Gastrointestinal carcinoid: epidemiological and survival evidence from a large population-based study (n = 25 531)

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Background: Owing to its rarity, the published evidence on gastrointestinal (GI) carcinoid is often based on small series of patients or population-based studies regarding all neuroendocrine tumors. Here, we present a comprehensive epidemiological and survival analysis of the largest cohort of patients with GI carcinoid ever reported.

Patients and methods: Patients with histological diagnosis of GI carcinoid (n = 25 531) were identified from the Surveillance Epidemiology End Results (SEER) database (including 18 USA cancer registries and spanning the 1973–2009 time frame). Demographic and disease data were used for epidemiological and survival analyses.

Results: The incidence of GI carcinoid is steadily increasing over the past three decades at a rate higher than any other cancer [annual percentage change (APC) = 4.4, 95% confidence interval (CI) 4.0–4.8]. These patients have a higher risk of further primary tumor (standardized incidence ratio, SIR = 1.15, 95% CI 1.10–1.21), but also a reduced risk of skin melanoma (SIR = 0.64, 95% CI 0.41–0.95). Despite the overall favorable prognosis (5-year disease-specific and relative survival rate: 91.3% and 87.4%, respectively), the mortality rate is increasing over time (APC = 3.5, 95% CI 3.0–4.0) and the 5-year survival rate of patients dying of GI carcinoid (28.5%), though better than that reported for GI cancers in general (8.4%), cannot be considered satisfactory. Finally, a nomogram is provided to predict patient survival on the basis of clinico-pathological factors independently associated with prognosis at multivariate analysis.

Conclusions: These findings can be clinically useful for the management of patients with GI carcinoid and eagerly prompt the continuous effort to develop more effective therapeutic strategies against this slow-growing but chemoresistant tumor.

Key words: carcinoid, gastrointestinal, epidemiology, survival analysis, SEER, population-based study

introduction

Neuroendocrine tumors (NET) originate from the cells of the diffuse neuroendocrine system and include three main subtypes, gastrointestinal (GI) carcinoid, pancreatic endocrine tumors (which are often referred to as gastroenteropancreatic tumors along with GI carcinoid [1]) and lung carcinoid, although other organs (e.g. gallbladder, kidney, ovary and testis) can occasionally develop this type of malignancy [2, 3].

GI carcinoid is a rare NET that can arise from as many as 14 different cell types scattered throughout the mucosa of the GI tract and producing (like virtually any other NET) a variety of hormones [4–6]. These biologically active molecules are responsible for the so-called carcinoid syndrome, which occurs in <20% of patients (mainly in the presence of liver metastatic disease) and is characterized by flushing, abdominal pain, diarrhea, bronchoconstriction and carcinoid heart disease [7].

Although the prognosis of patients with GI carcinoid is on average better than that of patients with GI carcinomas, this tumor is often diagnosed late during its natural history, which accounts for the relatively high proportion of patients presenting with advanced/metastatic disease [5]. Despite some recent advances in our understanding of carcinoid biology [1, 8, 9], surgery remains the treatment cornerstone for primary carcinoid and some selected cases of advanced carcinoid; metastatic disease is typically resistant to chemotherapy and remains a therapeutic challenge [4, 10, 11], although somatostatin analogs such as octreotide—initially used to control the carcinoid syndrome symptoms—have been recently associated with significantly prolonged time to disease progression in patients with functional carcinoid [12].

As witnessed by the growing number of scientific articles published each year (over 2000 per year over the last decade) [13], the interest for carcinoid tumors is increasing, which is probably due (at least in part) to the reported increase in
incidence [14–17] and a link (though purely theoretical) with the wide use of proton pump inhibitors [18]. On the other side, given its rarity, most evidence regarding this tumor relies on small (or very small) series from single institutions [19–25]; moreover, population-based studies have never specifically focused on GI carcinoid, but rather addressed the issue of carcinoid tumors either in general (e.g. including lung carcinoid) [14, 17, 26, 27] or from one single GI site (e. g. stomach [28], rectal [29], small bowel [30], appendix [31]). Overall, findings are often conflicting and no GI tract-specific comprehensive (i.e. including both epidemiological and survival data) analysis is available.

In this article, we present the results of the largest population-based study on GI carcinoid ever reported, with the aim of providing an in-depth analysis of robust data on clinically useful epidemiological and survival aspects of this disease by exploiting the largest publicly available cancer registry, that is, the US Surveillance Epidemiology and End Results (SEER) database.

**materials and methods**

Data were obtained from all 18 USA cancer registries (covering about 28% of the US population) participating in the SEER program [32] by using the Seer*Stat software (version 8.0.2) [33]. We identified patients with histologically confirmed malignant carcinoid (ICD-O-3 code: 8240/3) of the GI tract (i.e. esophagus, stomach, small intestine, colon, rectum and anus) diagnosed between 1973 and 2009 (postmortem diagnoses were included). As only 10 cases of esophageal carcinoid were identified, this patient subset was not included in the following analyses.

