Epidemiology. Brazilian experience: GEP-NETs registry

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Carcinoid tumors can appear in any part of the body. They originate from neuroendocrine cells. The word carcinoid was created by Siegfried Oberndorfer more than a hundred years ago, and it is still there. Now we do not use the word carcinoid any more; we talk about neuroendocrine tumors (NETs).

The frequency of the location of the tumor depends on the concentration of neuroendocrine cells in each organ. If you look at our largest endocrine organ, the intestine, 60% of all NETs originate there. This is followed by lungs, with a higher density of Kultschitzky cells, where 25% of NETs appear.

There is a wide spectrum of tumors. They go from the typical carcinoid, well-differentiated neuroendocrine tumor to the undifferentiated, small-cell neuroendocrine carcinoma. They have a different biology and behavior.

Most NETs are non functional. So we are not expecting to see and have endocrine symptoms. Less than 10 - 15% of these tumors actively secrete peptides, hormones or amines. They are slow-growing and often go clinically undetected for years.

Nowadays, with the new technology we have in our hospitals and clinics, with the use (or overuse) of endoscopy, US, CT, MRI, we are detecting more and more clinically silent disease.

GEP-NETs are rare tumors. There are 2-5 cases / 100,000 people in some places or even in 1,000,000 in some others, depending on the statistics you are looking at. Less than 1% of all malignancies appear in lungs and gastrointestinal tract.

The statistics between 1970 and 2005 show an increase in the number of new cases of neuroendocrine tumors in every organ. Some are almost the same, but if you look at the trend, it has been climbing. The number of NETs is increasing all over the world (Figure 1).

Regarding malignant, or aggressive NETs, you will see that the largest increase is found in early-stage neuroendocrine tumors. This is due to the new technologies that we now use to find them. If you look at the statistics for 1986, there is a sharp increase in the number of new cases found in the United States. This is different from findings in other conditions.

This increased incidence is very likely due to diagnosis. Advances have been made in equipment, through which we can detect tumors in an early stage. We have better pathologists, and awareness in physicians the world over increase the chances of making a good diagnosis. For so many years some of the cases we saw at our hospitals and other hospitals were said to be adenocarcinoma. Those patients would live for many years, and when they returned and pathologists looked at their histology, it was found that they had neuroendocrine tumors. Now we have better pathologists and better immunohistochemical analysis.

Also, there is an increase in awareness. Since the 1980s new methods of treatment and technical advances and equipment have allowed us to see and stage this tumor, and even to consider its existence. Now we know that this awareness among the physicians around the world has increased the number of diagnosed cases. And if we look at what happens with the daily clinic and the way we look at the patients, we use CT scans and MRIs as our usual techniques to diagnose stage and even evaluate these tumors. The accuracy of these methods is about 70 - 80%, but now, with new techniques and nuclear medicine advances, it has climbed up to 100% in the localization, staging and identification of tumors. More and more often we can see better diagnosis and staging through this technology (Figure 2).

Figure 1.

