# Pathology-based clinical considerations. Introduction to the ENETs guidelines

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Our working field is increasing day after day. For this reason we need to work in teams and make group efforts. We need teachers, physicians who are able to teach.

What about consensus guidelines?

Guidelines are just an agreement. When you have a patient in front of you, or you face a scientific problem you need to make decisions, and when you find the solution you know if you were right or not.

Our job as physicians is the job of the *deja –vu*.

We have two consensus guidelines, one from 2006: *"Consensus Guidelines for the management of Patients with Digestive Neuroendocrine Tumors: Why such Guidelines and how we went about it"*, and another from 2008: *"Consensus Guidelines for the management of Patients with Digestive Neuroendocrine Tumors: The Second Event and some Final Considerations"*, published in Neuroendocrinology. Of course it was not easy to put together the people and the papers to finally come out with these guidelines.

With respect to neuroendocrine tumors (NETs), it should be underlined that despite the fact that guidelines are published by expert national and international groups, Consensus on patient management is difficult to reach, especially in the light of the relatively limited evidence available in the current literature.

ENETS, European NeuroEndocrine Tumor Society, managed to define consensus standards on the diagnosis and treatment of tumors among international experts. The same premise lead to the consensus, gold standards, guidelines for the management of patients with NETs. Consensus is achieved thanks to research; guidelines are the validation. This includes registry design and papers to be published.

Which are the basis of diagnosis and therapy?

To detect the presence or absence of the syndrome; the diagnosis is then based on biopsy. Then, stage of the disease based on imaging, histology, molecular staging, biological markers. This will eventually lead to treatment design and treatment options. In other words, without staging, there is no treatment. We need standarization for guidelines.

***If you don't suspect it, you don't detect it!***

As for the number of new patients in 2006: 668 were diagnosed in France, and less than 250 in Italy. We are more southern, they are more northern.

The number of patients under treatment: 95,000 in the USA, and less than 8,000 in Italy. However, the number of patients under treatment in Italy should be around 18,000.

If we look at the SEER survival graph for digestive tumors for the year 2004, we can see that the best rate corresponds to GEP-NET, colon and rectum, and then stomach, esophagus, and pancreas. The prevalence reveals a clinical problem, since the rate for GEPs are too low. So, the question arises: where are patients with GEPs?

This means our diagnostic methods are improving. It is not due to a virus, a bacteria or pollution.

Without a chronology and events in the natural history of disease, we do not know, we do not understand what we are doing. We have to consider both inherited and acquired risk factors, the biologic onset, the symptoms, and the morbidity or mortality outcome. I would like to underline these points just to try and give an answer to the question you have asked me to address. Otherwise this is just like playing cards and waiting for the other player to stand up and leave for a minute to then have a chance to look at his cards.

It is known that inherited risk factors are related to MEN 1 and MEN 2; this is part of the story. As for acquired risk factors, there is no much information.

Our paper includes a graph (G. Delle Fave. *Aliment Pharmacol Ther: 2003*) showing the number of sealed units of proton pump inhibitors (PPIs) and H2-Receptor antagonists market (1990-1998) comparing the Italian and the US market. Both in Italy and in the USA the number of PPIs (proton pump inhibitors) is higher.

Another graph showing the number of Zollinger Ellison patients diagnosed both in an Italian and American center. The graph shows a downward trend in the number of referrals in both centers.

In the 90s these patients presented singular tumors and few metastases. Now, most of these patients with ZE come with gastrinoma and advanced disease.

Panzuto et al described the prognostic factors in 156 patients with GEP NETs, considering the primary tumor site (pancreas vs. GI tract) - the site is a negative prognostic factor - the tumor degree of differentiation (poor vs. good), the Ki 67 value, and the presence of distant metastasis in order to address the question of survival. As for the Ki-67 value over 2 and below 2 differ significantly at 3 years survival rate.

Is all this good enough? In fact it is all we have.

If we make a comparison from the pathological point of view of the Ki-67 in the primary and liver metastasis, we can see that the lat ter is much more aggressive. (1% vs. 15%, respectively. As for gastrinoma liver metastasis, we detect high Ki-67 levels in the border, and low levels in the middle. When we

do FNA we do it in the border and the middle. In this case, we know nothing about the biological onset. We do know about the natural history of the disease in terms of morbidity and mortality. In other words we are starting from the very end, and as you know we should begin from the very beginning, i.e., no more a retrospective but a prospective approach.

A prospective study was conducted in Verona, Milan, Torino and Rome including 318 well selected patients with advanced disease, not resectable, with residual disease after surgery. The goal of this study was to establish the time for the first progression. The mortality rate for a 1-12 year follow up period reached 39%. The progression rate was 74%; and the absence of progression was 26%, which means 25% of the patients did not exhibit progression, even with advanced disease and liver metastasis.

We do not know about the onset of symptoms. The symptoms and signs may be associated to hypersecretion of bioactive hormones and amines, or due to a mass effect, that is proliferation and invasion. The clinical presentation depends on localization. If localized in small tubes, the symptoms are severe; in large tubes symptoms are mild. It also depends on the disease extension, that is dimension and metastasis, either in bone or liver. As you can see in this case, we do not have specific symptoms for carcinoids in the digestive tract. Symptoms may include dyspepsia, macroanemia, abdominal pain, subocclusion, diarrhea, rectal bleeding. And therefore the diagnosis is delayed 4-6 years. The same applies to the pancreas (abdominal pain, weight loss, anorexia, vomiting, jaundice, diarrhea) and to metastasis (jaundice, bone pain). Therefor we are not able to reconstruct the natural history of the disease, and in conclusion 30 to 50% of the diagnosis is made by chance. It usually happens that patients come only for screening and a spot is found in the liver. Then, the biopsy confirms the presence of a neuroendocrine tumor. As for predictors of response to therapy we always find that cell proliferation and the proliferative fraction are good predictors. Then, differences in terms of size of the stomach, appendix, colon and rectum exist. The size determines the symptoms.

Predictors for tumor response to analogs are crucial to determine the response to therapy. Pancreatic tumors respond less than carcinoid tumors. No previous surgery is crucial to determine survival.

Finally, molecular prognostic factors: SSRT 2 and SSRT 2+5 should be considered; and the deregulation of the m-Tor pathway, which is a negative prognostic factor. m-Tor can be addressed now by only one drug. Other risk factors can be the TNM and G degree pathology classification. From the clinical point of view, hypersecretion and localization, time to progression (slow vs. rapid), and previous surgery and ablations are important.

To conclude, this disease should be managed in a particular center where the radiologists, pathologists, surgeons, clinicians and oncologists work together.