Perioperative Management of Patients with Carcinoid Syndrome/Neuroendocrine Neoplasm

Summary

Background: Carcinoid tumours are neuroendocrine tumours that originate in the digestive tract. Carcinoid syndrome refers to a constellation of symp-
toms such as flushing, diarrhoea and bronchospasm that are mediated by
elevated serum serotonin or its metabolites. Carcinoid crisis is a life-threatening
complication of carcinoid syndrome.

This review article provides an overview of clinical aspects relevant to the peri-
operative management of patients with carcinoid syndrome. It provides the re-
levant pathophysiological mechanisms. Special attention is paid to prevention
and management of perioperative complications.

Methods: This review article is based on
a selective literature search in PubMed
(Medline). Special attention is paid to
current international guidelines and
classification criteria.

Results: Carcinoid syndrome is char-
acterised by cutaneous flushing, bron-
chospasm and diarrhoea. Patients with
carcinoid syndrome require careful pre-
operative evaluation and interdisciplinary
preparation to avoid perioperative complica-
tions. Carcinoid heart disease is characterised by fibrotic plaques result-
ing in tricuspid regurgitation and pulmonary stenosis. Carcinoid crisis may
be provoked by stress, anxiety, induction
of anaesthesia, surgery, hypotension and
hypothermia. Intravenous administration
of somatostatin analogues can reverse
an intraoperative carcinoid crisis. Drugs
that stimulate catecholamine or histamine release should be used with cau-
tion as they may worsen hypotension.

Conclusion: Endocrine disturbances
and carcinoid crises increase the risk of
surgery. Specific preparation and inter-
disciplinary collaboration are required
to prevent potentially life-threatening
circulatory complications. This review
article provides recommendations for the
perioperative management of carcinoid
syndrome. Special attention is paid to
pathophysiological and anaesthesiological
aspects in the perioperative setting.

Introduction

This article aims to provide an overview of the interdisciplinary perioperative
management of patients with carcinoid
syndrome. A special emphasis is placed
on pathophysiologic and anaesthesiologic
aspects such as preoperative evalua-
tion and premedication of patients
with carcinoids or carcinoid syndrome,
as well as on strategies for optimisation
of intraoperative haemodynamics es-
pecially for major (abdominal) surgery.
Because carcinoids and the associated
carcinoid syndrome are especially
relevant in the context of perioperative
management, the emphasis will be on
this aspect of neuroendocrine neoplasia,
whilst other gastrointestinal neuroendo-
crine neoplasms (NEN) and their spe-
cifics will also be touched upon. NEN
occurring primarily outside the gastroin-

Conflict of interest

T. Wiesmann: lecture fees/consulting for
B. Braun, Vygon, Pajunk
H. Wulf: fees for lectures and consulting for
Pajunk, Edwards, CSL, Sintetica, Grüenthal

Keywords

Carcinoid – Carcinoid syndrome – Carcinoid Heart
Disease – Neuroendocrine Neoplasm – Perioperative
Management
The occurrence of carcinoid syndrome has been observed (10.8% NEN has been reported in literature to continue to rise throughout the past decades. Carcinoid syndrome in patients with tumour remains asymptomatic with regard to their hormonal effects, as secreted substances are subject to liver metabolism within the first pass effect. This effect is bypassed following dissemination of gastrointestinal carcinoids, as it is for those carcinoids with an extraintestinal primary location, opening the possibility for the typical symptoms of carcinoid syndrome to occur [13].

Further NEN such as insulinoma, glucagonoma, VIPoma and PPoma affect the pancreas. They can cause excessive production of those hormones physiologically produced by the organ, causing corresponding symptoms. Insulinomas, which are the most common endocrine tumour of the pancreas, are typically benign neoplasms, whereas glucagonomas have typically reached an advanced metastasised stadium by the time they manifest themselves clinically. The same can be said for VIPoma and PPoma, which by the time they are diagnosed are typically found to be malignant tumours which have metastasised to the liver.

