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ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Pre- and Perioperative Therapy in Patients with Neuroendocrine Tumors

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Introduction

Preoperative Diagnostic Procedures

Prior to surgery or other interventional treatment in patients with neuroendocrine tumors (NET), the tumor type and hormone production must be assessed in order to provide appropriate treatment and also to avoid sometimes life-threatening crises that may occur due to presence of hormonal syndromes associated with some of these tumors.

Gastric NET: Perioperative Therapy

An atypical carcinoid syndrome may be encountered in 5–10% of patients with sporadic type 3 gastric carcinoids, and with poorly differentiated gastric NET, but is rare with the typical small type 1–2 ECLomas (<1%). The syndrome consists of patchy, intensely red flush, sweating, itching, sometimes also cutaneous oedema, bronchoconstriction, salivary gland swelling and lacrimation [1]. It is usually coupled with presence of liver metastases and is due to release of histamine and serotonin. Urinary estimates of the histamine metabolite methylimidazole acetic acid (MeImAA) serve as a tumor marker [2–4]. The patients have decarboxylation deficit and therefore seldom have excess urinary excretion of the serotonin metabolite 5-hydroxyindole acetic acid (5-HIAA) [1, 4]. Surgery or hepatic artery embolization can be dangerous, and may occasionally be contraindicated due to risk for uncontrolled release reactions.

In the presence of an atypical carcinoid syndrome, the patients should before and during surgery or intervention be treated with octreotide [1, 4]. It is recommended that octreotide be given 100 μg × 3/day subcutaneously for 2 weeks prior to surgery. In addition, routine perioperative prophylactic treatment is provided with subcutaneous or intravenous octreotide. Combination with H_1 receptor blockers (loratadine) and H_2 blockers (ranitidine) is recommended in the presence of severe symptoms, and sometimes also cortisone (dexamethasone), since histamine release and its peripheral actions may not be blocked by somatostatin analogues [1, 4, 5]. Histamine-liberating substances like morphine or tubocurarine and adrenergic drugs should be avoided during anaesthesia. Octreotide can be given by subcutaneous injections already prior to surgery. Most efficient is intravenous administration during surgery (octreotide 500 μg in 500 ml saline, 50 μg/h started before anaesthesia), as with midgut carcinoids (see below). Patients with the most severe reac-

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tions (e.g. most common in patients with lung carcinoids) may require higher doses of octreotide (100 μg/h) and sometimes also saline infusion [1].

Small Intestinal NET: Pre- and Perioperative Therapy

Carcinoid Syndrome

NET of the small intestine (or the occasional large bowel tumors with serotonin secretion) are the most common cause of carcinoid syndrome. The syndrome occurs in 20–30% of patients with liver metastases from NET. The syndrome is occasionally encountered in patients with large retroperitoneal or ovarian lesions (primary or metastases), where secretory products exceed the capacity of detoxification by the liver, or bypass the liver and drain directly into the systemic circulation.

Preoperatively, patients with small intestinal NET need to be carefully evaluated and treated for manifestations of carcinoid syndrome, emphasizing abnormalities in case of severe diarrhoea, possibility of carcinoid heart disease, and the required protection to prevent carcinoid crisis during surgery [6, 7].

Preoperative Fluid, Electrolyte and Protein Abnormalities

Diarrhoea in patients with carcinoid syndrome may cause dehydration, electrolyte abnormalities, and hypoproteinaemia [6, 7]. In the presence of carcinoid syndrome, the essential amino acid tryptophan is converted to serotonin, leaving inadequate amounts of tryptophan for conversion to niacin and proteins, which contributes to hypoproteinaemia [7]. Niacin deficiency may cause pellagra, with dermatitis, diarrhoea and dementia. Patients with severe diarrhoea, weight loss and hypoproteinaemia require parenteral nutrition with adequate supplementation before major surgery is undertaken.

