panel will make recommendations for RN therapy for NETs patients in the province, based on evidence and consensus. In conjunction with the Program in Evidence-Based Care (PEBC), the panel will produce one or more reports, which include:

- Current state analysis and assessment of practice considerations with regards to the treatment of neuroendocrine tumours, situating radionuclide (RN) therapy within the context of the overall management of the tumours.

- Guidance on the types of patients with NETs for which there is evidence for efficacy of treatment with RN therapy.

- Guidance on which diagnostic agents would be most predictive of response to RN therapy based on sensitivity, specificity, and safety profile.

- Guidance on which RN therapies demonstrate the best evidence for efficacy in each NET type.

- Guidance on the safety and regulatory requirements associated with the radiopharmaceuticals.

APPENDIX B: EXPERT PANEL MEMBERSHIP

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1. Pathology of Neuroendocrine Tumours

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The endocrine system represents a group of organs and dispersed cells that have, as their primary function, the production and secretion of hormones. They are classified into three broad categories: 1) peptide hormone-producing, 2) steroid hormone-producing and 3) thyroid hormone-producing.

Most endocrine cell types fall into the first category and these are the origin of tumours that are known as "neuroendocrine tumours." This group of endocrine tissues is composed of cells that have a characteristic morphology and function that is closely related to neurons, hence, they have been called "paraneurons" (DeLellis & Tischler, 1998). In earlier literature, they were classified as the APUD (amine precursor uptake and decarboxylation) system and it has been suggested that they derive from the neural crest embryologically; however, this has not been proved for all members of this group of cells, many of which arise from the primitive endoderm. Nevertheless, functionally they act as neuron-like cells that secrete peptides that are often also produced by neurons. The relationship between these cells and neurons is rather like the comparison between wireless and conventional communication. Neurons produce messengers that are released at synapses and activate receptors in adjacent cells, while neuroendocrine cells produce the same types of messengers that are released into the bloodstream to activate cells throughout the body. The wide array of peptide hormones that they produce is essential for regulation of most metabolic and reproductive functions. These cells are found in classical endocrine organs, such as the pituitary, parathyroid and adrenal medulla, in neural structures known as paraganglia, and as members of the dispersed endocrine system scattered within other organs, such as the calcitonin-secreting C cells of the thyroid and the endocrine cells of the lung, gut and pancreas.

NOMENCLATURE/TERMINOLOGY

The term "carcinoid" meaning "carcinoma-like" was originally introduced by Oberndorfer in 1907 to describe peculiar tumours that resembled cancers but had unusually indolent clinical behaviour (Oberndorfer, 1907). Use of the term "carcinoid" has become entrenched in the medical literature to describe well-differentiated endocrine tumours of the lung, gut and pancreas. The term also is used to describe the syndrome caused by serotonin excess. It has become apparent that a "carcinoid tumour" in one site is not equivalent to a similar tumour in another site and that these tumours, initially thought to be benign, display a full spectrum of behaviours from very low-grade to high-grade malignancy. Thus the term "carcinoid" has led to misunderstanding of the malignant potential of these tumours and the use of the term has been increasingly discouraged in favour of more precise terminology.

Endocrine tumours in the pancreas were originally thought to derive from the islets of Langerhans, hence, the previous terminology "islet cell tumours." More recent evidence indicates that they actually derive from

precursors in the ductal epithelium, so this terminology has been abandoned in favour of "pancreatic endocrine tumours."

The terms "endocrine" and "neuroendocrine" have been used to describe these tumours in lung, gut and pancreas. The cells that comprise these lesions, like their normal counterparts, express several antigens that are commonly expressed by neuronal elements: neuron-specific enolase (NSE), protein gene product 9.5 (PGP 9.5), chromogranin A, B and C and synaptophysin. (Kloppel, Rindi, Anlauf, Perreb, & Kommonoth, 2007). For this reason "neuroendocrine" has become the preferred designation and the term "neuroendocrine tumour" (NET) is becoming prevalent and has been recommended by the WHO (Bosman, Carneiro, Hruban, & Theise, 2010).

Tumours arising in the sympathetic and parasympathetic ganglia are also neuroendocrine tumours. They are composed of peptide-hormone secreting cells that are more closely related to neurons. They also express NSE, PGP 9.5, chromogranins and synaptophysin, but in addition, they also express tyrosine hydroxylase, the enzyme responsible for catalyzing the conversion of L-tyrosine to dihydroxyphenylalanine (DOPA), the precursor for dopamine, which, in turn, is a precursor for norepinephrine (noradrenaline) and epinephrine (adrenaline). Unlike the NETs arising in structures of endodermal origin, they are negative for keratins. These lesions are classified as paragangliomas unless they occur in the adrenal medulla, where they are called pheochromocytomas. (DeLellis, Lolyd, Heitz, & Eng, 2004).

EPIDEMIOLOGY

Tumours of endocrine differentiation are considered to be rare and, because they have not been accepted as conventional malignancies, epidemiological data are weak. There are, however, several statistics of note.

Pituitary tumours are found in about 20% of the general population (Ezzat et al., 2004). While some are incidental findings, clinically significant lesions are being diagnosed with increasing frequency (Daly et al., 2006; Fernandez, Karavitaki, & Wass, 2009). Some forms of pituitary neoplasia, including corticotroph adenomas causing Cushing's disease and prolactinomas, are more common in women than in men, but overall there is no sex predilection of pituitary neoplasia. These lesions tend to increase with age and are rare in children (Asa, 1998).

Primary hyperparathyroidism due to parathyroid neoplasia occurs in 1% of the adult population (Apel & Asa, 2002). In contrast to the common benign adenomas that are most common in middle-aged to elderly women, parathyroid carcinomas are rare, have no predilection for women, and have onset about one decade earlier.

Pheochromocytomas of the adrenal medulla have a reported incidence of 2–8 per million per year and extra-adrenal paragangliomas are even rarer. These lesions have no sex predilection and are rare in children (Lack, 1997; Tischler, 1998).

Well-differentiated tumours of the dispersed endocrine system are rare. Tumours of thyroid C cells, medullary thyroid carcinomas, represent about 5% of thyroid cancers that predicts a prevalence of about 1–2 per 100 000 (LiVolsi, 1990; Moley, 2000). Neuroendocrine tumours of the GI tract and pancreas are increasing in incidence (Yao et al., 2008), an unusual trend that may be reflective of better diagnostic markers. The tumours show no significant gender predilection and occur at all ages, with a peak incidence between 30 and 60 years (Oberg &

Eriksson, 2005; Grimelius, Hultquist, & Stenkvist, 1975; DeLellis et al., 2004). A significant proportion of patients with these tumours have familial syndromes of predisposition, including MEN types 1 and 2, VHL, Carney's complex, SDH mutations, and Neurofibromatosis (DeLellis et al., 2004).

Small-cell carcinoma of the lung, the most poorly differentiated endocrine neoplasm of this type, represents one of the four major types of lung cancer, the second most common cancer in men and women and the number one cancer mortality site (Greenlee, Murray, Bolden, & Wingo, 2000); this variant has an annual incidence of almost 10 per 100 000 population.

PATHOLOGY

Tumours of neuroendocrine cells arise either in classical neuroendocrine tissues, such as pituitary, parathyroid or adrenal medulla, or in other tissues where the dispersed cells reside, such as thyroid, lung, gut or pancreas. These lesions exhibit a wide spectrum of biological behaviours. They may be slowly growing, well-differentiated neoplasms that are considered benign (adenomas), because they do not metastasize. The most aggressive neoplasms are poorly differentiated (small-cell) carcinomas that are rapidly lethal. Many tumours fall into intermediate categories and the prediction of outcome can be very difficult.

These tumours may be clinically silent in terms of hormone function, but they are almost always found to produce and store hormones. Some elaborate hormones that give rise to colourful clinical syndromes of hormone excess; the pattern of hormone production may be eutopic to the tissue of origin or ectopic, reflecting derepression of genes that are expressed in related cells.

Tumours of neuroendocrine cells are generally well-delineated but unencapsulated lesions that have a characteristic histopathology. They are composed of small nests, trabecula or sheets of epithelial cells in a highly vascular stroma. They occasionally form gland-like structures. The stroma may, in some instances, form amyloid. The tumour cells usually have poorly defined cell borders and abundant cytoplasm that may contain eosinophilic, amphophilic or basophilic granules. Characteristically, the nuclei of tumour cells are bland; nuclear pleomorphism that generally defines malignancy in other epithelial tumours is not a reliable indicator of aggressive behaviour. The more poorly differentiated carcinomas have less cytoplasm, lack granularity and have larger more hyperchromatic nuclei.

These lesions are readily classified by the immunohistochemical localization of common markers of neuroendocrine differentiation (Asa & Ezzat, 2002). They almost uniformly stain for synaptophysin, and most express chromogranins and other markers of neuroendocrine differentiation (CD57/Leu7, NCAM/CD56, NSE and PGP 9.5). Of these, only chromogranins are specific for neuroendocrine differentiation. They may also exhibit immunoreactivity for specific peptide hormones or, in the case of hormones that cannot be localized (such as adrenaline and noradrenaline), the enzymes involved in hormone production (such as tyrosine hydroxylase).

Neuroendocrine cells and their tumours express somatostatin receptors as a distinguishing feature. While the subtype of the five distinct receptors varies among different endocrine tumours, they all bind somatostatin. This feature has provided a novel tool for the imaging of these lesions and their metastases, using a radiolabelled somatostatin analogue, ^{111}In-octreotide; it allows the localization of occult metastases or, in some patients with metastatic disease, an occult primary lesion. There may be a role for localization of somatostatin receptors as

predictive markers for the use of somatostatin analogues in the therapy of these tumours, both to control hormone secretion and as radiolabelled targeted therapies. Of note, not all NETs are labelled with iodine-131-meta-iodobenzylguanidine (mIBG); this substrate is valuable mainly in cells that express tyrosine hydroxylase to synthesize dopamine, and therefore is valuable for imaging pheochromocytomas and paragangliomas.

The ultrastructure of these lesions is highly characteristic, with well-developed rough endoplasmic reticulum, reflecting the levels of peptide hormone synthesis, prominent Golgi complexes that are responsible for packaging of hormones for secretion and membrane-bound secretory granules that store hormones for secretion in response to stimulation. The development of these organelles varies with cell differentiation and hormonal activity; the numbers of secretory granules reflect the balance between synthesis, storage and secretion. The morphology of secretory granules is generally reflective of cell type and hormone content, and experts in the field of electron microscopy can classify neuroendocrine cells based on these ultrastructural parameters.

Pituitary tumours (Asa, 1998) and tumours of the adrenal medulla and extra-adrenal paraganglia (Lack, 1997, Tischler, 1998) are generally considered benign unless there is evidence of metastatic spread. In parathyroid, malignancy is based on identification of vascular invasion or metastasis. In contrast, tumours of the dispersed endocrine system, including medullary thyroid carcinomas and endocrine tumours of the lung and gut, are not reliably considered benign (Capella, Heitz, Höfler, & Kloppel, 1995); even in the absence of invasion, there may be delayed recurrence or metastasis.

Classification

Given the variability of cytodifferentiation and the many sites in which neuroendocrine tumours develop, it is not surprising that a single classification spanning all body sites does not exist. In 2000, Wick proposed a generic classification for neuroendocrine neoplasia, irrespective of site, based on a three-tiered grading system (Wick, 2000). Consistent with this proposal, the recent World Health Organization (WHO) classifications have placed NETs into three broad categories (Bosman et al. 2010; DeLellis et al., 2004; Kloppel, Perren, & Heitz, 2004; Kloppel et al., 2009) :

1. **Neuroendocrine tumour, low grade (G1)**

2. **Neuroendocrine tumour, intermediate grade (G2)**

3. **Neuroendocrine carcinoma, high grade (G3)**

The first two categories include well-differentiated neuroendocrine tumours, and categorization is based on tumour size, mitotic count and proliferation index. Grade 3 tumours are poorly differentiated large or small cell carcinomas.

Unfortunately, these standards have not been as well accepted by pulmonary pathologists, creating confusion in terminology and classification.