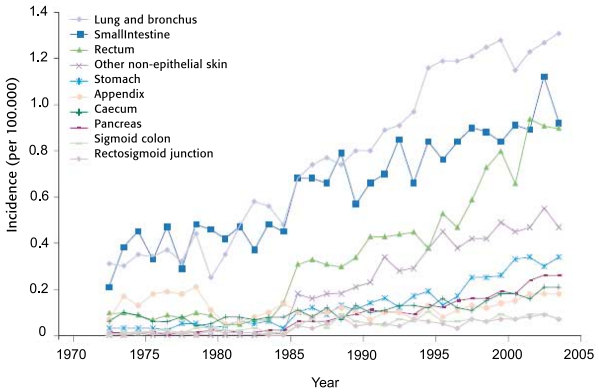
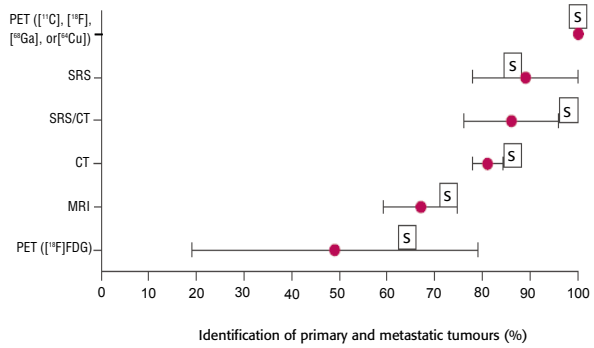
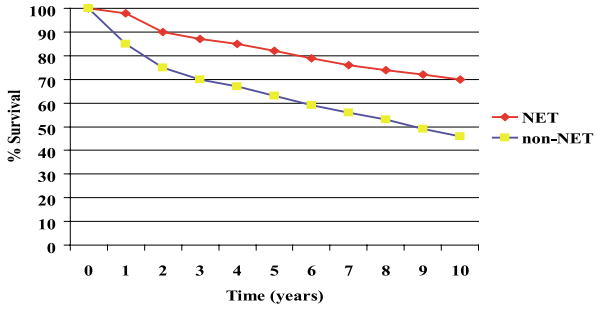


Figure 2.

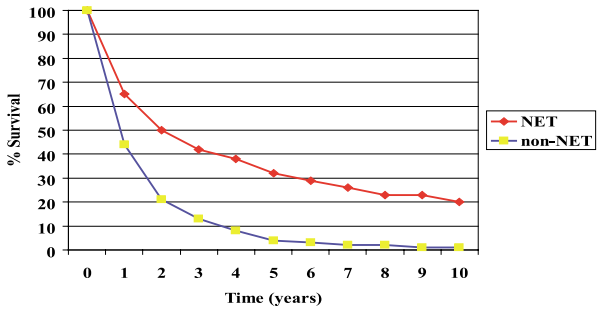


What can we do about survival? We see more patients. Are we doing any better? Patients with any new neuroendocrine tumor in the same stage, compared with a non-neuroendocrine, malignant tumor in the same organ will have a significantly better survival rate. This is valid for all stages, for locally advanced and for metastatic disease. Neuroendocrine tumors are better (Figure 3).

Figure 3.



Early-Stage Disease



Metastatic Disease

Very few patients with carcinoma in the GI tract will be alive after 5 years. In neuroendocrine tumors, 1/5 patients will live 5 or more years after diagnosis, even with metastatic disease. Neuroendocrine tumor patients live longer, and thus require extended care and treatment.

The survival rate has expanded since 1995. Everywhere you go, if we compare tumors diagnosed before and after 1995, statistics show that survival is climbing more and more. This is in part due to new treatments but also to the fact that most patients are diagnosed at early stages.

The survival rate depends on many factors. Something that blurs statistics is that these tumors depend on the site of origin. The median survival in months or years depends on the organ or site of the primary tumor. Also the registry and numbers and types of patients need to be considered. Many times you will find these tumors in the colon or in the appendix; more often in the colon. If you have more cases in the colon, your survival rate will go down. You have to be careful with statistics because they depend mainly on the type of patients.

These are rare tumors. Delayed diagnosis is a very common problem, being the average delay 5-7 years. We need to create awareness and build suspicion in physicians.