Somatostatinomas and gastrinomas can develop both in the pancreas and in the duodenum. Again, somatostatinomas have typically already reached a metastasised stadium by the time they are diagnosed. Somatostatin inhibits the secretion of a large number of hormones and peptides in the gastrointestinal tract, including insulin, glucagon, gastrin, growth hormone, cholecystokinin, secretin, VIP and serotonin. This causes diarrhoea, steatorrhoea and hypo- as well as achlorhydria. Diabetes mellitus caused by the inhibition of insulin secretion is the cardinal syndrome. Gastrinomas metastasise from a small size on. Those in a duodenal location occur more commonly in conjunction with multiple endocrine neoplasia type 1 (MEN 1).

Aside from general signs and symptoms such as anaemia, mass effects and symptoms caused by metastases, functionally inactive NEN remain asymptomatic and are often chance finds.

Table 2 shows the incidence of manifest clinical syndromes of functionally active NEN according to the German NET registry.

The typical symptoms of the various functionally active NEN are set out in Table 3 [4,14–17].
Signs and symptoms of carcinoids
The classic carcinoid syndrome is characterised by a triad of flush, diarrhoea and bronchospasm [18]. Further signs and symptoms include changes in blood pressure and heart rate, arrhythmias, nausea and vomiting, abdominal pain, telangiectasia and pellagra-like facial lesions. The combination of symptoms can be highly variable. Also, the intensity and incidence of specific symptoms can vary throughout the course of the disease [8].

In rare cases, rheumatoid arthritis may occur; arthralgia, mesenteric fibrosis, pulmonary fibrosis and cognitive deficits have also been described [12,19].

Cardiac manifestations in patients with carcinoids
Cardiac involvement – also known as Hedinger syndrome and often incorrectly termed “carcinoid of the heart” – entails fibrosis of the endocardium as a consequence of high serotonin concentrations associated with hepatic metastases without evidence of actual cardiac tumour. The prevalence of cardiac involvement, which is often underestimated, is reported to be between 20 and more than 50% [8,20], but has decreased in the past years due to treatment with somatostatin analogues [20]. Due to a lack of manifest clinical symptoms, cardiac involvement is not diagnosed in approximately one third (37%) of patients with carcinoid syndrome [21]. It is assumed that high serotonin concentrations lead to fibrotic restructuring of the endocardium of the right side of the heart with plaque deposition [22]. This results in thickening of the valvular cusps and shortening of the chordae tendineae leading to tricuspid regurgitation and pulmonary stenosis. Whilst the tricuspid valve is affected in 95% of patients, the pulmonary valve is less commonly diseased.

Left-sided valvular dysfunction is less common because the mediators undergo pulmonary inactivation. The left side of the heart can, however, be affected in the presence of a right-left-shunt or pulmonary carcinoid [13,23]. Only in rare cases, the left side of the heart is affected without right-left-shunting and in the absence of a pulmonary carcinoid, presumably then due to exhaustion of the capacity for pulmonary inactivation of serotonin [24].

A level of 5-hydroxyindoleacetic acid (5-HIES) ≥300 µmol/24 h and more than three flush episodes per day are independent predictors of a development of new or progression of pre-existing cardiac involvement [20].

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Current guidelines offer partly divergent advice in respect to screening for and diagnosis of cardiac involvement [25, 26]. All patients with carcinoid syndrome should be screened every six to twelve months for cardiac involvement. In addition, determining serum levels of N-terminal brain natriuretic peptide (NT-proBNP) annually is to be recommended. NT-proBNP has a high sensitivity (87%) and specificity (80%) in predicting cardiac involvement and correlates with mortality [27]. NT-proBNP and 5-HIES plasma levels are both considered sensitive and specific parameters for cardiac involvement, although NT-proBNP correlates better with the severity [28]. Echocardiography is recommended in patients with signs or symptoms of heart failure or valvular disease, in those with elevated levels of serum NT-proBNP >260 ng/ml and for patients prior to elective liver or abdominal surgery [26]. Transthoracic imaging is the procedure of choice. When results are ambivalent, transoesophageal echocardiography, magnetic resonance imaging or computed tomography can be performed.

