Abstract

Little is known about patients with malignant digestive neuroendocrine tumours (MD-NETs). Although their incidence is increasing, MD-NETs remain a rare cancer, representing 1% of digestive cancers. Most MD-NETs are well-differentiated. MD-NET poorly differentiated carcinomas account for 20% of cases on average. Anatomical localisation of MD-NETs varied according to geographic region. Stage at diagnosis and prognosis for patients with MD-NETs in the general population are considerably worse than often reported from small hospital case series. Prognosis varies with tumour differentiation, anatomic site and histological subtype. There are significant differences in survival from MD-NETs among European countries, independent of other prognostic factors. Early diagnosis is difficult; new therapeutic options appear to represent the best approach to improving prognosis.

Introduction

Little is known about the epidemiology of malignant digestive neuroendocrine tumours (MD-NETs). The epidemiology of this rare disease has not been sufficiently studied because it includes a diverse group of cancers that occur in different areas of the body. Also, changes in tumour classification have resulted from new clinical and biological findings, which make studying these cancers over long periods more difficult (see Focus below). The most recent classification incorporates the concept of grade based on both morphology and proliferative index (1). Two parallel classifications are now in use: one is proposed by the European Neuroendocrine Tumour Society (2, 3) and the other by the American Joint Committee on Cancer/Union for International Cancer Control tumour, node, metastasis (TNM) classification (4) (see Supplementary data, see section on supplementary data given at the end of this article). They follow the same TNM terminology but different types and extent of disease are remaining. Cancer registries record only malignant tumours. Registration is based on a morphology code of the ICD-O (5) with a malignant behaviour. Malignancy is easy to define in cases of invasion of contiguous structures, or documented lymph node or distant metastasis. Classification can be more difficult for tumours invading the muscularis propria or beyond. A Ki-67 index exceeding 20% allows malignancy to be determined. Therefore, we cannot rule out the fact that the reliability of data may partly vary between clinical series and cancer registries, which may explain some of the reported differences.

Very little information is available on the management and prognosis for patients with MD-NETs. Most of the available data are drawn from small case series, usually provided by specialised centres, and cannot be considered as a reference because of unavoidable selection bias. Population-based studies that include all cases arising in a well-defined population represent the only way to approach the reality of a disease at a population level. Such studies are rare. The objective of this review is to appraise the available data on MD-NET incidence, management and prognosis provided by population-based studies. Endocrine cancers that arise as part of familial cancer syndromes (multiple endocrine neoplasia type I and Recklinghausen syndrome) are not included.

Incidence by sex and age, prevalence

MD-NETs are very rare: they account for <1% of digestive cancers in France (6) and the UK (7) and 1.5% in Austria (8). In France, when MD-NET incidence rates are compared with other cancers, they are 15 times less common than oesophageal cancers and twice as frequent as biliary tract cancers. The estimated number of incident cases in France in 2004 was 900 (4). Figure 1 shows the incidence for different digestive cancers for men and women (6, 9, 10, 11). Overall age-standardised incidence rates were 0.8/100 000 in men and 0.5/100 000 in women (6), over the 1976–1999
period, using the world standardised population. They were 0.6 and 0.7/100 000 in England and Wales respectively (7) (1986–1999) and 0.8 in Austria (8) (2004). Similar figures are found in the United States (6) but comparisons are more difficult because incidence rates were standardised using the US standard population (see Focus on standardised incidence). The sex ratio is almost equal (7, 12). In England and Wales, the relative frequency of MD-NETs was twice as high among the most deprived as among the affluent, and this distribution was very similar for both well-differentiated and poorly differentiated NETs (7).

Data from the Surveillance, Epidemiology and End Results (SEER) programme allowed the prevalence of MD-NETs to be estimated for the first time. The number of prevalent cases in the USA was estimated to be 103 112 (including lung-NETs), corresponding to a prevalence rate of 35/100 000. This high figure, which contrasts with the low incidence rates, can be explained by the relatively good prognosis for well-differentiated MD-NETs. The prevalence of other digestive cancers, with the exception of colorectal cancers, is lower than that of MD-NETs.

Incidence by histology

Most NETs are well-differentiated. Only a few hundred cases have been reported in the literature (13).

In a study performed in Austria, 83.0% were well-differentiated and 17.0% were poorly differentiated (8). The corresponding figures in England and Wales were 80 and 20% (4). However, the distribution of MD-NETs according to their differentiation is not uniform across Europe. The EUROCARE database revealed that poorly differentiated MD-NETs were more frequent in eastern Europe (24.9% of all cases) and in the United Kingdom (30.3%) than in western continental Europe (14.9%) or in northern Europe (3.4%) (14). Among well-differentiated NETs, a slight male predominance with a sex ratio of 1.5 was found in France (6) and Switzerland (15) while it was almost equal in England, Wales (7) and the USA (16). Women were significantly more common among patients with poorly differentiated tumours (7).