Staging

Tumour-node-metastasis (TNM) staging systems have been proposed for neuroendocrine tumours of the GI tract and pancreas, and have been incorporated into the seventh version of the cancer staging protocols endorsed by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) (Edge, Byrd, Carducci, & Compton, 2009) and these are reflected in the new College of American Pathologists (CAP) synoptic reports available at:
http://www.cap.org/apps/cap.portal?_nfpb=true&cntvwrPtlt_actionOverride=%2Fportlets%2FcontentViewer%2Fshow&_windowLabel=cntvwrPtlt&cntvwrPtlt%7BactionForm.contentReference%7D=committees%2Fcancer%2Fcancer_protocols%2Fprotocols_index.html&_state=maximized&_pageLabel=cntvwr.

BLOOD AND URINE TUMOUR BIOMARKERS

Chromogranin A has emerged as the single-most useful general marker of neuroendocrine neoplasia. Urinary 5-hydroxyindoleacetic acid (5-HIAA) and blood serotonin appear to have specific utility as markers of midgut and foregut NETs. Specific hormones secreted by the various GI and pancreatic NET types serve as useful markers of tumour progression (Table 1) and CEA is used in the monitoring of medullary thyroid carcinomas. Pancreatic polypeptide, other granins such as chromogranin B and molecular markers of tumourigenesis have either little or no demonstrated clinical utility at this time. Table 1 includes the phases of development of each marker along with the level of evidence (LOE) supporting the proposed clinical use. Table 2 summarizes recommendations for the clinical use of blood and urine markers in the diagnosis and management of tumours of the dispersed neuroendocrine system.

Chromogranin A

Granins are ubiquitously distributed in neuroendocrine cells where they are co-secreted with resident peptide hormones and biogenic amines. Immunoassays are available that specifically measure intact chromogranin A (CgA), while others detect peptide fragments derived from the parent molecule (Stridsberg, Eriksson, Oberg, & Janson, 2004). To date, measurement of intact CgA in plasma has yielded superior diagnostic sensitivity for neuroendocrine tumours than measurement of fragments (Stridsberg et al., 2004); intact chromogranin is not stable in serum. Two methods are available, EIA and RIA; the results of both CgA methods correlate well (Tsao & Wu, 2001). The detection limit of CgA EIA may be lower than that of RIA, whereas RIA methods tend to have a wider dynamic assay range (Tsao & Wu, 2001). At least three commercial kits that detect intact CgA are available for the measurement of CgA in clinical samples.

Elevation of circulating CgA is not specific to neuroendocrine malignancy, as elevated levels are found in a number of other conditions including impaired renal function (Hsiao, Mezger, & O'Connor, 1990) and liver and heart failure (Corti, Ferrari, & Ceconi, 2000). CgA is also elevated in individuals with chronic gastritis type A and in those undergoing treatment with proton pump inhibitors (Hsiao et al., 1990). Elevated CgA has been documented in primary parathyroid hyperplasia, thyroid C-cell hyperplasia, and gastric enterochromaffin-like cell hyperplasia (Lamberts, Hofland, & Nobels, 2001; Ferrari, Seregni, Bajetta, Martinetti, & Bombardieri, 1999).

Finally, potentially confounding the interpretation of blood levels in the management of established neuroendocrine malignancy, treatment with somatostatin analogues may reduce levels of circulating chromogranin A independently of any effect on tumour burden (Tomassetti et al., 2001).

Levels of serum chromogranin A are elevated in about 80% of patients with gastrointestinal NETs and appear to correlate with tumour load and can therefore be used to predict prognosis, particularly in patients with midgut type of endocrine tumours (Granberg et al., 1999). As elevation of chromogranin A levels can precede radiographic evidence of recurrence in foregut NETs, this may prove a useful marker in monitoring the course of disease. Chromogranin A may be elevated in 93% of patients with metastatic pulmonary NETs (Nobels et al., 1997). The sensitivity and specificity are approximately 92% and 96% respectively, which is significantly better than the discrimination that has been obtained with neuron-specific enolase and the alpha chain of human chorionic gonadotropin, two other markers that have been examined in the diagnosis of NETs.

Serotonin and Urinary 5-Hydroxyindoleacetic Acid

Serotonin is synthesized from tryptophan by hydroxylation and decarboxylation, and stored in secretory granules prior to its release locally and into the circulation upon appropriate stimulation. Most of the secreted serotonin is taken up by platelets, while free serotonin is rapidly degraded by monoamino oxidase in the liver and lung. The major product of degradation is 5-hydroxyindoleacetic acid (5-HIAA), which is eliminated in the urine in free and conjugated forms.

Urinary 5-HIAA is the most important marker for midgut NETs, often heralded by the carcinoid syndrome. Measurement of urinary excreted 5-HIAA is most accurately done by high-performance liquid chromatography (HPLC). Two 24-hour collections of urine are recommended, avoiding foods and medications that interfere in the assay or physiologically modulate the urinary output. Some centres recommend instead measurement of serotonin in plasma, and it has been reported to be more sensitive than urinary 5-HIAA. A problem with monitoring plasma serotonin is its wide fluctuation in concentration with time, which makes it an unreliable marker for long-term follow-up. Elevated 24-hour urinary 5-HIAA levels have about 73% sensitivity and 100% specificity in detecting a NET (Lamberts et al., 2001).

Pancreatic Polypeptide

Elevated levels of pancreatic polypeptide in the circulation are found with most NETs. Unfortunately, pancreatic polypeptide is also elevated in renal failure, laxative abuse and diarrheas of uncertain origin. Elderly people have higher-circulating concentrations of pancreatic polypeptide than younger people (Adrian, Uttenthal, Williams, & Bloom, 1986). Sensitivity was quite poor at 45% in the 323 patients examined with proven PETs. Only 144 of the group exhibited circulating concentrations above the 300 pmol/L positive threshold. One milligram of atropine administered intramuscularly improved specificity by differentially suppressing tumour-associated and non-tumour-associated elevations of pancreatic polypeptide. Elevations due to the former were not suppressed, whereas those due to the latter were suppressed more than 50%. Pancreatic polypeptide was much less sensitive than CgA in detecting both functioning (54% vs. 98%) and non-functioning (57% vs. 75%) tumours. However, combining the two markers boosted the detection of non-functioning tumours to 95%, a significant increase (Panzuto et al., 2004).

Summary of recommendations for the clinical use of tumour markers (Table 2)

1. Measurements of plasma chromogranin A is the most useful general marker for neuroendocrine tumours of the gastrointestinal tract. It not only reflects the metabolic activity of the tumour but generally correlates with tumour burden. It is, therefore, also a useful marker for monitoring patients during treatment, with the caveat that circulating levels may decline due to the suppressive effect of somatostatin analogues without corresponding reduction in tumour mass. Conversely, falsely elevated levels can be seen in patients with impaired renal function, congestive heart disease, liver failure, chronic atrophic gastritis and in those receiving proton pump inhibitors.

2. Patients with the clinical carcinoid syndrome, both of the foregut and midgut type, should have measurements of 24-hour urinary 5-HIAA together with plasma chromogranin A. Two 24-hour urine collections are recommended under appropriate restriction of food and medication.

3. Other markers of potential value in selected patients include plasma gastrin in gastrinoma, insulin/pro-insulin in hypoglycemic syndromes, glucagon in glucagonoma, and plasma VIP in the Verner-Morrison syndrome of watery diarrhea.

4. Other general neuroendocrine tumour markers such as neuron-specific enolase, pancreatic polypeptide and chromogranin B have much lower sensitivity and specificity than chromogranin A, and consequently are not recommended for routine investigation.

Table 1 – Established Circulating Markers of Neuroendocrine Carcinomas

Marker	Proposed Use	Level of Evidence[1]	Phase of Development
Chromogranin A (serum)	Diagnosis, recurrence, and monitoring treatment of most types of neuroendocrine tumours	I	**In clinical use (widely available)**
5-hydroxyindolacetic acid (5-HIAA) (24-hour urinary)	Diagnosis, prognosis, recurrence, and monitoring of pulmonary and small bowel neuroendocrine carcinomas	I	**In clinical use (widely available)**
Serotonin (serum)	Diagnosis, recurrence, and monitoring of pulmonary and small bowel neuroendocrine carcinomas	IV	**In clinical use (limited availability)**
Pancreatic Polypeptide (serum)	Diagnosis and recurrence of pancreatic neuroendocrine carcinomas	III	**In clinical use (widely available)**
Insulin, proinsulin (serum)	Diagnosis, recurrence, and monitoring treatment nearly exclusively of pancreatic insulinomas	III	**In clinical use (widely available)**
Glucagon (serum)	Diagnosis, recurrence nearly exclusively of pancreatic glucagonomas	III	**In clinical use (widely available)**
Gastrin (serum)	Diagnosis, recurrence, monitoring treatment nearly exclusively in gastrinomas	III	**In clinical use (widely available)**
Vasoactive intestinal polypeptide (VIP) (serum)	Diagnosis, recurrence, and treatment nearly exclusively in VIP-producing tumours	III	**In clinical use (widely available)**

[1] graded according to (Hayes et al., 1996)

Table 2 – Recommended use of Tumour Biomarkers for Neuroendocrine Tumours

Specific Neoplasm	Marker	Clinical Use
Serotonin-producing small bowel neuroendocrine carcinomas	24-hour urinary 5-hydroxyindolacetic acid (5-HIAA)	**Diagnosis and monitoring of neuroendocrine tumour associated with clinical carcinoid syndrome**
Most carcinomas of the dispersed neuroendocrine system	Serum chromogranin A	**Diagnosis and monitoring of most neuroendocrine carcinomas including those not associated with clinical endocrine syndrome**
Insulinoma	Fasting serum insulin	**Diagnosis and monitoring of pancreatic insulinomas**
Gastrinoma	Fasting serum gastrin	**Diagnosis and monitoring of pancreatic gastrinomas**
Vasoactive intestinal peptide neuroendocrine bowel carcinoma	Fasting serum vasoactive intestinal peptide (VIP)	**Diagnosis and monitoring of VIP-producing tumours**

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2. Diagnostic Imaging

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Neuroendocrine tumours (NET) encompass a heterogenous group of rare neoplasms of endocrine cell origin, which present with variable clinical behaviours that reflect their anatomic location and origin, secretory characteristics, and histologic differentiation and proliferation. This diversity in presentation creates distinctive imaging profiles. Anatomic imaging modalities include computed tomography (CT), magnetic resonance (MR), and ultrasound (US). Functional nuclear imaging modalities broadly include radiopharmaceuticals that target somatostatin receptors, catecholamine transport and storage mechanisms, and cellular glucose metabolism.

ANATOMIC IMAGING

Computed Tomography *(CT)*

Modern CT employs fast, helical multidetector scanners to offer both high-resolution 1–3 mm multiplanar reconstruction and high-temporal resolution to accommodate several contrast-enhancement phases. Detailed examination of the whole abdomen and other body regions can be obtained in the same imaging session. The role of CT includes detection of regional and distant metastases in gastroenteric NETs, and characterization of endocrine pancreatic NETs. CT should be a first choice for imaging and must be part of any radiologic investigation when a recurrence or progression is suspected, since it provides accurate anatomic description.

CT can be used for the diagnosis of neuroendocrine tumours; CT enteroclysis may be required for the demonstration of small bowel tumours. CT is also used for the staging of disease and the demonstration of response to therapy. For this latter application, evaluation of the images using standardized reporting criteria (e.g. RECIST criteria) is important.

Magnetic Resonance *(MR)*

Current standards for MR include 1.5 T or higher magnetic field strength and produce images of 3–5 mm sections. Optimal technique requires all proper sequences, dynamic contrast enhancement, administration of an anti-peristaltic, and limitation to as small a field of view as possible. As such, MR is regarded as a "problem-solving" technique. Extent of tumour is often best appreciated by MR, while better soft tissue contrast facilitates detection of smaller primary and metastastic lesions.

Ultrasound (US)

US is an operator-dependent modality that plays a complementary role to CT. It is useful in detecting and characterizing extent of endocrine pancreatic NETs, and metastases to liver, mesentery and abdominal lymph nodes. Optimal technique includes use of multiple transducer frequencies to balance the trade-off between tissue penetration and spatial resolution, Doppler to evaluate vascularity, and intravenous bubble contrast enhancement. US is well-suited to guiding biopsy.

