Surgical Therapy for Neuroendocrine Tumors

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Preliminary considerations

The decisive prognostic factor for curation of a neuroendocrine tumor (NET) of the gastrointestinal tract is complete resection according to onco-surgical criteria. More than half of NETs originate in the appendix, small bowel, or rectum (*Table 1*). These tumors are often detected by chance during surgery undertaken for a different suspected diagnosis. Since approximately 40% of all new manifestations of a NET are cured of disease through surgical or endoscopic interventions, the correct primary operation or second resection is essentially decisive here in terms of the course of the disease. Following the surgical/interventional therapy, the patient remains in regular post-tumor care after the appropriate R0 resection.

Localization	Frequency (%)
Appendix	30 - 40
Jejunum / Ileum	25 - 38
Rectum	15
Duodenum	5
Stomach	4
Colon	2
Esophagus/Bile duct/Extra-gastrointestinal	2

Table 1: Localization and Frequency of NETs

If a cure is not surgically possible, operative interventions concentrate on controlling tumor growth through resection of the primary tumor, tumor debulking, removal of symptomatic metastases, and procedures that make enteral feeding possible again. A significant role is also played by preventive interventions regarding NETs based on germline mutations, such as prophylactic thyroidectomy in cases of MEN type 2.

Surgical Therapy of NETs

According to their localization, differentiation, infiltration depth, size and endocrine function, both lymphatic vessel invasion and regional lymph node metastases which often appear larger than the primary tumor develop. Hematogenous metastases in areas of venous drainage usually occur after circulating through the lymph nodes.

Medullary **thyroid** carcinoma appears in families in approximately 25% of cases within the context of multiple endocrine neoplasia (MEN) type 2. The cause is a mutation in the RET proto-oncogene. Molecular genetic diagnostic testing is a reliable basis for the decision to intervene prophylactically. Thyroidectomy takes place surgically with systematic lymph node dissection of the central compartment. In the case of already present medullary thyroid carcinoma and the corresponding lymphatic metastasis, systematic lymphadenectomy of the central and both lateral compartments is indicated, along with the thyroidectomy.

NETs of the **esophagus** are usually localized in the lower third, but are rare. At the time of diagnosis, most are in a metastatic condition.

Surgical therapies of NETs of the **stomach** are oriented toward the pathological grouping into types 1 – 4, dignity, and tumor size. ECLomas of type 1 stomach NETs can usually be resectioned endoscopically without difficulty, while for types 2 – 4 surgical therapy is to be preferred. In the course of this, it is to be noted that NETs of the stomach types 2 – 4 can already form distant metastases in a T2 stage. The exact pathological and pathogenetic classification of the NETs of the stomach is therefore essential prior to surgical therapy. Benign tumors <1 cm are removed endoscopically; benign and low-grade malignant tumors 1-2 cm in size can be endoscopically removed or surgically excised. If the tumors occur in patients with MEN 1, an oncological stomach resection with lymphadenectomy is indicated since increased lymphatic metastasis is known to occur in these cases. Low-grade malignant NETs of the stomach >2 cm and high-grade malignant NETs of the stomach are treated surgically according to oncological criteria and also given adjuvant therapy (radioreceptor therapy, chemotherapy).

Especially in the **duodenum**, the functional, structural, and biological specifics of various entities allow themselves to be differentiated accordingly:
Two-thirds of duodenal NETs produce gastrin, are <1 cm, and metastasize early (60-90%). They are found to be sporadic or associated with MEN 1. 50-70% of gastrinomas are in the duodenum, 30% of all MEN 1-associated gastrinomas in the pancreas; few are also extra-pancreatic or extra-duodenal. The surgical strategy depicts the so-called gastrinoma triangle between gallbladder, duodenum, and pancreas; tumor removal is surgically realized according to THOMPSON (left pancreas resection with retention of spleen, enucleation of foci from the pancreas, longitudinal duodenotomy with separate palpation of the anterior and posterior walls – if applicable with diaphanoscopy – and regional lymphadenectomy).
15-20% of duodenal NETs show somatostatin production and are in the ampulla region. Regional lymph nodes appear here from a size of 2 cm. A combination with a one- or double-sided pheochromocytoma (without connection to von Hippel Lindau syndrome) has been described.
Gangliocytic paragangliomas are described 10% and duodenal NETs with serotonin production 5%. Undifferentiated duodenal neuroendocrine carcinomas are a rarity.