The mean age at diagnosis for well-differentiated MD-NETs (65–67 years) is lower than for other digestive tract cancers (about 70 years for epithelial tumours) (6, 7, 12). In hospital-based series, age at diagnosis is generally lower, suggesting that the older patients are less frequently seen in specialised centres (17, 18). MD-NETs are rare before the age of 40 in both sexes, and incidence then increases more rapidly in men than in women.

Among well-differentiated malignant pancreatic-NETs, the most common types are, in decreasing frequency, non-functioning tumours (46.2%), serotonin-secreting tumours (27.0%), insulinomas (17.6%), gastrinomas (5.0%) and glucagonomas (4.2%) (14). VIPomas are extremely rare in a population with based study from the National Registry of England and Wales, only one case being described in 16 years of recording. Somatostatinomas are very unusual (7).

Incidence by site

About three-quarters of well-differentiated tumours arise in the large or small bowel, whereas two-thirds of poorly differentiated tumours arise in the oesophagus (6, 7, 12, 19). The small bowel is the most frequent site for well-differentiated MD-NETs. The predominance of this site has already been noted (6, 7, 12, 19). The large bowel and pancreas are the two other main sites.

Well-differentiated tumours were not often found in other parts of the body. Well-differentiated NETs of the appendix are quite common but they are seldom malignant (3, 17). In a series of 150 well-differentiated appendix NETs treated at the Mayo Clinic over a 50-year period, only two deaths due to distant metastasis have been reported. Metastasis has never been observed in patients presenting tumours smaller than 2 cm in this series (20).

In a recent analysis of the SEER database on ‘carcinoid tumours of the appendix’, the 10-year overall survival rate was 100% for all patients with negative lymph nodes and 90% or better for all patients with positive lymph nodes, regardless of the primary tumour size (21).

Primary hepatic NETs may account for 1% of endocrine primaries of the gastrointestinal tract (6, 22). Most of these tumours are non-functioning and well-differentiated. Analysis of the EUROCARE database (14) showed that the anatomical location of MD-NETs varied significantly from one geographic region to another. The proportion of MD-NETs located in the small intestine varied between 19.4% in eastern Europe and 46.9% in northern Europe. For pancreas MD-NETs, the proportion...
varied between 12.2% in northern Europe and 20.0% in western continental Europe. Poorly differentiated MD-NET carcinomas were mainly located in the oesophagus. The proportion of poorly differentiated NETs among oesophageal MD-NETs varied between 64.0 and 100% according to the geographic area (7, 14).

Few data on epidemiology of NETs according to ethnic groups are available. However, disparities exist. The incidence rate of NETs is twice among African Americans than that among Caucasians (12). Concerning sites, African Americans develop mostly rectal NETs. This feature is also found in a Norwegian population-based study (23).

Trends in incidence

European and US studies showed an increasing incidence of MD-NETs (6, 8, 12). However, this increase differed among histological types of MD-NET. The number of well-differentiated tumours more than doubled over three decades in France (0.88 to 1.91/100,000, age-adjusted to the world standard population). A slightly greater increase was described in the US. This trend is difficult to explain. Improved technology or diagnostic criteria probably had some limited impact for gastrointestinal tumours. Due to the scarcity of these tumours, and the absence of analytical studies, etiological factors are unknown at the present time.

Stage at diagnosis

Most MD-NETs are often already at a late stage at the time of diagnosis. There was a wide variation in the proportion of advanced cases (metastatic or unresectable cases) in the hospital-based series ranging from 32% (24, 25) to 60% (14). In European population-based studies, the results are more uniform: in the Austrian study, distant metastases were documented in 63% of cases (8) and the corresponding percentage was 53% in Burgundy (3). Stage at diagnosis is linked to differentiation. Among US patients (12), around 25% of well-differentiated NET cases had synchronous distant metastasis at diagnosis, compared with 50% of those with poorly differentiated MD-NET. The vast majority of distant metastases were located in the liver: 63% in Austria and 60% in Burgundy. The other metastatic sites were peritoneum, bone, lung and ovary. There was no significant change over time; the proportion of cases diagnosed at each stage remains stable.

Treatment

It is generally accepted that removing the lesion by surgery is the preferable solution. Just over half the cases in Burgundy were resected for cure (10). The resection rates for these patients were lower than those calculated using the hospital-based series, where they varied from 80 to 90% (17, 18, 26). This difference is, however, to be expected as unavoidable selection bias is incurred when specialised hospital units provide the data, which thus cannot serve as a reference.