FUNCTIONAL IMAGING

Somatostatin Receptor Imaging

Somatostatin (SS) is a regulatory peptide widely distributed throughout the body. Five subtypes of SS receptors (SSTR) exist. Since the majority of gastroenteropancreatic NETs express SSTR, functional imaging with a radiolabelled SS analogue is a high-yield modality. Several SS analogues, all based on variations of the cyclic octapeptide octreotide, have been conjugated with different chelators and with different metallic radionuclides to create positron emission tomography (PET) and single photon emission computed tomography (SPECT) radiopharmaceuticals with varying affinities to the different SSTRs. The radiotracer used in routine clinical practice is indium-111-DTPA-octreotide (Octreoscan™, Mallinckrodt). Indications include localizing primary tumour, staging disease extent and metastatic spread, prediction of response to therapy, monitoring treatment response, and as a precursor study if therapeutic radiolabelled SS analogs are being considered as a systemic treatment modality. The diagnostic radiopharmaceutical, Octreoscan™ is approved for use by Health Canada, but this procedure is not an insured benefit in Ontario.

With Octreoscan™, good-quality planar and SPECT acquisitions require 220 MBq of activity with at least 10 ug of peptide. To localize and distinguish pathologic from physiologic uptake, imaging protocols are optimized by obtaining at 4, 24, and 48 hours, use of a mild laxative, and the employment of hybrid SPECT/CT cameras.

Among the newer peptide agents, ^{68}Ga radiolabelled SS analogs have shown indication of improved performance, coupling the superior resolution of PET with the convenience of in-house ^{68}Ga generator-production of the radiopharmaceutical.

Catecholamine Transport and Storage

Several radiotracers exist that target specific catecholamine uptake and storage mechanisms. The most commonly used agent is metaiodobenzylguanidine (mIBG), which shares the same active amine uptake and active intracellular storage mechanism as norepinephrine. Metaiodobenzylguanidine is used clinically for imaging in functioning NETs, which include pheochromocytoma, paragangliomas, neuroblastomas, medullary thyroid carcinomas and carcinoids. Indications for imaging are similar to those of SSTR imaging, and due to clonal heterogeneity of the tumours, the two functional modalities are often complementary.

Proper patient preparation by blocking thyroid uptake of free iodine and discontinuation of drugs and foods that interfere with uptake and granule storage mechanisms is mandatory. High-specific activity is desired for mIBG radioiodinated with either 370 MBq I-123 or 37 to 74 MBq I-131. I-123-mIBG is the agent of choice for good-quality planar and SPECT acquisitions and favourable patient dosimetry. However, ^{131}I is still routinely used due to the lower non-cyclotron-dependent costs, and for prolonged imaging to facilitate dosimetry where systemic high-dose ^{131}I-mIBG is being considered. As with SSTR imaging, multi-day imaging and SPECT/CT is useful to localize imaging findings and distinguish abnormal from physiologic uptake.

Several newer PET agents also behave as catecholamine analogs or precursors (e.g. C-11-epinephrine, F- and F-18-fluorodopa) and have demonstrated good diagnostic performance, albeit limited by the costs and availability associated with cyclotron-produced radionuclides and regulatory oversight of the radiopharmacy.

Cellular Glucose Metabolism

F-18-fluorodeoxyglucose (FDG) is the most common oncologic PET tracer, and is particularly effective in imaging aggressive tumours with high-glucose metabolism and cellular proliferation. However, detection of NETs by FDG PET is variable, since many NETs are of slow-growing well-differentiated histology.

Tumour Characterization by Functional Imaging

Several papers have explored the use of two or more of these functional imaging agents in the evaluation of patients with neuroendocrine tumours. Ezziddin et al. (2006) studied 57 consecutive patients with both Octreoscan™ and ^{123}I/^{131}I-mIBG scintigraphy. Fifty-two patients were Octreoscan™ positive and 28 were mIBG positive. Five patients were negative for both tracers. All patients who were mIBG positive also showed avidity for Octreoscan™. Some individual lesions were better seen with mIBG.

Gabriel et al. (2007) compared ^{68}Ga-DOTA-TYR[3]-octreotide PET (PET) with Octreoscan™ (OCT) in a group of 84 patients, 13 studied for the detection of an unknown primary tumour, 36 studied for staging of a known neuroendocrine tumour and 35 patients studied for follow-up after therapy. The patients also underwent CT imaging. The gold standard utilized was based on all available histologic, imaging and follow-up findings. PET showed improved diagnostic efficacy as compared with OCT, sensitivity 97% vs. 52%, specificity 92% vs. 92%, accuracy 96% vs. 58%.

Kayani et al. (2008) studied 38 consecutive patients with a diagnosis of primary or recurrent neuroendocrine tumour with ^{68}Ga-DOTATATE (DOTA) and ^{18}F-FDG PET-CT (FDG). Although DOTA showed improved sensitivity as compared with FDG (82% vs. 66%) in the group as a whole, there was greater uptake of FDG than DOTA in patients with high-grade tumours (Ki67 index >20%). This suggests the possibility that FDG PET-CT imaging might serve as an in vivo indicator of tumour grade.

Finally, Haug et al. (2009) compared ^{68}Ga-DOTATATE (DOTA) and ^{18}F-DOPA (DOPA) PET in 25 patients with histologically proven neuroendocrine tumours (9 gut, 5 pancreas, 6 lung, one paranasal sinus and 4 with unknown primary). Patient-based sensitivities were 96% for DOTA and 56% for DOPA. Overall, DOTA was

superior to DOPA in 13 patients, and comparable in 12. DOPA uptake tended to be increased in patients with elevated serotonin levels. The authors concluded that DOPA should only be employed in patients with negative DOTA studies and elevated serotonin levels.

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3.Radionuclide Therapy

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INTRODUCTION

The treatment of neuroendocrine tumours with radiopharmaceuticals is dependent upon the presence of specific receptors or metabolic pathways in the neoplastic cells. Treatment with ^{131}I-metaiodobenzylguanidine (mIBG) was introduced to the management of neuroendocrine tumours nearly 30 years ago and is most frequently used for radiotherapy of chromaffin tumours (neuroblastomas, pheochromocytomas, and paragangliomas), but has also been used for the treatment of carcinoid tumours. The use of mIBG has diminished with the introduction of peptide receptor radionuclide therapy (PRRT). In 1989, Krenning and colleagues identified that a radioiodinated somatostatin analogue would bind to a somatostatin receptor positive tumour, enabling detection of the tumour by imaging with a gamma camera (Krenning et al., 1989). Beginning in the 1990s, attempts were made to treat patients with inoperable or metastasized neuroendocrine tumours with radiolabelled somatostatin analogues. Over the last 20 years, a number of different PRRT agents and regimens have been developed. This section of the report will provide a brief summary of PRRT and mIBG therapies. It is important to note that although multiple reviews of PRRT therapy have been written and some summative information is available regarding mIBG therapy, there has been no systematic review of either until that recently performed by the Cancer Care Ontario Program in Evidence-Based Care (PEBC)(Gulenchyn et al., 2012).

PRINCIPLES OF RADIONUCLIDE THERAPY AND DOSIMETRY CONSIDERATIONS

Radionuclide therapy of tumours relies upon the ability of the tumour to concentrate and retain a radiopharmaceutical (a radioisotope or radiolabelled molecule) to a greater degree than surrounding normal tissue. This results in the delivery of a radiation dose to the tumour and resultant cell death with sparing of normal tissues. The effectiveness of the treatment will be dependent on a number of factors including: the delivery of the radiopharmaceutical to the tumour, which is dependent upon the blood supply of the tumour if the material is injected intravenously or intra-arterially; the affinity of the radiopharmaceutical for the tumour; the physical characteristics of the labelling radionuclide; the biological half-life of the radiopharmaceutical; and, the rate of clearance of the radiopharmaceutical from non-malignant tissue.

The radionuclides used in the therapy of neuroendocrine tumours are ^{131}I, ^{90}Y, ^{111}In, and [177]Lu.

[131]I emits both beta- (E_{max} 0.61 MeV) and gamma-radiation (364 keV) and a half-life of 8.04 days. The range of the beta-particle is considered to be medium, from 200 µm to 1 mm.

^{90}Y is a pure beta-emitter with an E$_{max}$ of 2.27 and half-life of 2.67 days. Because of the high energy, this is considered to be a long-range therapeutic nuclide, with the beta-particle traveling more than 1 mm.

^{111}In is a gamma emitter with two energies, at 172 and 245 keV. Additionally, Auger electrons with tissue penetration of 0.02 to 10 μm and conversion electrons with tissue penetration of 200 to 500 μm are emitted. It is these latter two properties on which the use of ^{111}In-labelled therapeutic radiopharmaceuticals is dependent. The half-life is 2.8 days.

^{177}Lu emits both beta- (E$_{max}$ 0.5 MeV) and gamma-radiation (113 and 208 keV). The half-life is 6.75 days, and the range of beta-radiation is considered to be low, or <200 μm.

Gamma-emitting radionuclides facilitate post-therapy imaging, but have the disadvantage of increased potential of irradiating caregivers. The irradiation of the public can be controlled by radiation safety measures, which are delineated in a separate section of this document. The value of post-therapy imaging has yet to be established.

Low- and medium-range beta-emitting radionuclides are theoretically more advantageous for therapy, as their energy is deposited within the tumour, minimizing non-target damage.

Barrone el al. (2008) estimated the absorbed doses for ^{111}In-DTPA-D-Phe^1-octreotide and ^{90}Y-DOTA-D-Phe^1-Tyr^3-octreotide in the same patients to compare the potential effectiveness (tumour dose) and safety (kidney and red marrow dose) of these drugs. Six patients with neuroendocrine tumours underwent quantitative ^{111}In-DTPA-D-Phe^1-octreotide and ^{86}Y-DOTA-D-Phe^1-Tyr^3-octreotide (as a cogenor of the ^{90}Y-labelled compound) scans at intervals of one week. All studies were performed with a co-infusion of amino acids for renal protection. PET and SPECT images were reconstructed using iterative algorithms incorporating attenuation correction. Tissue uptakes were measured at standardized time points and used to calculate residence times. Absorbed doses to the tissues were estimated and the maximum allowed activity, defined as delivering 23 Gy to the kidneys or 2 Gy to the red marrow, was calculated and the resulting tumour-absorbed doses were computed. For the maximum allowed dose to the kidney of 23 Gy, the mean absorbed dose to the red marrow was lower for ^{90}Y-DOTA-D-Phe^1-Tyr^3-octreotide than for ^{111}In-DTPA-D-Phe^1-octreotide (1.8 $\pm$ 0.9 Gy vs. 6.4 $\pm$1.6 Gy; p<0.001). Conversely, the median absorbed dose to tumours, at this level, was two-fold higher for ^{90}Y-DOTA-D-Phe^1-Tyr^3-octreotide as compared with ^{111}In-DTPA-D-Phe^1-octreotide (30.1 vs. 12.6 Gy; p<0.05). This would indicate that there is a theoretical advantage to the use of ^{90}Y-DOTA-D-Phe^1-Tyr^3-octreotide, over ^{111}In-DTPA-D-Phe^1-octreotide.

Cremonesi et al. (2010) recently published a review of dosimetry considerations for treatment with radiolabelled somatostatin analogues, ^{90}Y-DOTATOC (8 publications) and ^{177}Lu-DOTATATE (5 publications). For ^{90}Y-DOTATOC whole body radiation dose estimates ranged from 0.08 to 0.28 Gy/GBq, and for ^{177}Lu- DOTATATE 0.03 to 0.90 Gy/GBq. Renal doses ranged from 1.7 to 6.1 Gy/GBq for ^{90}Y-DOTATOC, and 0.32 to 1.7 Gy/GBq for ^{177}Lu-DOTATATE, provided that renal protection is used.

 Cremonesi et al. concluded that: 1) Fast blood clearance and urinary excretion lead to low exposure of the whole body; 2) the spleen, kidneys and liver receive the highest absorbed doses; 3) the kidneys are the dose-limiting organs; 4) the absorbed doses are affected by wide intra-patient variations; 5) the absorbed doses to all

organs studied, for the same activity administered are higher with ^{90}Y-peptides than those observed with the same activity of ^{177}Lu-peptides.

Cremonesi et al. further summarized median dose estimates from 13 PRRT trials. These trials resulted in tumour doses of 0.6 to 56 Gy/Gbq for ^{90}Y-DOTATOC, and 2 to 42 Gy/GBq for ^{177}Lu- DOTATATE. In each of the following categories, the radiation dose was lower for the 177Lu-labelled compound: kidneys (unprotected), kidneys (protected), liver, red marrow, spleen, testes, bladder.