NETs of the **small** (mostly ileum) **and large bowel** are often first diagnosed in later stages, have therefore usually already metastasized, and for this reason are prognostically less favorable. Up to 5% of small bowel NETs <1 cm show lymph node metastases, tumors >2 cm up to 85%. Clinically they can appear as pain or intestinal obstruction, but can also cause mesenteric ischemia through "desmoplastic reaction" via contraction of the mesenterium or kinking. Since they can occur multi-centrically, the intra-operative search for synchronous second tumors (20-40%) is obligatory.

The operation focuses on radical resection of the part of the bowel affected by the tumor and the relevant lymphatic drainage channels. If involvement of lymph nodes can be macroscopically detected, these foci should be resectioned, if applicable all the way into the area of the mesenteric root. Eradication of the primary focus according to the current guidelines is recommended even in the metastatic stage (IV).

NETs of the **colon** account for approximately 3-8% of all intestinal NETs and, in contrast to adenocarcinomas, show a decreasing incidence from oral to anal. With a preferred localization in the right hemicolon, the tumor is usually noticeable through intestinal obstruction. The average risk of metastases is already about 20% for tumors <2 cm, for those >2 cm about 70%, which justifies a standard colonic resection, including lymphadenectomy, even following prior endoscopic removal of the primary NET. The therapeutic goal is complete surgical resection of the part of the bowel

affected by the tumor along with the relevant lymph nodes and metastases.

Across all stages, NETs of the **rectum** show a five-year survival rate of 70%. In the case of lesions <1 cm, endoscopic resection is the therapy of choice due to the minimal risk of metastasis; lesions >2 cm should be treated surgically as a rectal carcinoma in accordance with their metastatic risk of 60-80%.

NETs of the **appendix** are usually small at diagnosis and following resection offer a 90-100% survival rate of five years. Located at the tip of the appendix 70% of the time, 20% in the middle, and 10% at the base, these have a risk of metastasis beginning with a size of 2 cm and require an appropriate second resection adapted to the tumor. Appendectomy with tumor-free basis is the procedure of choice for NETs of the appendix <1 cm. The five-year survival rate is 99% in these cases. For tumors >2 cm, a right hemicolectomy with lymphadenectomy is indicated. NETs of the appendix with a size between 1 and 2 cm are then treated with a right hemicolectomy if the tumor is near to the base, lymphatic or vessel invasion is present, the mesoappendix is infiltrated, or if mucous production and a cellular pleomorphism with a high mitotic rate are detected in the histological analysis.

Intraoperative detection of NET in the **pancreas** during open surgery requires mobilization of the duodenum according to Kocher and opening the bursa omentalis with bi-manual palpation of the pancreas. In case of necessary duodenotomy, the variable position of the papilla is to be considered. Intraoperative sonography is an important tool for locating tumor formations and also for clarifying the tumor's position in relation to vessel and ductal structures.

Regarding endocrinal pancreatic tumors (insulinoma, gastrinoma, Vipoma, glucagonoma, tumors in cases of MEN 1 and von Hippel Lindau syndrome), it should be attempted to resect in a way that spares organs and, if possible, to retain the spleen. According to the localization of the tumors, different surgical strategies are possible for tumor resectioning, for instance, enucleations out of the pancreatic head, body, and tail regions. To treat defects existing in the pancreatic parenchyma (fistula risk approximately 30%), attachment of a detached Y-Roux loop to the pancreas has established itself alongside sufficient drainage of the area under operation.

According to tumor size and lymph node status, resection of the pancreas head (Whipple, Longmire/Traverso), left pancreatic resection, and if applicable also pancreatectomy, are indicated. Goals of the operation are removal of the tumor and resultant eradication of symptoms. The result of the operation should be verified in a timely manner by instantaneous sectioning and through appropriate tests (e.g. blood sugar monitoring in cases of insulinoma).