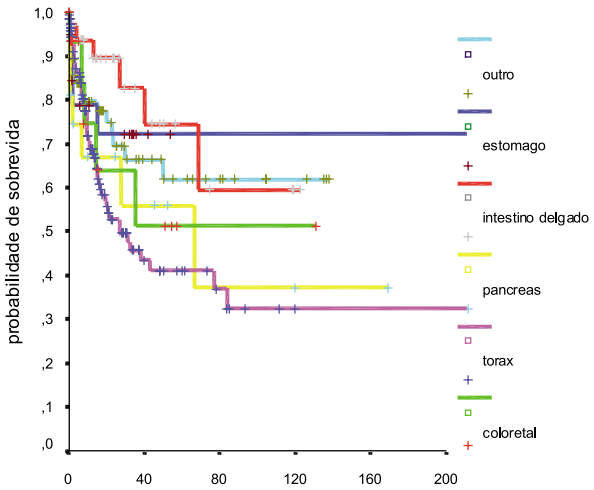
They are sporadic most of the times. Some of them come from familial syndromes, Von Hippel-Lindau or neurofibromatosis type 1 or MEN 1. If we look at patients with MEN1 disease, many will have one or more GEP tumors by age 40. These are the tumors that can arise in MEN1 disease: parathyroid adenoma, gastrinoma, insulinoma, PPoma, glucagonoma, VIPoma, non-functioning tumors and pituitary tumors.

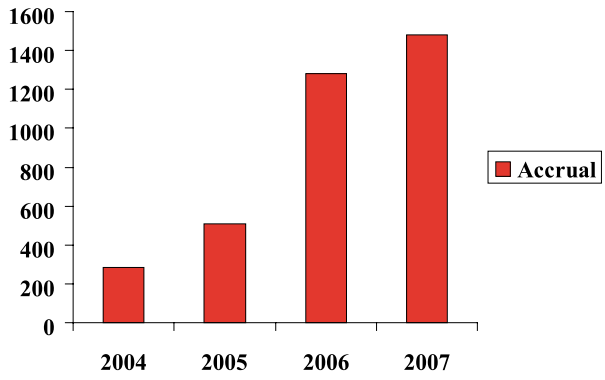
The diagnosis incidence is on the rise all over the world. With Argentum we see more and more cases than those we saw 10 years ago. There are 2 or 3 new cases a month out of 60 or 70 patients screened a month. This is due to awareness and just thinking that the disease can be there. We have different outcomes in comparison with more common neoplasms of the same anatomic site.

It is not easy to diagnose and find new strategies to treat and manage these patients. In Brazil, such as in Argentina, we have the GETNE (Grupo de Estudos de Tumores Neuroendócrinos) group. This is a group of doctors who work like Argentum and try to understand this disease better. We started 4 years ago. Up to October 2007 (the latest statistics that we have got) we had 87 centers interested in joining the group.

Accruing centers are now 38. Our database shows 1482 patients up to October 2007 and this figure is going up nicely. The accrual rate, however, is slower than last year. These centers are distributed throughout Brazil, but there are some areas from which there is no accrual for this registry. We run tests on our patients and that helps us see the survival rate of those in our data base (Figure 4).

Figure 4.





Patients with GEP (gastroentheropancreatic) NETs are different from patients with neuroendocrine tumors in thoracic organs. Looking at their numbers, we should focus on this and spread the knowledge out in our countries to physicians in every specialty, so that they can take actions in the future.

A better understanding, testing and treatment of our patients with neuroendocrine tumors are needed. A universal classification and grading systems, to share between clinicians and pathologists are required. There are problems to classify and grade tumors. There are publications which still in 2008 do not conform to WHO guidelines. A universal classification system is needed.

Future in neuroendocrine tumors

More basic research is needed (cell biology to establish cell lines for research). Also molecular / genetic research is required. There are different options to treat. New serum markers (screening) are needed. There is now no way to screen patients for early detection. Tissue markers area also required (not only for prognosis, such as Ki67, but site specific).

Better staging for each site and tumor are also needed, new molecular targets for therapy and scanning, new treatment strategies (adjuvant / neoadjuvant). Up to now we do not have any real indication for adjuvant or neoadjuvant treatment in any patient, except that we only have it for small cell carcinoma in the lung.

More specialized centers and study groups, such as Argentum, are necessary. We need people to become part of Argentum, to create centers. We need more funding for research in the neuroendocrine tumor area.

For us to get an idea, between 1994 / 2002 – the US NIH contributed with US$ 6 billion for breast cancer research and US$ .008 billion for carcinoid research. Thus, carcinoid is still short of funding and interest from the world but it is about time to change this.