Societies and Guidelines for Neuroendocrine Tumors

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33.1 Historical Background

Neuroendocrine tumors (NETs) are increasing considerably in both incidence and prevalence in the last decades [1]. In previous years, the beginning of the 1980s, there was very little interest in this field. There were discussions whether the tumor should be called endocrine tumors or NETs. Although one had the old publications from Obendorfer (1907) on carcinoid tumors and later in the 1950s publications on Zollinger-Ellison syndrome and Verner-Morrison syndrome, there was very little known and written about these so-called rare diseases. In the late 1970s and early 1980s, the most important center in the world for taking care of patients with NETs was the Mayo Clinic in the USA with Professor Charles Moertel and Dr. Larry Kvols with documented interest in managing these patients. The only treatment in metastatic disease at that time was streptozocin plus 5-fluorouracil or doxorubicin which was given to all the different subtypes of neuroendocrine tumors. At the end of the 1970s and early 1980s, the era of radioimmunoassays was established, and a lot of different antibodies to hormones and amines were developed which were used both for immunohistochemistry and for developing radioimmunoassays and Elisa. These developments became a new dawn of the NET field. At the same time, the development of new therapies came along with somatostatin analogues as well as alpha interferon for slow-growing NETs. Later on, in the 1990s, long-acting formulations of somatostatin analogues were developed. New cytotoxic treatments such as temozolomide were presented in the beginning of 2000, and during the most recent days, we have the development of the so-called targeted agents such as everolimus and sunitinib. In parallel, new imaging techniques were developed, somatostatin receptor scintigraphy and positron emission tomography.

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Another development during this last decade was prospective randomized controlled trials: the PROMID study with octreotide for carcinoids, the RADIANT 2 and 3 trials with everolimus, as well as the sunitinib trial for pancreatic NETs. Most recently, we also have the CLARINET study for nonfunctioning enteropancreatic tumors. The most important general biomarker chromogranin A was established worldwide. Molecular imaging paved the way for radioactive treatment with peptide receptor radionuclide therapy (PRRT). All these factors contributed to the accelerated increase in the incidence and prevalence of NETs together with increased awareness. Educational programs and the establishment of societies contributed to the increased interest in NETs. The first professional society that was developed in the field of NETs was the European Neuroendocrine Tumor Society (ENETS) which started as a small discussion group of 30 people in 1995. The aim of this group was to try to establish common diagnostic and therapeutic models. In 2001, this small group decided to establish a society (ENETs) which increased the number of members. The first guidelines were developed in 2005/2006 for different kinds of NETs [2]. This was the first comprehensive guideline that was developed in the field and was also appreciated by WHO which in 2010 made a new classification system [3]. The grading of NETs into NET G1, NET G2, and NEC G3 is based on the ENETS classification system. The work by the ENETS was appreciated by colleagues in North America which in 2006 formed the North American Neuroendocrine Tumor Society (NANETS), which has started to develop their own guidelines, partly based on the previously developed guidelines by the ENETS [4]. Later on, in 2010, the Latin American Neuroendocrine Tumor Society (LANETS) was established, including countries in South America and Mexico. In 2013, the Asia Pacific Neuroendocrine Tumour Society (AP-NETS) was founded in Kuala Lumpur covering the countries in Asia and the Pacific region, including Australia, ranging from India to Japan. All these latter societies are spin-offs from the ENETS, which have had yearly conferences in Europe since 2001. For these conferences, colleges from all over the world have been attending, and last year, almost 2,000 participants were registered at the meeting in Barcelona (2014). Today, the ENETS has around 1,100 members. The sister organizations are significantly smaller, even the North American Neuroendocrine Society which has around 200 members and around 250 participants in their yearly conference, the last one in Nashville, TN (2014). I myself, being a chairman of ENETS (2011–2014), have tried to establish a close collaboration between our sister organizations to develop programs for the management of NETs and to establish common clinical trials and educational programs.

Furthermore, ENETS has developed an accreditation program for hospitals interested in taking care of patients with NETs, so-called centers of excellence. At the moment, 27 centers have been accredited all over Europe. These centers are supposed to follow the ENETS guidelines in terms of diagnosis and treatment of NETs. They are also expected to work in a multidisciplinary way and to have regular tumor boards to discuss the patients. Furthermore, the patient's influence of their management is secured. It is obvious that centers working in multidisciplinary teams significantly improve the outcome for patients with NETs. Not only in Europe but also in the USA. The centers of excellence are reviewed every

3 years by a special organization based in Germany. The work by these specific societies such as the ENETS, NANETS, APNETS, and LANETS to develop guidelines has generated a new interest for NETs in larger oncology organizations such as the European Society for Medical Oncology (ESMO) and American Society for Clinical Oncology (ASCO) to further work on these guidelines and to spread them out to the general oncology practice. Therefore, the ESMO has generated their own guidelines based on the ENETS guidelines [5], and National Comprehensive Cancer Network (NCCN) in the USA has developed guidelines that are based on the NANETS guidelines as well as ENETS. Today, NETs are well recognized at different conferences and symposia in the fields of oncology, surgery, gastroenterology, endocrinology, and pathology which usually have large sessions related to neuroendocrine tumors. Besides the international societies, most countries have their own national societies for NETs.

Patient organizations have developed their own societies over the last two decades in parallel with the professional societies. Most countries in Europe have a well-developed patient organization. These European societies are working in networks with other societies in the USA, Latin America, and Australia to form an International Neuroendocrine Cancer Alliance (INCA).

Conclusion

The development of professional societies in the field of NETs with established guidelines for the management of NETs has significantly contributed to the development of the field and also improved the quality of life and the survival of many patients with malignant NETs. The patient organizations are important supporters. Patients with these diseases are regularly in contact with professionals from different organizations to get the latest developments in the field of diagnosis and treatment of NETs. One example of the developments in the management of NETs is that patients with carcinoid tumors and carcinoid syndrome had a median survival in the early 1980s of about 2 years and today, with modern treatment, follow-up, and the availability of different treatment modalities, have a median survival of more than 16 years at centers of excellence.

References

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