PEPTIDE RECEPTOR RADIONUCLIDE THERAPY (PRRT)

The PEBC systematic review (Gulenchyn et al., 2012) describes the literature published on regarding PRRT therapy between January 1, 1998 to November 4, 2010. The number of studies reported in the literature is small and with the exception of the Kwekkeboom study of ^{177}Lu-DOTATATE describing 310 of the 504 patients they had treated from January 2000 to August 2006 (Kwekkeboom de Herder et al., 2008) the patient numbers are small in each report. There are no reports published from the Canadian groups in Edmonton, Alberta or London, Ontario, although the London work has been the subject of four published abstracts between 2001 and 2006, as well as three more recent, unpublished presentations, all of which incorporate both PRRT and mIBG therapy (personal communication, Dr. Robert H. Reid). There is also only a limited report in the English literature in abstract form from the Zentralklinik Bad Berka (Baum, 2004) which is known to have treated many patients. Consensus guidelines for the treatment of patients with neuroendocrine tumours (including PRRT) have been published in 2010 by a Canadian National Expert Group (Kocha et al., 2010) and also by the North American Neuroendocrine Tumor Society (NANETS) (Chen et. al, 2010), in 2009 by the European Neuroendocrine Tumour Society based on a consensus conference held in 2007 (Kwekkeboom, Krenning, Lebtahi, 2009), and in 2008 by the European Society of Medical Oncology (Oberg & Jelic, 2008).

Since November 4, 2010, two additional papers of note have been published. One ongoing trial (Imhof et al., 2011) published its main results in June 2011; this is the largest PRRT trial published. Patients received one to 10 cycles (median 2) of ^{90}Y-DOTATOC at a dose of 3.7 GBq/m^2. During a median follow-up of 23 month on 1109 advanced NET patients, longer survival was found in patients with morphologic, biochemical, or clinical response to treatment with ^{90}Y-DOTATOC. The overall tumour response rate was 34.1%, which is consistent with the reports from other included articles for ^{90}Y-DOTATOC. However, it found that 9.2% of patients experienced grade 4–5 permanent renal toxicity, especially for older patients with low glomerular filtration rate or high renal tracer uptake at the baseline. This rate of toxicity is greater than that identified in the systematic review.

The second study by Kunikowska et al. (2011) was a non-randomized comparison of therapy with ^{90}Y-DOTATATE alone (Group A), with combined (1:1 ratio) ^{90}Y/^{177}Lu-DOTATATE (Group B) in 50 patients with disseminated neuroendocrine tumours of a variety of types. The administered activity was 3.7 GBq/m^2 body surface area in 3 to 5 cycles, with amino acid infusion for nephroprotection. Overall survival in Group B was significantly higher than in Group A (p=0.027). Median event-free survival time in Group A was 21.4 months and in Group B 29.4 months; this was not a statistically significant difference. There was no difference observed in the size response to therapy of the largest tumours in each patient. Side effects were rare and mild in both groups.

PATIENT SELECTION

To date, all published reports have treated patients with inoperable residual or metastatic disease that was measurable on anatomical imaging and detectable with ^{111}In-octreotide (Octreoscan™). There are no data to correlate treatment response with newer imaging agents that appear to be more sensitive in the detection of disease (e.g. ^{68}Ga-DOTATATE). It should be noted that these newer diagnostic agents have not received Health Canada approval for routine use. Likewise, there is no literature to indicate that elevated tumour markers (e.g. chromogranin A) have been used to select patients for therapy. One could hypothesize that earlier detection of disease by more sensitive imaging or tumour markers might result in a more favourable outcome after PRRT, as the tumour burden would be smaller, but there are no data with which to confirm this perspective.

There appears to be agreement that patients should have a Karnofsky Performance Score of >50% and a life expectancy of at least 3–6 months. The London, Ontario program has required a Karnofsky score of at least 60% for inclusion.

Consensus guidelines support the use of surgery and other cytoreductive therapy (e.g. radiofrequency ablation, laser therapy and embolization) prior to PRRT. Although there is no specific data to support this recommendation, it is consistent with recommendations regarding the use of ^{131}I therapy for thyroid cancer.

ENETS (Kwekkeboom, Krenning & Lebtahi, 2009) recommends the following relative and absolute exclusion criteria:

1. Pregnancy and lactation

2. Renal impairment (creatinine clearance <40 ml/min)

3. Impaired hematological function (Hgb<5 mmol/L; platelets<$75x10^9$/L ; WBC<$2x10^9$/L)

4. Severe hepatic impairment (total bilirubin>3 times the upper limit of normal, or albumen<30 g/l and PT increased)

5. Severe cardiac impairment

The London, Ontario centre has used more stringent exclusion criteria [personal communication, Dr. Robert H. Reid] as follows:

1. Renal Impairment (creatinine clearance <50 ml/min, or, Serum creatinine >130 µmol/L)

2. Impaired hematological function (Hgb>5 mmol/L; platelets<$100x10^9$/L; WBC<$3x10^9$/L)

3. Hepatic Impairment (total bilirubin >2 times the upper limit of normal,or ALT/AST >2 times the upper limit of normal)

4. Known brain metastases unless treated and stabilized

5. Radiotherapy, chemotherapy, surgery or other experimental therapy within 3 months.

PATIENT PREPARATION

There is consensus among the published guidelines (Kocha, Chen, Phan, Kwekkeboom, Oberg) regarding the preparation of patients for PRRT. When clinically possible, long-acting somatostatin analogue formulations should be stopped 6 weeks prior to treatment, and patients switched to short-acting formulations to be discontinued 1 day prior to PRRT. If it is not possible to discontinue long-acting preparations (LAR), patients should be treated at the end of a 28-day LAR treatment cycle. Patients on long-acting formulations should be instructed to co-administer short-acting formulations in the first 7–10 days after their long-acting formulation has been restarted.

An antiemetic (e.g. ondastron 8 mg IV) should be administered prior to initiation of any planned amino acid infusion and radionuclide therapy.

If either a ^{90}Y- or ^{177}Lu-labelled compound is used, then infusion of amino acid solutions that contain lysine and arginine is essential to reduce kidney radiation-absorbed dose. 2.55 lysine, 2.5% arginine in 1 liter of saline can be infused in 4 hours, starting 30 minutes before the administration of the radiopharmaceutical. Commercially available amino acid solutions can also be used (Aminosteril N-Hepa 8%, Fresenius AG, Bad Homburg, Germany combined with 30 ml magnesium sulphate 10% and 500 ml Ringer's Lactate given at an infusion rate of 500 ml/hr) (Baxter Synthamin infused at 500 ml/hr).

Treatment is, in general, performed on an out-patient basis in a specifically designed suite to facilitate safe handling of the therapeutic radiopharmaceutical. Hospitalization may be required if patients are unable to follow radiation safety precautions or if adverse events are experienced during infusion.

TREATMENT SCHEMES

Available treatment guidelines do not recommend specific treatment administration regimens. Multiple treatment administration schemas are identified in the literature; the maximum cumulative administered dose utilized to date has been with ^{177}Lu-DOTATATE at 29.6 GBq over a period of 24 to 40 weeks. The PEBC systematic review(Gulenchyn et al., 2011) in Table identified that the administered dose and treatment schema varied significantly among the studies. From personal communication, it is known that interval maintenance therapy has also been used at treatment centres in London, Ontario and Great Britain.

TREATMENT VARIATIONS

A number of variations in treatment administration have been used with PRRT. These include concomitant administration of 5FU as a radiation-sensitizing agent (Kong et al., 2009), the intra-arterial administration of PRRT (Limouris et al., 2008) and the use of pre-therapy scanning to determine individual dosimetry and thus maximize the radiation dose administered (Sandstrom, Garske, Granberg, Sundin, & Lundqvist, 2010). These variations do not appear to be widely practiced. There is no evidence that they improve outcomes.

RESPONSE TO THERAPY

The PEBC systematic review (Gulenchyn et al., 2012)summarizes the response to therapy based on survival time and rate, imaging response by various criteria, and quality of life. The majority of imaging responses have been partial responses; disease stability in a population of patients with pre-therapy progressive disease is the most common outcome. There is limited evidence based on a historical comparison of studies from a single centre that ^{177}Lu-DOTATATE may be associated with greater overall survival (OS), progression-free survival (PFS), and overall response rate (defined as the sum of complete response, partial response, and minor response rates) compared with ^{90}Y-DOTATOC or ^{111}In-DTPAOC. Quality of Life improved for some patients in all studies, but no comparison among different therapeutic radiopharmaceuticals could be made because of clinical heterogeneity.

TOXICITY

The systematic review summarizes toxicity in Table 4. (Gulenchyn et al., 2012). In general, toxicity was acceptable. Nausea and vomiting were common during therapy. The severe toxicities include: For ^{111}In-DTPAOC, 8% of patients developed myelodysplastic syndrome (MDS) and/or leukemia in one study (21); For ^{90}Y-DOTATOC, 0.9–3.4% of patients developed grade 4 renal toxicity in three studies (26–28), and 2% of patients developed MDS in one study (27); for ^{90}Y-DOTALAN, no severe toxicity was found in one study (22); for ^{90}Y-DOTATATE, 30% of patients developed grade 2 renal toxicity at two years in one study (33); for ^{177}Lu-DOTATATE, 0.6% of patients developed hepatic insufficiency, 0.8% of patients developed MDS, and 0.4% of patients developed renal insufficiency in one study (30). For studies investigating the effects of ^{90}Y-DOTATOC, ^{90}Y-DOTATATE, and ^{177}Lu-DOTATATE, lysine and arginine amino acid solution was infused to protect kidney function for each patient.

PATIENT MONITORING POST THERAPY

ENETS (Kwekkeboom, Krenning, & Lebtahi, 2009) recommends monitoring for hematological, renal and hepatic toxicity post therapy. Specifically, blood counts are to be performed every four weeks and repeated every two weeks if a WHO grade 3 or 4 toxicity is identified.

ENETS (Kwekkeboom, Krenning, & Lebtahi, 2009) further recommends that symptomatic, biochemical and imaging responses be assessed with established predetermined criteria.

The role of molecular imaging (Octreoscan™, ^{68}Ga-DOTATATE) has not yet been determined, but a very recent publication by Haug et al. (2010) suggests that decreased ^{68}Ga-DOTATATE uptake in tumours after the first cycle of therapy predicted time to progression and correlated with an improvement in clinical symptoms.

^{131}I-METAIODOBENZYLGUANIDINE THERAPY

[131]I-mIBG has been less frequently used to treat neuroendocrine tumours. The PEBC systematic review (Gulenchyn et al., 2012) identified eight studies describing its use. In all cases, ^{131}I or [123I] mIBG scanning was used to select patients with tumours that were mIBG avid. Five of the eight studies included only patients with neuroblastoma. One study described patients with midgut carcinoid tumours and the remaining two mixed groups of patients, including those with pheochromocytoma and paraganglioma. Figure 3 of the systematic review shows overall response rates with the tumour type indicated. The Canadian experience in Edmonton, Alberta is described in the paper by Sywak et al. 2004.

The preparation of patients for therapy with ^{131}I-mIBG is different than for PRRT; long-acting somatostatin analogue preparations do not need to be discontinued. EANM guidelines (Giammarile, Chiti, Lassmann, Brans, & Flux, 2008) provide direction regarding the discontinuation of other medications. Thyroid blocking agents should be utilized. Premedication with an antiemetic should be used. In the treatment of paragangliomas and pheochromocytomas, a hypertensive crisis may be induced and, thus, phentolamine should be readily available. Octreotide should be available to treat possible carcinoid crisis. Pre-treatment with amino acid solutions for renal protection, is not required.

Hematological toxicities appear to be the major severe side effect, particularly when high-dose ^{131}I-mIBG is used. Gonias et al. (2009) administered a mean dose of 30.8 GBq to a group of 30 patients with metastatic pheochromocytoma or paraganglioma following stem cell harvest; 4 patients required reinfusion of stem cells because of severe myelotoxicity.

SUMMARY

The lack of appropriately controlled trials and multiplicity of agents and treatment regimens results in significant challenges in recommending the development of a specific treatment protocol for neuroendocrine tumour patients in the province of Ontario. However, it is critical that treatment be administered within a framework that allows for proper data collection and analysis with a view to developing treatment protocols that improve the care of these patients.