Screening prior to liver or abdominal surgery is especially important because
Clinical Anaesthesia

Preoperative evaluation

Preoperative diagnostics with regard to the extent and activity of a NEN will in most cases already have been performed by the patient’s specialist in internal medicine and a specialised surgeon prior to elective surgery.

As such, it is the duty of the anaesthesiologist to assess those diagnostic investigations which have already been performed – such as lab tests and cardiac evaluations – and initiate further measures as required based on the results and joint evaluation.

As a rule, it is necessary to differentiate between functionally inactive and functionally active NEN, as findings and symptoms specific to the respective neoplasm are only to be expected in the latter (Tab. 4).

Insofar as a patient is suffering a symptomatic NEN, the symptoms and possible exacerbating factors should be inquired after in detail during the preoperative patient interview. Because these organs are commonly involved, special attention should be paid to the heart and lungs during the patient exam [8,37].

Every patient should undergo routine preoperative lab testing as, amongst other things, metabolic disorders, significant electrolyte imbalance, dehydration, hypo- or hyperglycaemia and hypoproteinaemia may be present [37, 38]. Depending on the extent of the respective disorder, these conditions should be treated prior to surgery [1].

In addition to routine lab tests, a number of specific tests are recommended. Chromogranin A is an important tumour marker for direction of treatment and aftercare in those with histologically proven NEN. The marker can be raised in the presence of various hormone producing but also some functionally inactive tumours. Neuron-specific enolase (NSE), a substance produced by cells of neuroectodermal origin, is a further robust marker especially for undifferentiated neoplasms. Typically, 5-HIES, a product of serotonin breakdown, is determined in 24-hour urine when investigating for carcinoids. Alternatively, serotonin serum levels may be determined directly. Further specific lab tests for respective NEN are set out in Table 4. Further details regarding sensitivity, specificity, normal and cut-off values can be found in the S2k guideline on neuroendocrine tumours, although it

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Material</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromogranin A</td>
<td>Serum</td>
<td>All histologically proven NEN</td>
</tr>
<tr>
<td>Neuron-specific enolase</td>
<td>Serum</td>
<td>All NEN G3</td>
</tr>
<tr>
<td>5-HIES</td>
<td>24-hour urine</td>
<td>All duodenal NEN and suspected carcinoid</td>
</tr>
<tr>
<td>Insulin, proinsulin, C-peptide</td>
<td>Serum</td>
<td>Suspected insulinoma</td>
</tr>
<tr>
<td>Glucagon</td>
<td>EDTA plasma</td>
<td>Suspected glucagonoma</td>
</tr>
<tr>
<td>VIP</td>
<td>Serum</td>
<td>Suspected VIPoma</td>
</tr>
<tr>
<td>PP</td>
<td>EDTA plasma/serum</td>
<td>Suspected pancreatic NEN, suspected PPoma</td>
</tr>
<tr>
<td>Gastrin</td>
<td>Serum</td>
<td>Duodenal NEN, suspected Zollinger-Ellison syndrome</td>
</tr>
<tr>
<td>Somatostatin</td>
<td>EDTA plasma/serum</td>
<td>Somatostatinoma</td>
</tr>
</tbody>
</table>

5-HIES: 5-hydroxyindoleacetic acid; VIP: vasoactive intestinal peptide; PP: pancreatic polypeptide.
is worth noting that for some parameters there are no agreed normal values, with these varying depending on the assay used. When specific lab tests are used to monitor the course of the disease, it is therefore imperative that the tests should be performed using the same assays to ensure comparability [14,39].

In addition to recording an electrocardiogram, it is recommended that trans-thoracic echocardiography should be performed to exclude cardiac involvement in the context of a carcinoid syndrome, or to evaluate the degree of cardiac dysfunction. With advanced valvular disease it may be necessary to replace or reconstruct the valve prior to surgery to remove the carcinoid [1,17,40]. Details regarding the investigation and assessment of cardiac involvement can be found in section „cardiac manifestations in patients with carcinoids”, above.