The rate of resection for cure varied with the site of the tumour and the histological subtype: it was higher for tumours in the large and small bowel than for those in the pancreas and higher for well-differentiated tumours than for small-cell tumours. The proportion of patients receiving chemotherapy has increased in Burgundy as this treatment was not offered before 1983 and then increased to 23% of cases (3). Chemotherapy remains relatively little used and has not yet reached its full development at a population level, where only two-thirds of patients are treated after palliative resection, and only one-fifth of those who do not have surgery receive chemotherapy. Changes in diagnostic strategies, with the spread of conventional (27, 28) and isotopic (29, 30) imaging techniques, have probably not reached their full development at a population level and have not yet contributed to an improvement in the management of MD-NET.

Survival and prognosis

Survival rates are similar for MD-NETs and large bowel adenocarcinomas. Table 1 shows 5-year survival rates for MD-NETs according to the main population-based studies. In the EUROCARE study, 5-year relative survival rates were 47.5% on average (11). This study revealed that there were wide variations in survival from one European country to another. The 5-year relative survival rates were 60.3% in northern Europe, 53.6% in western continental Europe, 42.5% in Iceland and 37.6% in eastern Europe.

Well-differentiated MD-NETs are considered as slow-growing tumours. The 5-year relative survival reported was 57% in a study performed in England and Wales (4) and 58% in the EUROCAR study (11). Higher survival for MD-NETs has been reported in the United States (6), as is the case for most common adult cancers (31). Survival rates are also higher in hospital-based series due to patient selection (17, 18, 32).

MD-NET poorly differentiated carcinomas are highly aggressive with 5-year survival rates in the EUROCAR study varying between 6.3 and 11.3% according to European region. The prognosis for MD-NET poorly differentiated carcinomas of the large bowel was slightly better (18%) than for other sites (<10%) (4). Morphologically, MD-NET poorly differentiated carcinomas are identical to small-cell lung cancers, and prognosis is comparable.

Well-differentiated pancreatic secreting tumours have a similar prognosis to non-secreting tumours. Due to the rarity of the different subtypes of MD-NETs of the
pancreas, little was known about their prognosis. Two large population-based studies recently provided data. The 5-year relative survival rate for insulinomas was 55.6% in the EUROCARE study and 49.2% in the UK study. The corresponding rates were 48.4 and 39.9% for gastrinomas, 33.4 and 17.1% for glucagonomas, 49.9 and 26.3% for serotonin-secreting tumours and 49.9 and 29.3% for non-secreting tumours.

Two series (12, 33) have reported a small improvement in the prognosis for patients with well-differentiated metastatic tumours. The authors reported a significant improvement from 1987 onwards in the USA, and from 1992 in Holland, dates that correspond to the commercialisation of somatostatin analogues on both continents. No significant progress in survival from well-differentiated MD-NETs or from small-cell tumours had been made until recent years. Some real improvements in therapy have recently been offered to patients (34, 35, 36), but their availability is too recent to be analysed. At the population level, novel imaging techniques and treatments including radionuclide have not really improved survival from well-differentiated MD-NETs (37, 38, 39, 40, 41, 42, 43).

In the EUROCARE study, multivariate analysis indicated that the geographic region, differentiation, site and age remained independent prognostic factors. It has been suggested that poorer access to both adequate diagnosis facilities, leading to advanced stage at diagnosis, and treatment services were key factors in lower survival rates found in eastern Europe. Differentiation is also a major determinant of prognosis. In the EUROCARE study, there was a fourfold increase in the relative excess risk of death from small-cell MD-NETs compared with well-differentiated MD-NETs. Survival was also related to cancer site. Survival was higher for MD-NETs located in the small and large bowel. Male sex and older age groups, even after correction for the higher background risk of death in the elderly, were also pejorative independent prognostic factors.

Well-differentiated MD-NETs develop slower and are less life threatening than other digestive cancers such as adenocarcinoma of the colon (41). It is essential to treat them because even patients with disseminated disease can survive for lengthy periods and can thus benefit from aggressive treatment (42).

### Table 1

<table>
<thead>
<tr>
<th>Studies</th>
<th>Period</th>
<th>Population</th>
<th>n</th>
<th>Differentiation</th>
<th>Countries</th>
<th>5-Year relative survival rate (%)</th>
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<tr>
<td>Lepage et al.</td>
<td>1976–1999</td>
<td>Burgundy</td>
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<td>WD MD-NETs</td>
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<td>3233</td>
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<td>1935</td>
<td>Overall</td>
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<td>337</td>
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<td>885</td>
<td>Overall</td>
<td>Continental Europe</td>
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<td>558</td>
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<td>PD MD-NETs</td>
<td>Overall</td>
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<td>1973–2011</td>
<td>USA</td>
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WD MD-NETs, well-differentiated MD-NETs; PD MD-NETs, poorly differentiated MD-NETs.