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4. Surgery

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Surgical treatment has a well-defined role in the context of multidisciplinary strategy in the treatment of neuroendocrine tumours (NETs). Its roles are best classified in the context of the following:

1. Primary resectable NETs
2. Resectable secondary (metastatic NETs)
3. Palliation for NETs-related symptoms

PRIMARY RESECTABLE NETS

For resectable NETs, as with many other malignancies, the primary modality of cure remains surgical resection. Surgical resection involves the complete, margin-free excision of the tumour along with regional nodal drainage as indicated. Not all NETs require mandatory resection of the nodal basin, and selection of the appropriate procedures are specific to the biology of the specific NETs in question. It is recommended that a surgeon with knowledge of the varying biologies of different NETs be involved in the planning of the surgery. Furthermore, surgical approaches to NETs can involve both minimally invasive and standard techniques, but choice of the exact approach should take into consideration both technical factors as well as tumour biology factors.

In primarily resectable NETs, where the disease is isolated to a surgically curable field, there is no clear data supporting the use of neoadjuvant or adjuvant therapy; however, surveillance and ongoing monitoring is recommended following surgery.

In patients with metastatic NETs (see below), the role of resecting the primary tumour has some controversy. There is some retrospective evidence that suggests removal of the primary tumour improves survival, and there is also data from prospective trials, such as the PROMID trial, that demonstrate that patients with their primary tumour resected (even with non-surgical treated metastases) are associated with improved survival in the cohort of patients. From a practical perspective, certainly in gastrointestinal NETs, even NETs with an indolent behaviour can progress over time and lead to direct mechanical problems such as bowel obstruction or vascular compromise resulting in bowel ischemia. In such situations, it is generally recommended that surgery be considered for palliative control of the primary tumour even in the presence of non-surgically treatable metastases. If surgery can also be applied to the metastatic disease, considerations for that should also be made, and this is further discussed below.

Once optimal surgical options have been employed, consideration of other therapies, including systemic, external radiation or radionuclide therapy would be useful for the ongoing treatment of remaining disease.

RESECTABLE SECONDARY NETS

Metastatic NETs can occur in many sites, but primarily, in the lung, liver, peritoneum, lymphatics and bone.

The general initial approach to metastatic NETs includes systemic therapy that can be chemotherapy based or hormonally based. Surgical palliation of these metastatic NETs is discussed in the next section; however, there are some situations in which metastatic NETs are potentially completely treatable with surgical options. This is especially true in the liver.

The liver represents an important area of consideration when deciding treatment for NETs, especially in those that are producing hormones such as serotonin that can lead to further collateral damage of other end organs, such as the cardiac valves. This is especially important in patients with indolent growth of NETs who end up having major morbidity and mortality from the effects of the biochemical production from the tumour rather than from ongoing growth and metastases itself.

Patients with metastatic liver NETs should be evaluated with an eye to the potential for surgical resection. Firstly, there is retrospective data to support improved survivals in patients with treated metastatic liver NETs compared with those who were not treated. Furthermore, this is supported in prospective trials, such as the PROMID trial, which demonstrated that the cohort of patients who received benefit from long-term hormonal therapy, were in the group with low-volume liver involvement of less than 10% of the hepatic volume. Patients with metastatic liver NETs would ideally be evaluated by a hepatobiliary surgeon in the context of a multidisciplinary team. If the liver metastates are considered resectable, this option should be included in the initial steps of the treatment plan.

Ablative techniques, such as radiofrequency ablation (RFA) and microwave, do play a role similar to surgery. However, they are limited by size of metastases (ideally <3 cm) and, to a degree, the number of metastases. These techniques are best considered along with surgery, early on in the planning, and may be used as an alternative to surgical "ablation" or as a complement, to maximize disease control.

Considering surgery early in the treatment plan is important, as surgery itself does not prevent future use of systemic therapy, embolization techniques, or radiation treatments either in the form of external radiation or radionucleotide therapy. Conversely, application of emoblization and radiation treatments may affect vascular flow or liver regeneration potential that may exclude the use of therapy in the future. Furthermore, surgical resection of the gallbladder in conjunction with liver metastatectomy may prevent future gallbladder-related treatment complications including cholelithiasis (somatostatin analogues) and ischemia/infarction (secondary to embolization-based procedures).

PALLIATION FOR NETS-RELATED SYMPTOMS

Finally, surgery has a role in the palliation of NETs. Consideration can be made for surgery even in the absence of the potential for complete disease resectability.

Palliation goals can be divided into prevention or treatment of direct mechanical effects of the NETs, as well as debulking to improve response to systemic and other adjunctive therapies.

Congruent to the discussion regarding primary tumours, especially in gastrointestinal NETs, the development of new nodal disease can result in crippling bowel obstructions or bowel ischemia. In this situation, surgery can be employed to palliate against the sequelae of the disease recurrence. In bowel obstructions for example, resection of the obstructed or ischemic bowel, regardless of the possibility of residual tumour post-surgery, can result in immediate palliative relief for the patient that could not be achieved by other therapies due to the mechanical effects of the recurrent disease. Furthermore, surgical involvement can optimize a patient for other adjunctive treatments that they may not have been eligible for prior to surgery due to the nature of the complications resulting from the recurrent NETs. However, involvement of a surgical team with some experience with NETs is recommended, as there is the potential for suboptimal outcomes in this situation. For example, a too aggressive approach to recurrent NETs in the nodal basin can result in short bowel syndrome and result in suboptimal palliation of the NETs patient with recurrence.

Aside from the mechanical benefits of surgery, there are biochemical reasons for the treatment of NETs. Again, the PROMID study demonstrated that the benefits of somatostatin analogues are seen only in the group of patients with <10% hepatic involvement. There are also retrospective studies demonstrating that patients who have 90% of their metastatic NETs resected can achieve similar improved survival to patients with a gross 100% resection of their metastatic NETs. It is difficult to glean all the specific reasons for this from the previous retrospective data, but it is clear from a practical perspective that prevention of mechanical problems (such as bowel obstruction) and potential synergistic improvement in the efficacy of systemic treatment leading to the control of biochemical effects of hormone (such as valvular heat disease) leads to improved patient outcomes.

It is typical for patients with metastatic disease to become tachyphylactic to systemic therapies. In this situation, reducing disease bulk has been shown to re-induce response to systemic therapies. Tachyphylaxis can occur despite serial dose escalation of systemic therapy and can be demonstrated either symptomatically or more objectively in the clear rise in tumour-related biochemistry such as 24-hour urinary 5-HIAA or chromogranin A. In these situations, it is optimal to include surgery in the multidisciplinary consideration of further therapy. Again, as mentioned previously, if surgery can result in a 90% debulking of the tumour, there may be considerable benefit for the patient in objective symptom palliation as well as even long-term survival. However, again, surgery cannot always be applied following other options such as excessive radiation exposure to the liver or embolization of key vascular structures. Therefore, surgery should be considered to optimize the options available for the patient in this situation. It is emphasized again, however, that experienced surgical input is required, as there can be complex situations in which suboptimal surgery should be avoided.

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5. Radiation

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NEUROENDOCRINE TUMOURS AND EXTERNAL BEAM RADIOTHERAPY

Neuroendocrine tumours consist of a diverse group of tumours with different clinical behaviour, calling for a tailored multidisciplinary approach. The role of radiotherapy (RT) varies depending on the site of the primary tumour, the grade of tumour, and the feasibility and outcomes of other localized as well as systemic modalities. Small cell carcinomas (SCLC), an aggressive form of neuroendocrine tumour, most commonly arise in the lung, but can also occur in other anatomical sites (e.g. rectum, esophagus) and are generally considered systemic at the time of presentation. SCLC-specific treatment algorithms and role of radiotherapy in this disease have been specifically defined and are excluded from this discussion.

Radiotherapy can be delivered in many ways. External beam radiotherapy is the most widely used, where photon energies are directed from outside the body to deep-seated tumours. Brachytherapy delivers radiation by introducing treatment catheters with radioactive sources into luminal structures or directly into the tumours. It has geometric advantages owing to the proximity to the tumour, but is in turn restricted in its utility due to the rapid fall-off of radiotherapy dose beyond the treatment catheters. Targeted radionuclide therapy is a specialized form of delivering radioactivity. The radionuclide is unstable and releases radiation through its decay process. It may be coupled, by design, with molecules with specific affinity to tumour cells of interest.

In contrast to the use of targeted radionuclide therapy, external beam radiotherapy has been variably described as having no role in the management of neuroendocrine tumours due to their radioresistant nature. The lack of randomized trials and higher-quality evidence has likely contributed to the under-utilization of radiotherapy, especially in the management of patients living with advanced disease. In retrospective reviews of large oncology centres where multidisciplinary opinions are available, external beam radiotherapy was used in 8% (Chakravarthy & Abrams, 1995), 14% of carcinoid tumours (Schupak & Wallner, 1991), and 14% of neuroendocrine tumours of the GI tract (Rothenstein et al., 2008).

The outcomes of interest that are important in assessing the effectiveness of external beam radiotherapy parallel the consideration for their epithelial counterpart tumours. For patients with local regional disease, long-term disease-free and overall survival, and local control are key primary outcomes. For low-grade tumours (e.g. typical carcinoid), where the metastatic potential is low, RT is typically considered as an adjunct to surgery at regional nodes or alone for un-resectable disease. Here, long-term survival and local control are important considerations. For patients with high-grade tumours and metastatic disease, the efficacy for symptom relief is arguably the most important outcome.

Despite the fact that the numbers are small in the available literature, the concept that neuroendocrine tumours are radioresistant needs to be challenged. From published case series of radiotherapy in patients with neuroendocrine tumours, a subjective response (50%–90%) and objective responses (25%–50%) to radiotherapy is expected. Contessa et al. (2009) explored the effect of dose response relationship in a cohort of 36 patients

(49 sites) and suggested better local control with doses >32 Gy, although the numbers were small and all the patients with progression had treatment for liver metastases, where dose is generally limited due to liver tolerance. In general, treatment for distant metastases such as brain and bone with dose fractionation typically used for epithelial tumours is effective in providing symptom response. While palliative radiotherapy is typically expected to provide relief of symptoms due to the local effect of the tumour, hormone-mediated symptoms such as diarrhea can also be influenced by radiotherapy (Tochner, Kinsella, & Glatstein, 1985).

In patients with an indolent pace of disease, the challenges of weighing the value of response against the toxicity risks and its contribution to the overall clinical course is difficult, but, similar to considerations for all other modalities, local or systemic. Careful integration with other local and systemic therapy cannot be over emphasized.

Author	Year	Institution	#	Sites	Dose	Subjective Response	Objective Response	Overall Survival
(Gaitan, 1975)	1975	PMH	10			-	5 (50%)	-
(Keane & Rider, 1981)	1981	PMH	28	Met GI carcinoids	20-205 Gy in 20-25 fr	Approx 50%	1 CR, 2 PR (11%)	Med 2.5 years
(Tochner et al., 1985)	1985	NCI	3	Liver met hormone secreting	24 Gy in 15 fr, 30.6 Gy in 17 fr, 30 Gy in 12 fr.	3	3 (100%)	-
(Samlowski, Eyre, & Sause, 1986)	1986	Univ of Utah	16	Unresectable Metastastic Carcinoids Abd, lung, brain, bone	20-51 Gy	6	4 (25%)	-
(Abrams, King, & Wilson, 1987)	1987	Med College Wisconsin	18	Carcinoid Unresectable and metastatic	30-64 Gy	-	7/13 evaluable (54%)	-

(Schupak et al., 1991)	1991	MSKCC	44	Carcinoid Unresectable and metastastic	Median dose 33 Gy	-		Brain met: 5/8 Epidural: 10/11 Bone: 7/8 Liver/abd: 15/17	Median 4 months
(Chakravarthy & Abrams, 1995)	1995	Johns Hopkins	18	Carcinoid Unresectable and metastastic	Median Brain 33 Gy Lung 51 Gy Skin 10 Gy Bone 25 Gy Liver 21 Gy	28/31 sites (87%)	-	Median 23 months
(Contessa et al., 2009)	2009	Univ Michigan	36	Pancreatic NET Unresectable and metastastic	Median Pancreas 59.4 Gy Met 24.2 Gy	22/28 (79%) evaluable sites	10/26 sites (39%)	Median 2 years

Search strategy:

Ovid Medline 1950-Sept. 2010

1.Neuroendocrine tumours/rt

2. exp octreotide

3. Exp radioisotopes/ or exp radiopharmaceuticals

4. 2 or 3

5. 1 not 4

6. Exp carcinoid tumour

7. Exp radiotherapy

8. 1 and 2

9. 5 or 8

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6. Systemic Therapy

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Neuroendocrine tumours (NET) are a heterogeneous group of malignancies often requiring a tailored approach to treatment. Multidisciplinary care is preferred, as treatment plans are often multimodal. Unfortunately, data are sparse in the systemic treatment of NETs due to the lack of randomized clinical trials (RCTs). Clinical trials have been difficult to conduct in NETs due to the uncommon nature of this disease, the heterogeneity of this malignancy as well as difficulties with clinical trial design. However, within the last two years, some new RCTs have increased our understanding of optimal systemic treatment of NETs.