Carcinoid crises can be triggered by emotional stress, making reassuring communication adapted to the needs of the patient essential. Preoperative anxiolytic drugs such as benzodiazepines can also help reduce stress, such that the indication for these drugs can be seen broadly [1]. Despite this, risks and benefits should be assessed on an individual basis (increased risk of adverse effects when benzodiazepines are used e.g. in elderly patients, those with obstructive sleep apnoea or myasthenia gravis).

**Intraoperative management**

Trigger factors for carcinoid crises, such as emotional stress, but also hypotension, hypertension or hypercapnia should be avoided in all phases. Because abrupt cardiovascular shifts can occur in the context of a possible carcinoid crisis, extended haemodynamic monitoring in the form of invasive blood pressure monitoring is recommended, augmented if necessary – and at the latest in case of a decompensated shock – by pulse contour analysis and echocardiography. As induction of anaesthesia is in itself a critical phase which can trigger a carcinoid crisis, it is recommended that invasive blood pressure monitoring should be established beforehand [8].

Propofol, thiopental or etomidate can be used for induction. So long as hypotension can be avoided, propofol would seem to be especially suitable as it demonstrates better suppression of laryngeal reflexes and lesser activation of the sympathetic nervous system [41]. Avoiding sympathoadrenergic activation is essential in these patients, as activation can lead to consecutive release of catecholamines. These in turn can cause the release of further tumour mediators. It is for this reason that the use of ketamine, a substance with sympathoadrenergic effects, should be avoided.

Furthermore, opioids such as fentanyl and sufentanil and nondepolarizing neuromuscular blocking agents such as rocuronium and vecuronium can be used safely. There is controversy surrounding the use of succinylcholine as it can lead to an increase in abdominal pressure and as such may lead to the release of mediators. Anaesthesia can be maintained using volatile anaesthetics. In general, drugs which cause liberation of histamine should be avoided. When complications occur, or for preoperative optimisation, the use of histamine receptor antagonists can be considered. Universal prophylactic histamine receptor blockade is not recommended [14]. Standard drugs of induction and maintenance considered unproblematic – and those to be avoided – are summarised in Table 5.

To ensure bronchospasm is recognised early, ventilation parameters and expiratory capnometry should be monitored closely [38].

Intraoperative right ventricular overload should be avoided [8,37]. An intraoperative flush can be a warning sign for cardiovascular instability.

Hypothermia can also trigger carcinoid crises. It follows that continuous monitoring of body temperature and early warming of the patient are recommended [8].

It is problematic that the usual treatment for intraoperative complications such as bronchospasm or hypotension can cause worsening of the symptoms in these patients because the use of catecholamines, β-receptor agonists or theophylline can lead to increased mediator liberation.

Hypotension in the context of carcinoid crises is generally refractory even in the face of volume substitution [42,43]. The use of vasoactive amines is still controversial [37,38,44]. Despite this, these types of drugs cannot always be avoided. As such it is paramount that when complications occur, the dose of somatostatin analogues should be increased, aiming to inhibit further mediator liberation.

The use of vasopressin as a pharmacologically reasonable alternative treatment for hypotension can be argued for. In contrast to the usual catecholamines, the

| Table 5 Unproblematic drugs and those to be avoided for induction and maintenance of anaesthesia. |
|---------------------------------|-----------------|-----------------|
| **Hypnotics**                  | Unproblematic   | To be avoided   |
| Propofol                       | Thiopental      | Ketamine        |
| Etomidate                      |                 |                 |
| **Analgesics**                 | Fentanyl, sufentanil | Caution: morphine (histamine liberation) |
| **Neuromuscular blockers**     | Rocuronium, vecuronium | Succinylcholine (controversial) |
|                                |                 | Caution: cisatracurium, mivacurium |
|                                |                 | (histamine liberation) |
| **Volatile anaesthetics**      | All             | –               |

Drugs which lead to an increased endogenous liberation of histamine and serotonin and those which cause release of catecholamines should be avoided.
use of vasopressin should not trigger the release of further mediators. The successful use of vasopressin during a carcinoid crisis has been described [45,46].