### Table 2

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<th>OMS 2010 (1)</th>
<th>OMS 2000 (4)</th>
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<td>Neuroendocrine tumours G1</td>
<td>Well-differentiated endocrine</td>
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<td>tumours with benign behaviour</td>
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<tr>
<td>Neuroendocrine tumours G2</td>
<td>Well-differentiated endocrine</td>
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<td>tumours with uncertain behaviour (Ki-67 ≤ 2%)</td>
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<tr>
<td>Small-cell neuroendocrine carcinomas</td>
<td>Well-differentiated endocrine</td>
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<td></td>
<td>tumours with uncertain behaviour (Ki-67 &gt; 2%)</td>
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<tr>
<td>Large-cell neuroendocrine carcinomas</td>
<td>Well-differentiated endocrine</td>
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<td></td>
<td>carcinomas</td>
</tr>
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<td></td>
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</table>
Conclusions

One of the merits of population-based studies is to provide unselected data from a large population on the frequency and survival of MD-NETs, in particular for small-cell MD-NETs. Most published data originate from specialised centres and cannot provide true reference values because of unavoidable selection bias. Population-based studies, including all cases diagnosed in a well-defined population, represent the best way to accurately assess the epidemiologic characteristics of such rare tumours accurately.

Although their incidence is increasing, MD-NETs remain rare, representing 1% of digestive cancers. MD-NETs are a diverse group of rare neoplasms that display a wide range of prognostic features. Histological differentiation and site where the tumour originated have a considerable impact on prognosis. Variations in survival are reported from one country to another. An efficient health care system is particularly important in dealing with MD-NET because of the difficulty of diagnosis and the complexity of treatment. Given that MD-NETs are very rare and that symptoms are not evident at first, it is difficult to establish an immediate diagnosis. Trials are required in the near future to make a reliable assessment of the merits of adjuvant and/or palliative therapies. New strategic trials to help physicians to deal with the new therapies are also required.

Focus on epidemiology

Incidence

Number of new cases of a specific disease occurring during a certain period in a well-defined population.

Standardised incidence rates

Each country has a population structure of its own. In industrialised European countries, the proportion of the elderly is high, which contrasts sharply with countries such as India or China. In terms of cancer, a disease linked with ageing, we cannot study the incidence rate without taking into account the age structure of the study population. Standardised incidence rates are used to neutralise the effect of possible differences in age structure when two populations are compared, using a defined population in an arbitrary standard called the reference population. These standardised rates are used to compare the incidence of disease between different countries by overcoming differences in population structure of the countries concerned.

Prevalence

Number of all cases of a disease occurring during a certain period in a well-defined population.

Relative survival rate

Ratio of the observed survival rate in the cancer patients under study to the expected survival rate in a population of similar sex and age distribution, subject only to the mortality rates of the general population. It reflects the excess mortality in the cancer patient group relative to the background mortality.

Focus histological classifications for NETs

The categorisation of MD-NETs in the International Histological Classification of Tumours (4), published in 2000, provides an innovative conceptual framework for the evaluation of their clinical and functional properties. This classification pools digestive carcinoids and pancreatic endocrine tumours and separates them from endocrine–exocrine cancers developed within the limits of a family pathology (multiple endocrine neoplasia type I and Recklinghausen syndrome). Under this classification, tumours are subdivided by anatomic site and by a schema common to all sites, under which well-differentiated endocrine carcinomas (with low-grade malignant behaviour) are distinguished from poorly differentiated endocrine carcinomas (with high-grade malignant behaviour).

In contrast to the 2000 WHO classification, in which morphological differentiation was the first criteria of classification, the 2010 WHO classification of digestive NETs is largely based on the histological grade. NETs are now classified into three main categories: NET G1 (mitotic count <2/10HPF and/or ≤2% Ki-67 index), NET G2 (2–20/10HPF and/or 3–20%) and neuroendocrine carcinoma (NEC) of small or large cell types. The classification states that NET G1 and G2 are well-differentiated tumours, while it implies that NETs are G3 tumours. A match between OMS 2000 and 2010 classifications (1, 4) for digestive sites is proposed in Table 2.

Supplementary data

This is linked to the online version of the paper at http://dx.doi.org/10.1530/EJE-12-0418.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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