For this summary, NETs will be considered as follows:

1. Poorly-differentiated NETs (Ki-67>20%)

2. Well Differentiated NETs

    a. Small bowel NETs

    b. Pancreatic NETs (pNETs)

    c. Bronchial NETs/others

Small Cell Lung Cancer (SCLC) has been excluded from this discussion.

SYSTEMIC CHEMOTHERAPY/CYTOTOXIC TREATMENTS

Cisplatin/Etoposide

Cytotoxic chemotherapy is useful in poorly differentiated NETs with ki-67 of >20%. Response rates to a treatment combination of cisplatin and etoposide in this patient group has been reported from 42%–67% (Moertel, Kvols, O'Connell, & Rubin, 1991; Mitry et al., 1999; Hainsworth, Spigel, Litchy, & Greco, 2006). Unfortunately, survival is poor despite treatment with a two-year survival rate of <20% (Oberg et al., 2004).

Steptozocin/Doxarubicin/5FU

Among the well-differentiated NETs, pancreatic NETs are considered to be the only chemo-sensitive group. Previous studies by Moertel, Lefkopoulo, Lipsitz, Hahn, & Klaassen (1992) and Moertel, Hanley, & Johnson (1980) reported response rates in this tumour group of over 60% (5, 6) with streptozocin-based treatment combined with either 5FU or doxorubicin. However, these results have not been reproducible to the same extent in recent trials. Recent studies have only reported response rates between 6%–39% (McCollum et al., 2004; Kouvaraki et al., 2004).

It should be noted the future availability of streptozocin in Ontario is unknown.

Temozolamide

Phase II trials have shown promising results for temozolamide-based chemotherapy, usually in combination with xeloda. Response rates have varied from 24%–70% (Strosberg et al., 2010; Kulke et al., 2009; Ekeblad et al., 2007; Kulke et al., 2006). There has been little response to Temozolamide therapy in small bowel well-differentiated NETs with response rates <10% (12). One study has shown a moderate response of temozolamide-based chemotherapy (31%) (Ekeblad et al., 2007). There is not enough data available to date to make conclusions in this patient group.

Phase III RCTs are needed to further establish the role of temozolamide in pNETs and possible bronchial NETs.

There is no current funding of temozolamide for pNETs in Ontario.

SOMATOSTATIN ANALOGUES

There currently are two commercially available somatostatin analogues (SSA) available in Ontario: octreotide (available in both a short-acting formulation as well as a long-acting depot LAR formulation) and lanreotide (available only as a long-acting depot).

SSA – symptom control

Approximately 40% of patients with NETs have carcinoid syndrome. SSAs have been shown to be very useful in the control of carcinoid-related symptoms (13):

- Reduction of diarrhea – 50%

- Reduction of flushing – 60%

Common side effects include GI discomfort, gallstones after long-term use, injection site pain. Rare side effects include gastric atony and elevated blood sugars.

The symptom improvement of SSAs in symptomatic patients with NETs have shown to result in improved quality of life scores among patients (Dong et al., 2010).

SSA - Anti-proliferative effects

SSAs have been shown to be effective in prolonging time to progression in well-differentiated small bowel NETs (Rinke et al., 2009). The recently published PROMID trial (Rinke et al., 2009) was a placebo-controlled, RCT comparing octreotide LAR 30 mg every 4 weeks to placebo. Median time to progression was 14.3 months in those receiving LAR vs. 6 months in the placebo arm (HR 0.34, p=0.000072). This effect was seen in both functioning and non-functioning tumours. In subgroup analysis, the most favourable effect was seen in patients with low tumour load (<10% of liver) and resected primary tumours. Overall survival could not be determined.

The anti-proliferative effects of SSAs in NETs from other origins are unknown. A large RCT evaluating the effect of SSAs on the time to progression in pNETs is currently underway (CLARINET study).

Pasrieotide – SOM 230

This is the latest generation SSA, with improved binding capacity to somatostatin receptors. Trials are currently underway evaluating symptom control. Anti-proliferative trials are planned for the near future.

BIOLOGICAL AGENTS

Sunitinib (Sutent)

A recent Phase III double blinded trial compared the effect of sunitinib vs. placebo in well-differentiated metastatic pNETs with disease progression (Raymond et al., 2011). The dose of sunitinib tested was 37.5 mg daily in 340 patients. Median progression-free survival was 11.1 months in the sunitinib arm vs. 5.5 months in the placebo arm (HR=0.397, p<0.001). The overall response rate was 9.3% with sunitinib and 0% with placebo, with a median duration of response of 8.1 months with the drug. Stable disease rates were 34.9% and 24.7%, respectively.

Health Canada has recently approved this drug for the treatment of non-operable pNETs.

Everolimus (Affinitor)

The results of two large studies investigating the use of everolimus in patients with NETs were released at the European Society of Medical Oncology Meeting in October, 2010 (European Society of Medical Oncology, 2010).

- Radiant 2 – RCT, double blinded placebo controlled Phase III trial of everolimus + octreotide LAR vs. placebo + octreotide LAR in patients with advanced NETs and a history of carcinoid symptoms.

    - Doses: Everolimus 10 mg orally daily, octreotide LAR 30 mg q 4 weeks

    - N=429

    - Median PFS in the experimental arm was 16.4 months vs. 11.3 months. HR = 0.77 {0.59,1.00} p=0.026 but did not meet pre-specified significance level of p=0.0246

    - Median PFS by local investigator radiology did meet significance

    - Further statistical analysis (IPCW) to correct for imbalances between arms and censoring results in a significant p-value

    - Toxicity: stomatitis, rash, fatigue, diarrhea

- Radiant 3 – RCT, double blinded placebo controlled Phase III trial of everolimus vs. placebo in patients with advanced pNETs (Yao et al., 2011).

    - Doses: everolimus 10 mg orally daily

    - N=410

    - Median PFS 11.0 months vs. 4.6 months. HR = 0.35 {0.26, 0.44}, p=<0.0001

    - Overall survival not reached

    - Toxicity: stomatitis, rash, diarrhea, fatigue, infections

    - Median time on Everolimus – 38 weeks

Notes: These data are very new. Novartis plans to apply for regulatory approval based on both trials. It is very likely regulatory approval will be granted for pNETs but much less certain for other NETs. There is no current funding of everolimus for NETs in Ontario.

Bevacizumab (Avastin)

Numerous trials of bevacizumab, either alone or in combination with other drugs, are underway or planned. Currently there is no established role for this drug in NETs.

Interferon Alfa

Small Phase II single-arm studies have shown a low-level activity of interferon alfa either alone or in combination with SSA (19). However, due to the toxicity, this drug is rarely used in Ontario for the treatment of NETs.

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7. Interventional Radiology

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Minimally invasive image-guided procedures including percutaneous thermal ablation and transarterial therapies have a role in the management of neuroendocrine tumours that have metastasized to the liver. The rationale for use is threefold: cytoreduction improves symptoms, may improve survival, and in some cases may downstage to eligibility for hepatic resection and occasionally hepatic transplantation.

PERCUTANEOUS THERMAL ABLATION OF NET LIVER METASTASES

Thermal ablation can be used as an adjunct to surgical resection or for limited disease if surgical resection is not feasible. It is usually reserved for situations in which there are no more than 3 to 5 lesions, each 3 cm or smaller.

Currently available technologies for ablative cytoreductive therapy are radiofrequency (RF) ablation, microwave (MW) ablation and cryoablation. RF ablation has been the most extensively studied in this setting and has demonstrated a clear role as an adjunct to surgical intervention as well as in patients for whom surgery is contraindicated; it may be undertaken at the time of open or laparoscopic surgery or at a different sitting, percutaneously. MW is newer and has not been as extensively studied; it may be more effective than RF in treating lesions adjacent to large vascular structures. Cryoablation is used to ablate a variety of tumours; recent improvements in technology have led to the introduction of smaller probes that permit percutaneous cryoblation under IV sedation/analgesia; its role in the treatment of NET metastases has not been extensively studied.

Percutaneous ablation is usually done with a combination of ultrasound and/or computed tomographic guidance. There is, at present, considerable interest in and research around novel navigating systems.

HEPATIC ARTERIAL THERAPIES FOR NET LIVER METASTASES

Transarterial liver directed therapies are typically reserved for patients in whom resection and/or ablation are not feasible; these are usually patients with more extensive disease. These therapies are possible because of differences in blood supply between normal liver tissue and tumours. Normal liver receives 60% to 80% of its supply from the portal vein (and the remainder from the hepatic artery), while liver tumours receive 80% to 100% of their supply from the hepatic artery. The hepatic arterial system can therefore be used to selectively target tumours while minimizing the effect on uninvolved liver. Three types of hepatic arterial therapy have been developed:

- *Transarterial embolization* (TAE or "bland" embolization). Particles of a size matched to the tumour vessels are injected into the hepatic circulation to produce ischemic necrosis of metastases.

- *Transarterial chemoembolization* (TACE). Arterial delivery of chemotherapeutic and embolic agents exposes tumour to high local concentrations of drug while minimizing systemic toxicity. There is also an

element of vascular occlusion, similar to bland embolization, the extent of which varies depending on technique used.

a) **Conventional TACE**. An emulsion of Lipiodol (oily contrast agent) and a chemotherapeutic agent is injected into the hepatic arterial tree and is (usually) topped off with bland particles. A wide variety of chemotherapeutic agents have been described in the literature including doxorubicin, cisplatin, mitomycin-C, 5-fluoruracil, Streptozocin, and vinblastine.

b) **DEB-TACE**. Drug-eluting beads (DEB) are injected into the hepatic arterial tree. These beads prolong exposure of tumour to drug. Reduced leaching into the systemic circulation minimizes systemic side effects.

- **Radioembolization**. Microspheres containing Y-90 are injected into the hepatic arterial tree and selectively internally irradiate tumours. There is currently a great deal of interest in this approach and it is being studied in a wide variety of liver tumours, including hepatocellular carcinoma, neuroendocrine metastases, and colorectal metastases.

There are two commercial versions: TheraSpheres , Y-90 embedded in glass spheres (MDS Nordion Inc, Kanata, Ontario, Canada) and SIR-Spheres, Y-90 bonded to the surface of resin spheres, (SIRTeX Medical Ltd, Sydney, New South Wales, Australia). Only TheraSpheres have received Health Canada approval.

Radioembolization is currently not available in Ontario, although it is available (in a limited fashion) in Montreal and Edmonton.

A recent non-systematic review by Nazario & Gupta (2010) has summarized the literature as regards transarterial liver-directed therapies for neuroendocrine hepatic metastases. The review indicates that many nonrandomized, retrospective reports have shown that TAE and TACE can reduce hormone levels, palliate symptoms and reduce tumour burden. Radiologic response rates (complete and partial by varying criteria) vary from 25% to 95% and symptomatic response (which are less frequently reported) vary from 53% to 100%. The wide range in response rates is related to the marked heterogeneity of these various studies. Many unanswered questions remain. These include: 1) the therapeutic benefit of TACE over TAE, 2) the selection of chemotherapeutic and embolic agents, 3) the degree of hepatic tumour burden that can be safely treated, and 4) the ideal time interval between treatment sessions. There have been no randomized controlled trials addressing the use of TAE or TACE in this setting.

Nazario & Gupta also summarized the literature regarding Therasphere and SIR-Sphere therapy. They identified 4 retrospective and 1 prospective reports describing a total of 226 patients with various neuroendocrine tumours. Radiologic response rates (complete and partial by varying criteria) vary from 12% to 67%.

Post-embolization syndrome (RUQ pain, fever, nausea, malaise) is a frequent occurrence with both TAE and TACE which is why TAE and TACE generally require multi-day hospital admissions unlike Y-90 radioembolization

which is very well tolerated and can be done on an outpatient basis. It should be noted, however, that ^{90}Y radioembolization requires diagnostic angiography, usually in a separate setting to determine the hepatic arterial anatomy and the pulmonary shunt fraction via ^{99m}Tc MAA infusion (Nazario & Gupta, 2010).