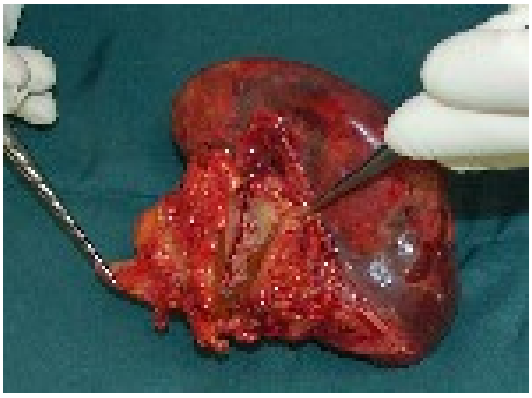

Figure 1: NET of the pancreatic cauda

Surgical treatment of **hepatic metastases** of NETs corresponds to the generally valid principles for **liver resection**. The goal is complete removal of the liver foci as R0 resection. In contrast to liver metastases of other primary tumors, tumor debulking is also recommended in the case of NETs. Right and left hemihepatectomy, trisectorectomy, and left lateral liver resection are the standard procedures. Segment-oriented and atypical resections are used in cases of complex patterns of involvement, expanded resection of the opposite side, recurrent surgeries, or in incidences of liver parenchyma damage.

The obligatory intraoperative sonography serves to detect tumors in the

liver, to estimate the extent of resection, and for anatomical orientation.

Radiofrequency ablation (RFA) combines intraparenchymatous tumor treatment with the sparing of the parenchyma. The advantages of this procedure (classified as palliative) are its frequent repeatability and application in cases of complex, non-resectable involvement of the liver and also in patients with damage to liver parenchyma. RFA can be used as a monopolar or bipolar procedure. Bipolar applicators allow for ablation of larger foci up to a maximum of 7.5 cm. In cases of accordingly high tumor burden in the liver, a multi-step surgical process is also advisable with RFA.

RFA of liver metastases can be realized with minimal invasion and consequently combinable with staging of the abdomen. Ascites or the proximity of the metastases to thermo-sensitive structures (bile duct, gallbladder) is no longer a contraindication if combined with laparoscopic cholecystectomy, for instance, instead of percutaneous procedures.

Figure 2: Hepatic NET metastasis next to the gallbladder

Intraoperative laparoscopic sonography makes an accordingly thorough detection of liver foci and their specific treatment possible.

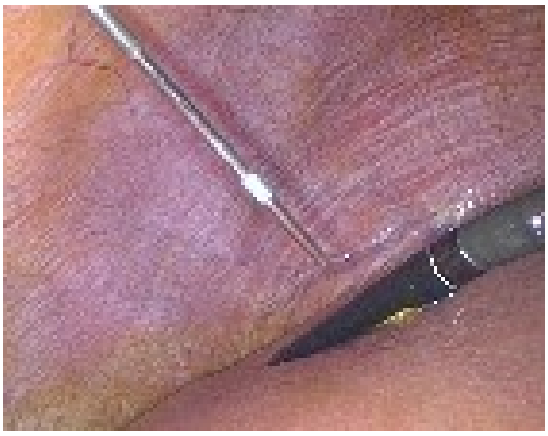

Figure 3: MIS – sonography-assisted RFA of hepatic NET metastases

Minimal invasive surgery (MIS) is currently used primarily as a staging procedure in terms of surgically treating NETs. Explorative laparoscopy, if applicable with sample taking and mainly in combination with laparoscopic sonography, allows for a precise determination regarding tumor spreading and histopathological confirmation. In principle, laparoscopic therapeutic options are possible in the form of stomach, small and large bowel resections, lymph node extirpations, and also treatment of liver metastases (**laparoscopic RFA**).

Figure 4: Surgery – exploratory laparoscopy / sonography with RFA

Operations regarding NETs must be accompanied by appropriate prophylactic measures due to the risk of perioperative carcinoid crisis. Special guidelines exist for

preventing carcinoid crises during anesthesia and surgery.

In terms of neuroendocrinal tumors and NET metastases, **cytoreductive therapy** (tumor debulking) is of high value. The usually slow growth and the known and published positive survival rates justify repeated surgical interventions, even in palliative situations.

Studies have shown the significance of active and progressive surgical procedure for tumor mass reduction, which in combination with multi-modal therapy concepts gives the patient an advantage in terms of survival.

Figure 5: Cytoreductive therapy – tumor mass reduction of intra-abdominal NET

In cases of symptomatic and non-resectable findings, meaningful surgical palliation is to be aimed for; this means making the highest possible quality of life available in terms of acceptable risk. In most cases, this involves surgeries to eliminate chronic intestinal obstructions (peritoneal carcinosis, involvement of lymph nodes, desmoplastic reaction) through intestinal bypass anastomoses and also the implantation of central venous port systems.

With neuroendocrine tumors, expanded tumor formations, hepatic and lymphogenous metastases do not justify surgical nihilism. Resectioning, even with palliative intention, is often possible and meaningful following appropriate neoadjuvant/adjuvant/additive therapy.