Carcinoid Heart Disease

Carcinoid heart disease occurs in more than half of the patients with carcinoid syndrome with serotonin as an important mediator [8–12]. Fibrotic plaques affect the valves and cavities of the right ventricle, with thickening of valvular leaflets and shortening of chordae tendinae, resulting in tricuspid regurgitation and pulmonary stenosis. Tricuspid valves have been affected in 90% of patients, while pulmonary valves have been less frequently involved. Left-sided valvular lesions are rare because mediators are cleared or inactivated in the lungs before reaching the left side of the heart, but can occur due to patent foramen ovale, lung tumors, or overwhelming disease [13]. Concomitant mitral and aortic regurgitation has occasionally been demonstrated. Long-standing, severe carcinoid syndrome and high 5-HIAA values predict development of carcinoid heart disease [9]. The diagnosis of carcinoid heart disease is difficult, and cardiac symptoms do not appear until late stages of the disease. Diagnosis of carcinoid heart disease requires two-dimensional echocardiography and Doppler examination to assess the severity of valvular stenosis and regurgitation. Severe tricuspid regurgitation strongly correlates with poor survival in patients with carcinoid syndrome.

In patients with carcinoid valvular heart disease, risks of abdominal operations are markedly increased. Patients may have incipient cardiac failure and be poor candidates of surgery, or fail to recover after operation. Moreover, right-sided heart failure increases central venous pressure and may markedly increase the risk of bleeding, especially in association with liver surgery. Echocardiography should be done in all patients with carcinoid syndrome, and patients with moderate carcinoid heart disease should also be discussed with cardiologists before surgery. In case of significant heart disease, a thoracic surgical evaluation and possible surgical revision of valvular heart disease may be required before major abdominal operation is undertaken [14].

Reconstructive valve replacement surgery has been reported to be of obvious value for patients with advanced heart disease and right ventricular failure, with low mortality in young persons but high risk in patients older than 60 years of age [8, 11–13, 15]. During cardiac surgery, risks for carcinoid crisis may be high because patients often require vasoactive medication to support the circulatory system, which may trigger carcinoid crisis.

Minimal Consensus Statement on Preoperative Evaluation and Therapy

Preoperatively, patients with NET and carcinoid syndrome need to be carefully evaluated. Patients with severe diarrhoea, weight loss and hypoproteinaemia require parenteral nutrition with adequate supplementation for reversal of fluid, electrolyte, and protein abnormalities, before major surgery is undertaken. Patients with carcinoid syndrome should be examined with echocardiography to diagnose the possible presence of carcinoid heart disease prior to abdominal surgery. Even patients with moderate carcinoid heart disease should be discussed with cardiologists before surgery. In case of significant heart disease a thoracic surgical evaluation and possible surgical revision of valvular heart disease should be considered before major abdominal operation is undertaken.

Carcinoid Crisis

Patients with carcinoid syndrome are at risk for developing a carcinoid crisis during surgery or other types of intervention, such as arterial embolization, radiofrequency ablation, or endoscopic procedures [1, 2, 6, 7, 10, 16]. The crisis may be provoked by induction of anaesthesia during washing of the abdomen, or as a result of tumor manipulation, or tumor necrosis during surgery or intervention. The patients may have sudden changes in blood pressure, most often hypotension, sometimes combined with prolonged and excessive flushing, hyperthermia, and occasionally bronchospasm. Some patients have attacks of hypertension and even hypertensive crisis, due to tumor release of catecholamines. Patients with large tumor load, high chromogranin A or high urinary 5-HIAA values are more likely to experience a carcinoid crisis during surgery. Catecholamines released from the adrenals or sympathetic neurons are thought to contribute to release of tumor products, and appropriate pain relief can reduce the stress response [6, 7]. Spinal anaesthesia may trigger secretion of serotonin and peptides, as hypotension activates adrenergic compensation with catecholamine secretion, making dural anaesthesia preferable for postoperative pain therapy in carcinoid patients [17]. Sometimes the crisis complication presents with vague symptoms, and patients continue to be unstable postoperatively, or fail to recover after surgery, which emphasizes the importance of being aware of an undiagnosed carcinoid crisis, possibly reversible with appropriate treatment.

Acute intravenous administration of octreotide has been reported to provide rapid reversal of carcinoid crisis, and current focus of carcinoid crisis therapy is to prevent mediator release with octreotide prophylaxis [1, 2, 6, 7, 14, 18–20]. This has largely replaced use of other drugs for acute treatment. If patients already have octreotide, this medication should continue. Otherwise, octreotide can be given 100 μg × 3/day subcutaneously for 2 weeks prior to surgery. With acute operations, octreotide is even beneficial if given for only 24 h before surgery, since this may add to acute drug administration by suppression of basal amine and peptide levels [21]. Perioperative prophylactic treatment is recommended with intravenous octreotide, 500 μg in 500 ml saline (50 μg/h), a dosage which has successfully prevented crisis during major surgery, with little side effects [6, 7]. Some patients may still have symptoms and require additional intravenous octreotide. A proposed alternative perhaps more suitable for minor procedures or lower risk patients is subcutaneous administration of octreotide 100 μg × 2–3 during surgery.