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APPENDIX D: CONSIDERATIONS FOR IMPLEMENTATION

1. Radiopharmaceutical Development

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RADIOPHARMACEUTICALS FOR DIAGNOSIS AND TREATMENT OF NETS

The use of radioisotope therapy for localization and treatment of NETs has a long history. A body of largely descriptive literature has been accrued describing the use of radiopharmaceuticals for a variety of indications. The best-known agents studied for their use in localization and therapy of NETs are classified into two main groups. The first group consists of agents based on the peptide somatostatin, and the second group includes agents that are variants of iobenguane (mIBG). Within these two groups of radiopharmaceuticals, only ^{111}In-Octreoscan™, (In-111 pentetreotide, Covidien/Tyco Healthcare), and ^{131}I-Iobenguane (^{131}I-mIBG, Edmonton Research Centre) are commercially available and approved for use by Health Canada. Despite literature accumulated internationally surrounding the safety and efficacy of a new generation of diagnostic and therapeutic agents for the detection, characterization and treatment of NETs, the availability of this next generation of radiopharmaceuticals in Canada is either non-existent or severely limited.

Four separate radiopharmaceuticals comprise the most promising next-generation agents for the localization and treatment of NETs. The four agents are broken down into two sets of diagnostic and therapy pairs.

Table 1: Radiopharmaceuticals used for the Localization and Treatment of NETs

	Agent	Use	Primary Indications	Existing Health Canada-Approved Agent
1	^{68}Ga-DOTATOC/^{68}Ga-DOTATATE	Tumour localization, staging for therapy	Carcinoid tumour Large cell neuroendocrine carcinoma Neuroendocrine carcinoma	^{111}In-Octreoscan™ (Tyco Healthcare)
	^{90}Y-DOTATOC/^{177}Lu-DOTATATE	Therapy		None
2	^{123}I-mIBG	Tumour localization staging for therapy	Neuroblastoma Phaeochromocytoma Paraganglioma	^{131}I-mIBG (Edmonton Research Centre)
	^{131}I-mIBG	Therapy		None

Octreotide-based agents

Agents based on the somatostatin analog octreotide have received intense interest recently from the international medical community. These agents have been built on the foundation laid by ^{111}In-Octreoscan™ and consist of novel variants of the pentetreotide peptide and are informally known as DOTATOC and DOTATATE (Froidevaux et al., 2002; Maecke & Reubi, 2011). The peptides DOTATOC and DOTATATE differ structurally by only two atoms (alcohol vs. carboxylate respectively) and have slight differences in their ability to bind certain

subtypes of somatostatin receptors; however, this has not been correlated to in vivo binding or pharmacokinetic studies (Antunes et al., 2007). Clinically, no compelling evidence has been provided to support one peptide over the other. The proponents for each peptide have typically been involved in the clinical development of the compounds, and initial comparisons, such as that published in the November 2006 issue of *European Journal of Nuclear Medicine* and *Molecular Imaging*, have not involved a sufficient number of patients (7 patients enrolled) to draw substantial conclusions. The intellectual property (IP) for the two agents is described in detail in latter sections.

Table 2: Affinity Profiles of Radiolabelled Somatostatin Analogues (Antunes et al., 2007)

	Affinity Profiles (IC_{50}) for Somatostatin Receptor Subtypes – sst_1 – sst_5				
Peptide	sst_1	sst_2	sst_3	sst_4	sst_5
DOTATOC	>10,000	14±2.6	880±324	>1,000	393±84
Y-DOTATOC	>10,000	11±1.7	389±135	>10,000	114±29
Ga-DOTATOC	>10,000	2.5±0.5	613±140	>1,000	73±21
DOTATATE	>10,000	1.5±0.4	>1,000	453±176	547±160
Y-DOTATATE	>10,000	1.6±0.4	>1,000	523±239	187±50
Ga-DOTATATE	>10,000	0.2±0.04	>1,000	300±140	377±18

A number of clinical research studies using DOTATOC and DOTATATE have been published beginning in the early 2000s. Most of the data have been collected in Europe, with the most recent study published in the June 2010 issue of The Journal of Nuclear Medicine comparing ^{68}Ga-DOTATATE PET scans with ^{111}In-Octreoscan™ scintigraphy and cross-sectional imaging (Srirajaskanthan et al., 2010). The study, which included 51 patients, demonstrated that the ^{68}Ga-based agent was significantly more sensitive than ^{111}In-Octreoscan™ for detecting lesions (168 of 226 lesions detected for ^{68}Ga, opposed to 27/226 lesions detected for ^{111}In) and that the information gained from the ^{68}Ga images would have changed the clinical management of over 70% of the patients studied.

The therapeutic surrogates for ^{68}Ga-DOTATOC/TATE are ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE. The primary indications for these agents are in the treatment of carcinoid tumours, which comprise over two-thirds of all NETs. For each of the agents, hundreds, if not thousands, of patients have been treated in a handful of clinical centres across Europe. Both agents show similar therapeutic benefits and toxicology. The largest single study of 310 patients was reported by Kwekkeboom (Rotterdam, The Netherlands) (Kwekkeboom et al., 2008). Several medium-sized studies of 20–70 patients have been conducted in Basel, Milan and Rotterdam (Waldherr, Pless, Maecke, Haldemann, & Mueller-Brand, 2001; Paganelli et al., 2002; Waldherr et al., 2002; Forrer, Waldherr, Maecke, & Mueller-Brand, 2006; Valkema et al., 2006; Iten et al., 2007). For both agents, the percentage of patients with complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) were similar, with approximately 30% of patients having either a CR or PR. Moreover, for both agents, the number of patients with stable disease or better following treatment was greater than 80%. These treatments have yielded an increased median-time-to-progression of 30 to 40 months as opposed to less than 18 months for conventional chemotherapy.

Iobenguane-based Agents

The second class of agents used for the localization and treatment of NETs consist of [123/131]I-iobenguane for imaging and localization of tumours and ^{131}I-iobenguane for therapy. mIBG has been used predominantly for NETs including neuroblastoma, phaeochromocytoma and paraganglioma. These agents have been in clinical use for decades and have USP monographs describing the quality specifications for the preparation based on pharmacy compounding. Largely the use of iobenguane has been as a diagnostic, but increasing attention has been given to its use in radioisotope therapy.

[131]I-Iobenguane is available in Canada as a diagnostic (Edmonton Research Centre); however, it is widely accepted that ^{123}I-Iobenguane is a superior imaging agent due to I-123 being a pure gamma emitter with energy emission better suited to detection by modern SPECT equipment and the lower dose to patient owing to the absence of beta emissions. On the other hand, ^{131}I-mIBG offers far greater benefit for therapy at increased doses due to the large proportion of high-energy beta emissions, which can deposit their energy near the site of localization. Various formulations for ^{131}I-mIBG exist including those with high-specific activity mIBG. This formulation contains less total mass of mIBG per radioactive dose, which may show lower toxicity because of reduced cardiac uptake and stimulation of the sympathetic nerves of the heart. However, for ^{131}I-mIBG the optimum dosing level as either low dose (<200 mCi/dose) or high dose (>200 mCi/dose), which may provide the best tumour response remains in dispute.

SUMMARY

It can be strongly argued that to enable treatment of the widest range of NETs patients, both octreotide-based and mIBG-based agents should be supplied for clinical evaluation and use. One consideration in the clinical application and availability of these radiopharmaceuticals is that, although within each set of agents the diagnostic and therapeutic surrogates differ only by the radionuclide utilized for imaging or therapy, they are all considered unique and independent radiopharmaceuticals by Health Canada and will require separate regulatory filings and development pathways to utilize them within clinical trials in Ontario.

A NEED FOR PROSPECTIVE CLINICAL TRIALS

The regulatory pathway in Canada that enables the use of certain drugs for the localization and treatment of patients that have rare diseases such as neuroendocrine tumours is known as the Special Access Program (SAP). The SAP is treatment-driven and is utilized to allow a practitioner to treat a patient with an unapproved product based on medical need and the physicians' expertise. The pitfall of using the SAP is that clinical protocols are not required and data is not normally collected to provide evidence to support a drug's safety and efficacy. Furthermore, Health Canada does not encourage this approach and prefers to limit its use. This approach is also not appropriate for selecting radiopharmaceuticals for the diagnosis and treatment of NETs, where objective evidence-based studies are needed to make conclusions on the agents' suitability for localization and treatment of NETs.

The vast majority of the clinical studies that have been reported to date lack prospective clinical trial design; the data analyses were performed *post hoc* and involved only small numbers of patients per study at single clinical centres. Notwithstanding these deficiencies, these initial studies for next-generation agents do provide sufficient data as well as an adequate number of patients to indicate the safety of the diagnostic and therapeutic agents. However, to provide objective and compelling data around, which to make conclusions as to the best agents to diagnose and treat patients with NETs a prospective clinical trial with definitive primary and secondary endpoints must be completed. The clinical trials must enrol a statistically relevant number of patients to support the conclusion of the endpoints selected and preferably should be conducted at multiple clinical sites.

CLINICAL ROADMAP TO OBJECTIVE OUTCOMES

International regulatory bodies including Health Canada typically require three phases of clinical trials to approve a drug for ongoing clinical use.

Phase I:

Phase I trials focus primarily on safety of the agent and enrol small numbers of patients (<100). Typically these studies are performed on healthy individuals, but for agents used in treatment of cancer, the subjects recruited would typically be cancer patients refractory to conventional treatments. Phase 1 trials may also evaluate escalating doses of the drug to determine maximum tolerated amounts. For radiopharmaceuticals such as those used to diagnose and/or treat NETs, phase I studies will also assess radiation dosimetry to various tissues and organs in the body.

Phase II:

Phase II trials are performed on larger groups of patients (>100) and are designed to assess the efficacy of the agents and to collect additional safety data. Phase IIa studies are designed specifically to assess dosing requirements (can be combined with Phase I), whereas Phase IIb studies are specifically designed to assess efficacy and, in certain circumstances, can be designed as pivotal trials to register the drug for marketing approval.

Phase III:

Phase III studies are large controlled multicentre trials that often involve hundreds or thousands of patients. They are designed to provide definitive data to support the agent's efficacy and safety. Often two phase III trials are required for marketing approval. For drugs that are used to treat rare diseases such as neuoendocrine cancers the studies may be smaller (<500) and could be performed as a randomized pivotal phase IIb study.

For the agents discussed above for the treatment and localization of NETs, it may be feasible to forgo formal phase I studies in favour of carefully designed Phase I/IIa trials based on the history and significant amount of clinical evidence for safety provided in the literature. Due to the small number of patients afflicted with NETs, it is feasible that lengthy phase III clinical trials may not be required and only phase IIb pivotal trials could be

initiated. The proposed clinical pathway and approach should be discussed directly with Health Canada to gain their input on the study approaches, endpoints, and data collected to gain approval for the agents' ongoing clinical use.

AVAILABILITY AND ACCESSIBILITY OF AGENTS FOR THE LOCALIZATION AND TREATMENT OF NETS

Selecting the most promising and appropriate agents to be used in a well-constructed prospective clinical trial is of primary importance. Also, importance must be given to selecting a manufacturing partner to provide the selected radiopharmaceuticals. It must be emphasized none of the most promising agents described above are currently manufactured or supplied through any Canadian institution or organization. A partner organization would have to be selected to develop the manufacturing processes and gain regulatory approval for producing these agents for clinical trials. Also, a strong understanding of the ownership and intellectual property rights that exist internationally and within Canada must be gained to protect against liability and patent infringement, which could impact supply. Institutions proposing to develop radiopharmaceutical agents for clinical use often overlook this latter issue.