To the best of our knowledge, the use of inhaled anticholinergic agents for treatment of bronchospasm in the context of carcinoid crises has not be described. Theoretical pharmacological considerations would suggest the use of inhaled anticholinergics instead of treatment with beta-sympathomimetics to avoid further release of mediators.

For patients with a carcinoid undergoing unrelated surgery, neuraxial blocks can be used. As with general anaesthesia, care should be taken to avoid stress and hypotension which can trigger carcinoid crises [1,8,42].

**Perioperative treatment with somatostatin and somatostatin analogues**

Somatostatin is a gastrointestinal peptide which reduces the production and secretion of gastropancreatic hormones. As such it is not only suitable for prevention of symptoms in patients with carcinoids, but – with the exception of somatostatinoma – also in those with other NEN.

The somatostatin analogues octreotide and lanreotide bind to somatostatin receptors on tumour cells and inhibit the release of bioactive amines highly effectively. In clinical practice, the synthetic somatostatin analogue octreotide is commonly used and currently recognised as the norm. Some centres, however, use somatostatin.

With respect to the prophylactic use of somatostatin analogues prior to surgery, available data are ambivalent. However, the side-effect rate is low so that many centres have established prophylactic use as a perioperative standard for all patients. Some studies have described intraoperative carcinoid crises even in those patients without carcinoid syndrome.

Furthermore, in the context of perioperative and perinterventional management, there is no universally valid, evidence-based drug administration schedule [8, 47]. It is usual for the requirement for somatostatin treatment to be discussed by the appropriate specialists prior to surgery. Due to the weak evidence base, this treatment is usually based on local standards in NEN-centres.

For elective abdominal or other major surgery, the preoperative use of 100 µg subcutaneous octreotide three times daily for two weeks has been well-established [1,8]. For urgent or emergency surgery, the use of octreotide is recommended for 24 hours preoperatively. Continuous intravenous octreotide should be administered prophylactically from at least 12 hours prior to elective surgery, starting with a dose of 50–100 µg/h, increasing the dose stepwise until symptom control has been achieved. Some patients require doses of up to 500 µg/h; the average dose is 100–200 µg/h. An additional bolus of 50–100 µg can be administered for induction of anaesthesia. Some studies have shown that stat use of intravenous octreotide can reverse carcinoid crises. Symptoms manifesting themselves during surgery can be treated with bolus of up to 500 µg.

As carcinoid crises can occur even in the course of minor surgery on low-risk patients, intravenous somatostatin analogues should be available at all times for treatment of unexpected complications [1,8,14,42,48–50].

**Excursus: Somatostatin and somatostatin analogues**

Somatostatin is a small molecule which exists biologically in two different forms, namely somatostatin-14 and somatostatin-28 (Figure 1), which both form a cyclic structure maintained by disulphide bonds. The so-called F-W-K-T (phenylalanine-tryptophan-lysine-threonine) region is important for the effect on the somatostatin receptor and can be mimicked by synthetic bioactive peptides such as octreotide acetate (Sandostatin). Somatostatin can be found

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**Figure 1**

Amino acid sequences of octreotide, somatostatin-14 and somatostatin-28.

<table>
<thead>
<tr>
<th>Octreotide</th>
<th>Somatostatin-14</th>
<th>Somatostatin-28</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>G</td>
<td>A</td>
</tr>
<tr>
<td>C</td>
<td>G</td>
<td>A</td>
</tr>
<tr>
<td>F</td>
<td>W</td>
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<tr>
<td>S</td>
<td>L</td>
<td>S</td>
</tr>
<tr>
<td>T</td>
<td>C</td>
<td>T</td>
</tr>
</tbody>
</table>

A: Alanine; R: Arginine; N: Asparagine; C: Cysteine; Q: Glutamine; K: Lysine; M: Methionine; F: Phenylalanine; P: Proline; S: Serine; T: Threonine; W: Tryptophan; S-S: Disulphide bond.
physiologically not only in the gastrointestinal tract, but also in numerous other organs. Following paracrine or endocrine secretion somatostatin binds to its G protein-coupled receptor, reducing intracellular cAMP and so exerting its antagonistic effect. The somatostatin molecule features an extremely short half-life of approximately 3 minutes. The synthetic somatostatin analogue octreotide has a duration of action of approximately 90 minutes following intravenous administration.

