Role of surgery in NETs in both primary and metastatic disease

Riad Younes

Hospital Sirio Libanés, San Paulo. Brazil.

The aim of this presentation is to describe the general aspects, what is important for surgeons to know; what questions surgeons, and even clinicians, should ask themselves, and what to do in the presence of a neuroendocrine tumor, mainly a gut tumor.

It is important to remember that cells are diffusely found in the body. So in order to describe how we operate on patients, we should consider a head-to-toe approach.

The histology is very important. The role of the pathologist is essential since he can tell us what kind of tumor it is and what prognosis we might expect.

We are all familiar with the NET classification by histology:

1. Well differentiated neuroendocrine tumor.

2. Well differentiated neuroendocrine carcinoma.
3. Poorly differentiated large-cell neuroendocrine carcinoma.
4. Poorly differentiated small-cell neuroendocrine carcinoma.

Surgical decisions and management vary depending on the site of origin of the primary tumor. These primary tumors may originate in the:

- Foregut: Respiratory tract, pancreas, stomach, proximal duodenum.
- Midgut: Jejunum, ileum, appendix, Meckel diverticulum, ascending colon.
- Hindgut: Transverse and descending colon, rectum.

The incidence is low (7/million), but very underestimated. Studies in autopsies conducted at Mayo Clinic revealed a much higher incidence. Many NETs are not clinically evident during the lifetime of many patients.

According to some statistics:

- 1/200 to 300 appendectomies will reveal a NET.
- 1/2500 colonoscopies will disclose the presenc of a NET.
- 5/ million/year lung NET (if we take out the Small cell lung carcinoma SCLC).

But if we include poorly differentiated SCLC into the equation these figures go up and 10% of all lung cancers are NETs. In Brazil about 11.000 new cases are diagnosed every year.

As for functioning NETs: morbidity and survival depend on hormonal symptoms and tumor progression. For some patients this is more important sometimes.

But from a clinical point of view, the main difference is between functioning and non-functioning neuroendocrine tumors. In the former group morbidity and mortality derive from hormone related symptoms and disease progression. While in the later group tumor progression is the sole cause of morbidity and mortality.

The clinical presentation depends also on whether tumors are functioning or non functioning, on the stage of the disease, and on organ invasion, if present. These are all important issues to he considered by the surgeon.

According to the well-known graph by Vinik A. et al. *(Dig Dis Sci 1989;34(suppl 89):14S-27S)* we are all so familiar with, about duration of disease, usually a couple of years go by between the growth of the primary tumor (metastasis, flushing, diarrhea) and death. Much time has been wasted by the time the surgeon appears, when a cure might have been provided instead of palliative care. In conclusion, the surgeon usually comes in late in the evolution of these patients.

As for diagnosis and localization, physical examination is important. Chest X-rays should be indicated since some of these tumors originate in the chest. Endoscopy or bronchoscopy will no doubt be useful for tumor biopsy. CT scans, MRIs or ultrasound are today mainstay indications before treatment. Selective venous sampling is very uncommonly used today thanks to the advent of OctreoScan. Therefore, it is very unlikely to need this sampling.

As for PET scanning, PET scan with FDG is rarely positive unless the patient has a poorly differentiated NET. In the future we will be hearing a lot about different PET scans (^{11}C-5-HTP).

However, the most useful and important diagnostic tool to stage, and even to find a primary tumor, today is the Somatostatin receptor scintigraphy (SRS), also known as OctreoScan. OctreoScan may tell us even that a patient is not a good candidate for surgery when he has multiple metastases.

We should underline the usefulness of SRS ^{111}In-OctreoScan (73% to 89% positivity).

Should OctreoScan not be available, even MIBG (Meta-iodobenzylguanidine scintiscan) might be positive. MIBG is available almost in every health care center.

What about the role of surgery? Definitely, and whenever possible, surgery is the mainstay treatment, and the only known method to treat localized disease and to cure patients with NETs.

The following are important points about NETs of the midgut for surgeons to bear in mind:

- Usual primary site: the most important part to look at is the ileum.
- If they are small, submucosal tumors, be very careful with the laparoscopy because sometimes the tumor may be missed, mainly when it is not on the surface of the bowel.
- If mean diameter, is 1 cm, again laparoscopy, and even laparotomy, might miss these small tumors.
- Don´t forget to palpate the rest of the small bowel

for multiple nodules in neighbouring area (30%).
- Mesenteric metastases are very common even in small tumors.
- Mesenteric metastases typically grow more than the primary in the gastrointestinal tract.
- Mesenteric fibrosis, fixed to the retroperitoneum, is one of the complications associated with these tumors. Fibrosis worsens with time, even if the tumor responds very well to octreotide, chemotherapy, or biological treatment. Sometimes patients develop mesenteric ischemia.
- Hepatic metastases are common (50% are positive on admission), and 10% of patients without lymph node metastasis might have metastasis in the liver. Therefore intraoperative ultrasound is advisable.
- These tumors are usually diagnosed as an acute abdomen or abdominal pain.
- Whenever possible, attempt complete resection (R0), as well as resection of the adjacent mesentery.
- Patients sometimes come to see us after an inadequate first operation. The pathologist or the surgeon did not suspect the presence of a NET, or an advanced adenocarcinoma was mistakenly diagnosed. In situations like this, do not think twice: reoperate. These surgical procedures may be difficult and lengthy but fruitful and beneficial to the patients.
- As a surgeon, be meticulous and patient.
- Avoid technical errors that might jeopardize the result of the surgery, such as fistulae, ischemia and short bowel.
- If hepatic metastases are found, remember they are usually multiple, diffuse and therefore not resectable. They may only be clinically managed.
- 8% to 20% are solitary or dominant metastases.
- Wedge resection is usually good enough. Sometimes lobectomy is an acceptable method.
- Forget about debulking: few cases have been reported, and no significant response to clinical approach has been described.
- A controversial issue at this stage is transplantation.
- Hepatic artery embolization, crioablation, laser, radiofrequency ablation should be discussed before deciding what kind of operation to perform.
- Use prophylactic somatostatin analogs to avoid crisis (severe hypotension, arrhythmia, intensive flushing, bronchospasm).
- Prophylactic preoperative therapy with somatostatin analogs in all patients with carcinoid syndrome is advisable before and during operation. Sometimes after surgery as well.
- Based on the results of surgery in 150 cases at the University Hospital, Uppsala, Sweden, even in advanced disease, it is concluded that surgery has a clear role in the management of this condition. The benefits of surgery in advanced disease include abdominal symptom relief with partial or complete remission in 80% of cases; the mean duration of improvement is about 61 months, and the median survival is 9 years.

Oncologists, endocrinologists and surgeons should try and make some recommendations and guidelines based on general consensus.

For example, a carcinoid of the appendix, 1-2 cm, located distant from the base, with no invasion of the mesoappendix, and no lymphovascular invasion (LVI) should be treated with appendectomy or with hemicolectomy upfront, that is, differently from a tumor which is near the tip of the appendix, and has no evidence of mesoinvasion.

Algorithms should be situation or symptom-specific.

As for diagnosis, when symptoms appear, endoscopy and then biopsy of the primary should follow; later, TAC-US guided percutaneous biopsy should be performed.

For staging TAC, MRI and US are useful methods. OctreoScan, MIBG and PET-CT are also useful tools.

Finally, in the case of hepatic metastases, the condition of the patient should be evaluated to detect any hormonal symptoms. Then, complete staging should be based on TAC, US, and nuclear medicine (OctreoScan, MIBG) to detect masses in the liver or extrahepatic masses. In the case of liver masses, resection is the option.