Octreotide-based agents, including ^{68}Ga/^{90}Y/^{177}Lu-DOTATOC/TATE, are thoroughly protected internationally and within Canada by two large pharmaceutical companies. The primary peptide necessary for the production of the diagnostic ^{68}Ga-DOTATATE and the corresponding therapeutic ^{177}Lu-DOTATATE are owned by Mallinckrodt Inc (St. Louis, MO) (PCT/US1996/009384, WO1996/040291, CA 2224153), who have licensed the technology to Biosynthema (St. Louis, MO), who have subsequently sublicensed to Advanced Accelerator Applications (St Genis Pouilly, France). The primary peptide necessary for the production of the diagnostic ^{68}Ga-DOTATOC and the corresponding therapeutic ^{90}Y-DOTATOC are owned by Novartis AG (Switzerland) (US 6277356/6183721, CA 2224153), who have licensed the technology to Molecular Insight Pharmaceuticals (Cambridge, MA). It is imperative that contractual agreements are made prior to commencing any unauthorized use of these agents in clinical trials with the current licensees. In addition to the considerations surrounding the peptides, thought must also be given to the availability and costs of isotope chosen for therapy. For example ^{90}Yttrium is a generator-produced isotope, whereas ^{177}Lutetium is a reactor-produced isotope.

Agents including ^{123}I-mIBG and ^{131}I-mIBG were disclosed and patented decades ago and the original patents have long since expired (PTC 4,584,187, Filed 1981). There exist a few patented manufacturing methodologies for preparation of special formulations (non-carrier added/high-specific activity) mIBG that could be sublicensed if warranted or alternative production methods that are unencumbered but produce the same formulation could be developed.

Although the intellectual property surrounding mIBG is far less encumbered, the primary indications for mIBG in the treatment of NETs comprises only a small fraction of total NETs (neuroblastoma, phaeochromocytoma and paraganlioma), whereas octreotide-based agents are primarily indicated for treatment of carcinoid tumours, which comprise more than two-thirds of all NETs. Therefore, securing an agreement with an organization that can legally provide the octreotide-based agents would be in the best interest of NETs patients in Ontario.

TIMELINE AND LOGISTICAL CONSIDERATIONS

Due to the current lack of availability in Canada and the need to establish a partnership with an organization that can develop the agents for clinical trials, the time in which radiopharmaceuticals can be ready for clinical trials must be carefully considered. The timelines will be greatly affected by the organizations' regulatory experience and relationships with Health Canada and by their experience with the chemistry, manufacturing and controls (CMC) (Health Canada Good Manufacturing Practices (GMP) Guidelines, 2009; Health Canada Annex to the Current Good Manufacturing Practices (GMP) Guidelines – Schedule C Drugs (Guide-0026); Health Canada Annex to the Current Good Manufacturing Practices (GMP) Guidelines – Good Manufacturing Practices for Positron Emitting Radiopharmaceuticals (PERs) (Guide-0071)) for these agents in addition to the organizations' ability to secure agreements to legally produce the agents.

For an organization with an existing production and distribution program, good regulatory expertise and experience with the CMC for these agents, the time to submission will be 6 – 8 months for each compound. Approvals for each agent can be done in parallel, which will require significant resources. Alternatively, a staggered approach can be taken, whereby the pairs of agents are approved sequentially.

CONCLUSIONS

Two classes of radiopharmaceuticals should be evaluated for the localization, staging and treatment of NETs. These include ^{68}Ga/^{90}Y/^{177}Lu-DOTATOC/TATE and $^{123/131}$I-mIBG. These agents should be studied for their safety and efficacy in well-constructed and managed, prospective clinical trials. The availability of these agents should be facilitated by partnering with a reputable organization with the technical, regulatory and operational experience to develop the technologies within Canada and to ensure a safe and consistent supply for the treatment of NET patients.

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2. Radiation Protection and Safety

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Therapeutic nuclear medicine requires special consideration because the high doses of radiation involved are at a level where a biological effect is produced. The levels of radiation constitute a much greater hazard to the patient, healthcare provider, and to the general public.

RADIATION SAFETY PROGRAM

Medical facilities that use unsealed sources of nuclear substances for therapeutic and diagnostic purposes must have a radiation safety program that undergoes an annual review to confirm that the program meets the operational objectives of the facility, and regulatory requirements. The program must include policies, practices and equipment to maintain radiation exposures to workers and the public as low as reasonably achievable (ALARA), with social and economic factors being taken into account. A facility radiation safety officer (RSO) must be designated. Of utmost importance is the commitment of senior management to support the program with sufficient resources to ensure compliance with personal exposure limits and the ALARA principle.

At a minimum, the facility must have policies in place that address the following:

1. Procedures outlining receipt, transportation, inventory and storage of therapeutic radionuclides.

2. Procedures outlining the safe handling of radionuclides including a description of protective clothing, handling devices, and the use of shielding.

3. Procedures outlining appropriate area monitoring including surveys for ambient and removable radioactive contamination.

4. Procedures for personnel monitoring.

5. Procedures for waste disposal.

6. Initial training for personnel and plan for refresher training at appropriate intervals.

7. Record keeping and retention procedures.

8. Procedures governing the care of the patient in the event of a medical emergency.

9. Procedures governing transportation and handling of the patient and patient specimens.

10. Procedures governing the determination as to whether therapy will be administered on an in-patient or out-patient basis.

11. Procedures governing use of therapeutic radionuclides on an out-patient basis.

12. Procedures documenting release criteria for patients treated on an in-patient basis.

REGULATORY REQUIREMENTS

The medical facility must secure and maintain a licence from the Canadian Nuclear Safety Commission (CNSC) for the possession and use of appropriate amounts of the therapeutic and diagnostic nuclear substances. The possession limits should be aligned to the planned program such that availability of treatment is assured. As this treatment and the related diagnostic procedures will be made available through a clinical trials agreement, a **Human Research Studies and/or Therapeutic and Diagnostic Nuclear Medicine licences** will be required. The *Nuclear Safety Control Act* requires that persons or organizations be licensed by the CNSC.

STORAGE AND ADMINISTRATION OF THERAPEUTIC RADIONUCLIDES

Areas for the receipt and storage of therapeutic radionuclides must be appropriately shielded and secured by robust security systems. Therapeutic doses shall be transported and administered with the use of sufficient shielding as to maintain exposures to personnel ALARA. For oral administrations, the vessel containing activity should be placed in a shielded, spill resistant container with a port or opening for administration. For intravenous use, the activity containing syringe should be placed within a syringe shield with a transparent window for visual monitoring. For beta-emitting radionuclides, a plastic (lucite) syringe shield should be used to reduce hand exposure and to minimize the production of bremsstrahlung. Infusion pumps used in the administration of radionuclide therapy should be placed within a suitable shielded container or behind an appropriate barrier. The advice of the RSO is essential in such decisions.

FACILITIES

Therapeutic radionuclides can be administered on either an in-patient or out-patient basis. Confinement within the hospital may be necessary because of the patient's medical status and concern that it may deteriorate with the initial effects of treatment, or as a step required to minimize the radiation dose to the public and to members of the patient's family. Many patients, however, can be safely treated on an out-patient basis, providing a more comfortable and supportive environment for the patients, at the same time reducing exposure to the medical facility's staff, who are, of course, occupationally exposed to larger quantities of nuclear substances. The nuclear medicine physician and facility RSO should determine the need for confinement based upon predefined criteria that consider the physical and mental condition of the patient, as well as the individual living circumstances.

Hospitals operating a program for the delivery of radionuclide therapy to patients with neuroendocrine tumours should have the capacity to offer both in- and out-patient therapy.

Patients receiving radionuclide therapy with a pure beta emitter, generally do not require isolation or limited access. Unless otherwise specified by the RSO, nurses, physicians and other healthcare providers can perform routine duties, including those requiring direct patient contact for brief periods of time. Standard precautions should be used as to avoid the possibility of skin contamination from direct contact to the beta-radiation from

the patient (i.e. body fluids). To the extent possible, verbal communication with the patient should be conducted from a distance (i.e. at doorway to room), and housekeeping, food service and other ancillary personnel should perform all essential routine tasks expeditiously and should avoid entering the room for nonessential tasks. All staff must receive basic awareness training before entering the patient room.

Patients requiring isolation (due to emissions from gamma radionuclides) shall be placed in an approved private hospital room with a private toilet and sink. Measures to control the radiation exposure must be established and documented; such as, identification of areas that can be accessed by staff and visitors and periods of time in which close contact is permitted. On the day of the planned treatment, the patient's hospital room should be prepared to minimize potential spread of radioactive contamination. The patient room should be prepared by placing plastic-backed absorbent pads (taped in place) in the areas most likely to become contaminated, such as, the floor, around the toilet and sink. Patients must be advised and must clearly understand the necessity to stay in the radionuclide therapy room. Instructions to patients should be given prior to the hospital admission in order to ensure that any questions from the patient can be addressed. The *CNSC Design Guide for Nuclear Substance Laboratories and Nuclear Medicine Rooms (GD-52)* must be consulted for the specific radionuclide therapy room design requirements. The radiation dose rate outside a radionuclide therapy room must not exceed 2.5μSv/hour so that other patients do not receive a dose in excess of 0.5mSv per hospital stay (for[131] I). Any contaminated items from the procedure must be labelled and held for complete decay in-storage, in an appropriately shielded and secured area. Following the patient discharge, the radionuclide therapy room must be monitored and, if necessary, decontaminated before further use.

Recommendations for discharge of a patient must take into account the dose rate external to the patient and the potential for the spread of contamination from an unsealed radionuclide excreted by the patient. The effective dose received by an adult family member or a caregiver, who is appropriately informed of the radiation risks, must be under 5mSv and the dose to members of the public must be less then 1mSv per annum. A caregiver may be a relative or friend over 18 years of age who is not pregnant. The period of time during which a patient, family and friends should observe restrictions will depend on the initial external dose rate from the patient and the rate of clearance of the radionuclide.

INSTRUMENTATION

The facility must possess radiation survey meters and counting equipment to support a monitoring program that includes both area monitoring and contamination monitoring.

MEDICAL EMERGENCIES INVOLVING PATIENTS UNDERGOING RADIONUCLIDE THERAPY

In life threatening situations, the patient's medical management will always take precedence over radiation safety considerations. In the case of a cardiac or respiratory arrest, only those staff essential for the patient's resuscitation should be involved. All other staff should remain at a minimum 2 metres from the patient. If the patient requires ventilation as part of resuscitation, ventilation should be by a mask-bag system. If urgent surgery or monitoring in an intensive care unit is required, precautions against external radiation and possible

contamination from body fluids need to be considered. Wearing two pairs of gloves will give some protection to the hands against beta-radiation. All staff involved in the management of the emergency should be monitored for radioactive contamination and, if necessary, decontaminated before leaving the area.

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3. Co-ordination of Care

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Discussions with patients with neuroendocrine cancer, healthcare providers and the Carcinoid NeuroEndocrine Tumour Society (CNETS) of Canada, have indicated the need to ensure that a high quality of care is provided to patients in a manner that ensures timely access, safety and accessibility, all elements that are consistent with the strategic priorities of Cancer Care Ontario.

As evidenced by this document, many separate healthcare disciplines are involved in the care of patients with neuroendocrine tumours. Two of the members of the expert panel that authored this report have written about their experiences in the establishment of a Multidisciplinary Reference Centre (MRC) for the care of NET patients. An MRC is a physical location in which patients are seen by multiple care providers, and these authors noted that MRCs in a number of areas (e.g. breast cancer and melanoma) have been associated with improvements in diagnosis, treatment planning, survival, patient satisfaction, clinician satisfaction and financial efficiency. Their report indicates several examples in which the institution of an MRC has resulted in a survival advantage for NET patients, as compared with historical data, likely as a result of improved use of somatostatin analogues and other medical treatment advances.

Most MRCs aim to facilitate multiple-patient consultations during a single visit. MRC care requires communication among the healthcare team, which is facilitated by the multidisciplinary case conference (MCC), in which healthcare providers of different specialties gather to review and discuss the next steps in a patient's treatment. The establishment of an MRC presents significant challenges. All of the participating healthcare professionals and their practice groups must be committed to make the scheduling changes that enable participation. Diagnostic imaging may need to make scheduling changes to facilitate access to special procedures on the day of the patient visit. Medical information, including diagnostic imaging, must be secured in advance of the case conference. Dedicated and experienced nurses are critical to provide consistent patient information, education and support.

An MRC for NETs patients will face additional challenges in that not all care can, or should, be delivered within the centre hosting the MRC. Many elements of a treatment plan are best delivered by the local cancer centre following communication to that centre, and preferably involvement of the local practitioner(s) in a case conference. There is clearly a need for ongoing two-way communication between the MRC and the local cancer centres with which it is affiliated.

In an era when multiple treatment options are available and the treatment of patients with neuroendocrine tumours is rapidly evolving, there is a need for ongoing provincial oversight of the delivery of care.

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