In addition to its endocrinologic effect ("somatostatin inhibits all other gastrointestinal hormones"), somatostatin exhibits further clinical effects. It is for this reason that the substance is used to treat secretory diarrhoea, to reduce splanchnic blood flow in the context of gastrointestinal bleeding and, based on its propensity to decrease exocrine pancreatic function, to reduce the rate of pancreatic fistulas following surgery.

**Postoperative management**

Even following surgery, symptoms may still emerge; furthermore, recovery from general anaesthesia is often prolonged. It follows that patients should initially be observed in a post-anaesthesia care unit. To avoid sympathetic activation, hypovolaemia and pain should be avoided as far as possible during the post-operative course.

The individually determined dose of somatostatin or somatostatin analogue required for symptom control should be continued for at least a further 24-48 hours following surgery. Insofar as the patient remains asymptomatic, the substance employed is subsequently reduced slowly and ultimately stopped or, depending on the centre, stopped directly [1,8,42].

**Conclusions**

Carcinoid patients require thorough interdisciplinary preoperative evaluation so as to avoid perioperative complications. Especially those patients with advanced or longstanding carcinoid syndrome often exhibit fibrosis of the endocardium together with severe right ventricular failure. High levels of 5-HIES and cardiac dysfunction are associated with an increased perioperative risk.

Carcinoid crisis is a potentially life-threatening form of carcinoid syndrome which can manifest itself due to manipulation of the tumour or during general anaesthesia. It is important to avoid known triggers of carcinoid crises, such as emotional stress, but also hypotension, hypertension or hypercapnia in the perioperative phase. Perioperative use of somatostatin (analogues) is the fundamental measure employed to avoid carcinoid crises. Treatment of an intraoperative carcinoid crisis is by administration of intravenous somatostatin analogues.

Important perioperative and perinterventional measures to be observed in these patients are summarised in Table 6.

**Literature**


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**Table 6**

Checklists for important pre-, intra- and postoperative measures.

<table>
<thead>
<tr>
<th>Preoperative</th>
<th>Intraoperative</th>
<th>Postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attain a thorough history of symptoms and trigger factors</td>
<td>Avoid trigger factors</td>
<td>(intensive care unit) Monitoring</td>
</tr>
<tr>
<td>Patient exam, ECG and assessment of cardiac function</td>
<td>Close blood pressure monitoring, consider extended hemodynamic monitoring</td>
<td>Avoid hypovolaemia</td>
</tr>
<tr>
<td>Evaluation of available results and initiation of further tests as required</td>
<td>Avoid hypovolaemia and hypotension</td>
<td>Avoid postoperative pain using adequate analgesic therapy (sympathetic activation)</td>
</tr>
<tr>
<td>Diagnosis and treatment of electrolyte imbalance, hypovolaemia and hypo- or hyperglycaemic disturbances</td>
<td>Monitor ventilation pressures, avoid bronchospasm</td>
<td>Continue treatment with somatostatin analogues for at least 24–48 hours</td>
</tr>
<tr>
<td>Special lab tests (see Tab. 2)</td>
<td>Aim for normovolaemia</td>
<td></td>
</tr>
<tr>
<td>Observe NEN-specific symptoms</td>
<td>Aim for normothermia</td>
<td></td>
</tr>
<tr>
<td>Avoid stress and premedicate with anxiolytics</td>
<td>In case of complications, increase the dose of somatostatin analogues</td>
<td></td>
</tr>
<tr>
<td>Use somatostatin analogues for substitution</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


49. Condron ME, Pommier SJ, Pommier RF: Continuous infusion of octreotide combined with perioperative octreotide bolus does not prevent intraoperative carcinoid crisis. Surgery 2016;159:358–365


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