During Ga-68 DOTA-NOC PET/CT, tumor distribution and burden are documented morphologically and metabolically in patients with NET. Receptors present in the tumorous tissue allow themselves to be imaged according to perioperative marking with radiopharmaceuticals through the intraoperative use of a **gamma sensor**. It is possible for the operator to make tumor detection and staging more exact and to differentiate the intra-abdominal findings in more detail.

Figure 6: Intraoperative use of the gamma senor for tumor detection

Figure 7: Measuring station for the gamma sensor

Multi-modal Therapy for NETs

Inclusion of therapy for NETs into a multi-modal concept promises the greatest advantage to the patient. Coordination

regarding which therapeutic approach is to be preferred at certain time points is done interdisciplinarily. The treatment concept is, as a result, constantly being adjusted, including in terms of the individual patient.

A 30 year-old female patient with histologically confirmed, expanded lymphogenous metastatic NET of the pancreas and classified by an external clinic as inoperable was given two rounds of radioreceptor therapy.

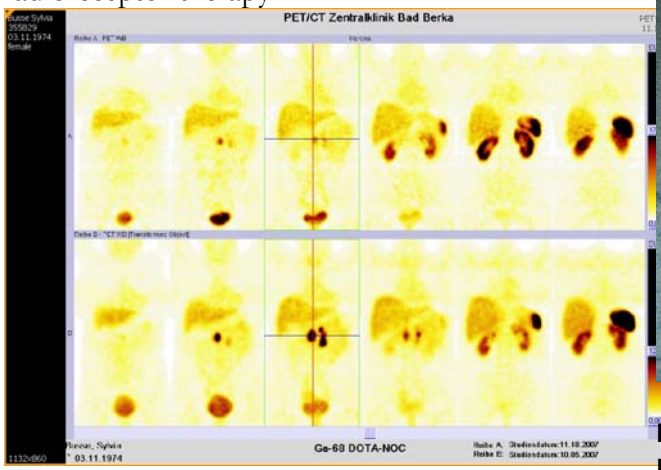

Figure 8: Ga 68 DOTA-NOC PET/CT (metabolic status prior to and following neoadjuvant radioreceptor therapy) PET-Zentrum ZBB Prof. Dr. R.P. Baum

A clear regression of the intra-abdominal tumor formations were able to be shown through Ga 68 DOTA-NOC PET/CT, so that the patient could be treated surgically with a classic resection of the pancreas head according to Longmire/Traverso and corresponding lymphadenectomy and presents as tumor-free in the current restaging.

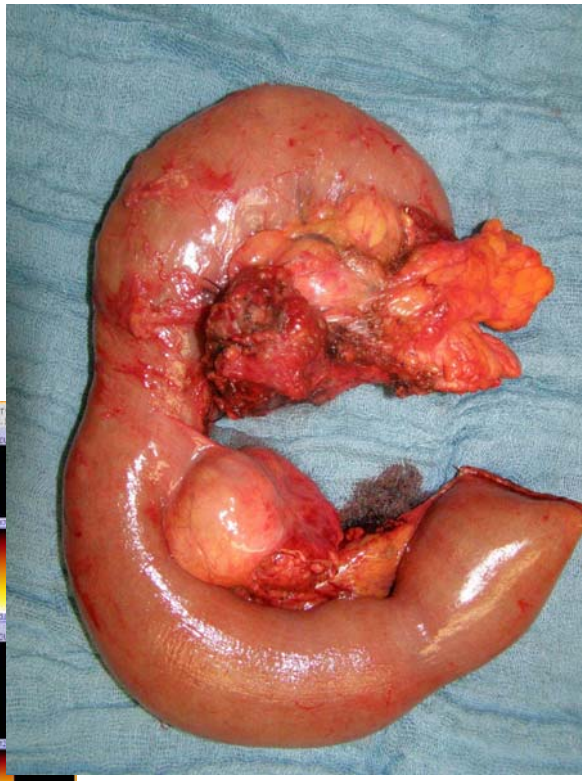

Figure 9: OP preparation following pancreatic head resection (Longmire/Traverso) and mesenteric lymph node dissection

Recommendations concerning surgical procedures are included in the current ENETS guidelines (www.neuroendocrine.net). It remains worth mentioning that regarding surgical procedures for treating NETs, there is still insufficient data underlining the importance of registries and prospective studies.

Literature available from the authors upon request

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