In case of a carcinoid crisis reaction with hypotension during anaesthesia, adrenergic drugs should be avoided since carcinoid cells may have adrenoceptors and a vicious cycle with excessive release of serotonin and tachykinins may begin [6, 7, 17]. The surgical tumor manipulation should be interrupted, and instead increased doses of intravenous octreotide should be given.

Minimal Consensus Statement on Perioperative Prophylaxis and Treatment to Prevent Carcinoid Crisis

Patients with carcinoid syndrome should receive octreotide prophylaxis to prevent development of carcinoid crisis during surgery. If patients already receive octreotide or other somatostatin analogues, this medication should be continued while awaiting surgery. Patients who have not received octreotide can be given 100 μg × 3/day subcutaneously for 2 weeks prior to surgery. If more acute operation is needed, octreotide is given for 1–2 days before surgery. Perioperative treatment is recommended with intravenous octreotide, 500 μg in 500 ml saline (50 μg/h), with infusion started before anaesthesia. Remaining symptoms of carcinoid syndrome indicate need of additional intravenous octreotide. In case of a carcinoid crisis reaction with hypotension during anaesthesia, adrenergic drugs should be avoided, and further octreotide should be given.

Specific Recommendations concerning Anaesthesia

Monitoring the central venous pressure may aid in fluid management, but interpretation may be difficult in the presence of carcinoid heart disease with tricuspid regurgitation or pulmonary stenosis [6, 7]. Arterial catheter monitoring is considered for major surgery. Preoperative anxiety may release catecholamines and trigger carcinoid mediators and anxiolytic premedication such as benzodiazepines should be prescribed. Drugs that stimulate the sympathetic nervous symptoms or cause histamine release, such as morphine, and *d*-tubocurarine should be avoided. Safe use of succinylcholine has been documented. Hypotension is the most common problem during anaesthesia, but in this situation sympathomimetic drugs should be avoided, since they may worsen hypotension by triggering further release of peptides. Intravenous octreotide can correct hypotension within 10 min and is used in combination with fluid filling. Hypertension is also treated by prevention of peptide release with octreotide, and by increasing the depth of anaesthesia.

Bronchospasm can occasionally be severe, and since β-receptor agonists and theophyllines may precipitate

mediator release and worsen bronchospasm, they should be used with extreme care [6, 7]. Octreotide may be used for release of bronchospasm, and steroids (dexamethasone) may still have a role in such patients. Hyperglycaemia due to high plasma serotonin levels has been reported and plasma glucose levels should be monitored perioperatively. Flushing may occur and may in itself not be problematic but is a warning of potential cardiovascular instability, and indicates increased requirement of octreotide. Recovery from anaesthesia may be delayed. Preoperative treatment with octreotide should continue and should cease slowly over the first postoperative week rather than stop abruptly. Hypovolaemia and pain causing sympathetic stimulation should be avoided in the postoperative period. Non-histamine-releasing opioids such as fentanyl have been used with no adverse effects for postoperative analgesia. Endocarditis prophylaxis may be required if significant carcinoid-induced valvular heart disease is present.

Minimal Consensus Statement on Recommendations concerning Anaesthesia

Monitoring of central venous pressure is of value during surgery for NET with carcinoid syndrome, but may be difficult to interpret in the presence of carcinoid heart disease with right-sided failure. Preoperative medication and anaesthesia should exclude drugs that may stimulate sympathetic system or cause histamine release. If hypotension occurs, sympathomimetic drugs should be avoided, and instead intravenous octreotide should be given. Hypertension is treated by prevention of peptide release with octreotide, and by increasing the depth of anaesthesia. In the presence of bronchospasm, β-receptor agonists and theophyllines should be used with great care or, instead, octreotide is recommended, possibly together with steroids (dexamethasone). Flushing during anaesthesia should constitute a warning of cardiovascular instability, and indicates increased requirement of octreotide. Preoperative treatment with octreotide should continue and be weaned slowly over the first postoperative week rather than abruptly stopped. Hypovolaemia and pain-causing sympathetic stimulation should be avoided in the postoperative period. Non-histamine-releasing opioids such as fentanyl have been used with no adverse effects for postoperative analgesia.

Pancreaticoduodenal NET: Pre- and Perioperative Therapy

Among patients with pancreaticoduodenal NET, pre- and perioperative treatment with adequately dosed proton pump inhibitors (PPIs) is needed for patients with gastrinoma, and perioperative glucose monitoring is used in patients with insulinoma. Patients with glucagonoma require somatostatin analogue treatment and nutritional supplementation to heal the skin lesion prior to surgery, and perioperative anticoagulation to prevent thrombosis. Patients with vipoma need to be resuscitated with preoperative somatostatin analogue treatment and intravenous fluid and electrolyte therapy before being subjected to surgery.

Perioperative somatostatin analogue treatment has in meta-analysis been demonstrated to result in significant reduction of pancreatic fistula rate after elective pancreatic surgery, without influence on postoperative mortality [22]. Octreotide 100–200 μg subcutaneously × 3–4/day for 6–8 days may reduce the risk for fistulation and minimize leakage after a difficult resection or enucleation of endocrine pancreatic tumors, but may not be routinely required. If octreotide has been used, it should be weaned slowly rather than abruptly stopped to reduce the risk of rebound effect.

Patients subjected to splenectomy in association with removal of an endocrine pancreatic tumor are given vaccinations against meningococcus and *Haemophilus influenza,* and Pneumovax® the day prior to hospital dismissal to prevent post-splenectomy sepsis.

Gastrinoma

Gastrinomas are predisposed to gastrointestinal perforation and haemorrhage, which may complicate surgery. During surgery, patients need adequate protection with PPIs to efficiently control the acid hypersecretion [23]. The dose of antisecretory drug is titrated to reduce the acid hypersecretion to ≤10 mEq/h, or to lower values in patients with previous acid-reducing surgery or severe reflux disease. Octreotide treatment can be used to treat Zollinger-Ellison syndrome but does not add significantly to the acid-reducing effect of PPIs, which is the preferred medication [24]. Patients should maintain their medication with PPIs for some weeks after surgery since many continue to hypersecrete acid for some time [25].

Insulinoma

Preoperative diazoxide treatment is sometimes used to control hypoglycaemia prior to operation, but may cause severe fluid retention and oedema in some patients. It is generally not recommended prior to surgery for benign insulinoma. Insulinoma patients with significant hypoglycaemia should preferably be submitted to surgery without delay, and without diazoxide. Patients with severe hypoglycaemia may require intravenous glucose infusion on the night prior to operation to avoid risk of unrecognized hypoglycaemia [26].

In the operating room, glucose is removed from the intravenous solution to allow glucose monitoring, with a rise in glucose anticipated within minutes to an hour after insulinoma resection [26]. Small doses of insulin may be required during the first postoperative days. After surgery for large insulinoma, patients may need glucose infusion as insulin effects may still prevail for some time, and blood glucose levels should be monitored.

Glucagonoma

Glucagonoma patients may have troublesome skin disease and some patients may be cachectic. Somatostatin analogue treatment, amino acid infusion, and antibiotics may improve the condition and heal the skin lesion before surgery [27]. Patients have substantial risk for deep vein thrombosis and pulmonary embolism, and should perioperatively receive prophylactic high-dose low-molecular heparin as anticoagulation treatment.

Vipoma

In vipoma patients, secretory diarrhoea is generally extensive, with severe loss of potassium and bicarbonate leading to metabolic acidosis, dehydration, and hypokalaemia [27]. Patients need to be resuscitated from life-threatening fluid losses and electrolyte abnormalities with somatostatin analogue treatment, as well as intravenous fluid and electrolyte therapy, before being subjected to surgery.

Minimal Consensus Statement on Pre- and Perioperative Management of Pancreaticoduodenal NET

Patients with gastrinoma require treatment with a titrated dose of PPI before, during and in the weeks after operation to be protected from acid hypersecretion. Insulinoma patients should be subjected to careful glucose monitoring during and after surgery. Patients with glucagonoma require somatostatin analogue treatment and nutritional supplementation to heal the skin lesion prior to surgery, and perioperative anticoagulation to prevent thrombosis. Patients with vipoma need to be resuscitated with preoperative somatostatin analogue treatment and intravenous fluid and electrolyte therapy before being subjected to surgery.

List of Participants

List of Participants of the Consensus Conference on the ENETS Guidelines for the Standard of Care for the Diagnosis and Treatment of Neuroendocrine Tumors, Held in Palma de Mallorca (Spain), November 28 to December 1, 2007

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