All incidence data were age-adjusted and normalized to the 2000 US standard population. Annual percent change (APC) was calculated using the weighted least squares method, as carried out by the Seer*Stat software. Survival analysis was conducted considering death by GI carcinoid the event of interest (disease-specific survival). The proportional hazards assumption of the Cox multivariate model was verified using a test based on Schoenfeld residuals [34]. Variable selection was carried out by a backward selection process using the Akaike information criterion (AIC) [35].

While building the prognostic nomogram, a prognostic score for each patient was computed according to the following formula:

$$\text{Score} = X_1 \times B_1 + X_2 \times B_2 + X_3 \times B_3 + X_n \times B_n$$

where $X$ is the value of a given covariate and $B$ is the multivariate model coefficient for a given covariate.

Then, the survival rate for each patient can be predicted according to the following formula: $S_1 = S_0 \times \exp(\text{Score})$, where $S_1$ is the survival rate at time $t$ (for all patients with the same specified values for each covariate), $S_0$ is the baseline survival rate at time $t$ (for a hypothetical patient population with the baseline value for all covariates) and Score is the above-mentioned prognostic score. Continuous covariates were categorized for clinical use purposes after verifying the linear relationship with death risk using fractional polynomials [36].

The performance of the nomogram was measured by concordance index (C-index, a measure of discriminative ability that quantities the proportion of all patient pairs for whom the predicted and observed survival outcomes are concordant; a value of 0.5 indicates no predictive ability when compared with chance alone, and a value of 1 indicates perfect discrimination) and assessed by comparing nomogram-predicted (considering the quartiles of the model-derived prognostic score) versus observed Kaplan–Meier estimates of 5–10- and 20-year survival probability rates. The bootstrap procedure (1000 replications) was used for internal validation purposes.

Relative survival rates were computed using the Seer*Stat software. We also calculated conditional survival estimates: to this aim, we assessed the probability of surviving an additional 5 years (CS5), given that the patient had already survived x years, according the formula: $CS5 = S_{x+5}/S_x$.

The risk of developing further primary cancer after GI carcinoid was measured using the standardized incidence ratio (SIR, as computed by the Seer*Stat software).

Statistical analyses not carried out with the Seer*Stat software were conducted using the Stata 11 SE software (StataCorp, College Station, TX).

**results**

**epidemiology**

Searching the SEER database, we found 25 531 patients diagnosed with GI carcinoid between 1973 and 2009. Patient and tumor characteristics are reported in supplementary Table S1 and Figure S1, available at Annals of Oncology online (age and year distribution). Most patients are white (72.7%), with a male to female ratio close to one and a median age of 60 years. The most frequently affected GI sites are small bowel (38%) and rectum (34%).

The age-adjusted incidence rate of this disease is significantly increasing over time (supplementary Figure S2, available at Annals of Oncology online), with an APC of 4.4 [95% confidence interval (CI) 4.0–4.8] which exceeds that of any other malignancy. This trend is quite similar across sex and race categories (supplementary Figure S3, available at Annals of Oncology online). As regards GI sites, the increase is greatest for stomach (APC = 7.0, 95% CI 6.2–7.8) and rectum (APC = 7.8, 95% CI 6.9–8.7) (supplementary Figure S4, available at Annals of Oncology online); only the carcinoid of the appendix ($n = 660$) presents a decreasing trend (APC = −3.6, 95% CI −5.0 to −2.1). These carcinoid-specific findings are in contrast with the trends for all malignancies of the stomach (APC = −1.6, 95% CI −1.7 to −1.5), colon (APC = −0.9, 95% CI −1.1 to −0.7), rectum (APC = −0.8, 95% CI −0.9 to −0.7) and appendix (APC = 2.5, 95% CI 2.0–3.1), and in line with the trend for all cancers of the small intestine (APC = 2.3, 95% CI 2.1–2.5).

Considering disease presentation at diagnosis, all stages show increased incidence rates, but the phenomenon is most evident for localized GI carcinoid (APC = 6.5, 95% CI 5.7–7.2) (supplementary Figure S4, available at Annals of Oncology online). Finally, all ages are also involved in this increase, although the occurrence is more remarkable for the 40–60 years age subgroup (APC = 5.5, 95% CI 5.1–5.9), the mean age at diagnosis remaining virtually unchanged over time.

Considering the last decade (2000–2009), the average incidence of GI carcinoid is 2.5 cases per 100 000 per year, being higher for blacks (4.6/100 000), localized disease stage (1.6/100 000), small bowel (1.0/100 000) and rectum (0.9/100 000) (supplementary Figure S3, available at Annals of Oncology online). According to the SEER data, the incidence rate of all cancers and of all carcinoid tumors from any site is, respectively, 475 and 3.5 per 100 000 per year over the same decade, which means that GI carcinoid represents 0.52% of all newly diagnosed cancers and 71.4% of all carcinoid tumors. For further comparison purposes, we recall that all GI cancers— with 65 cases/100 000/year—represent 13.6% of all malignancies (considering the 2000–2009 decade).
In the SEER 9 registries research data (released April 2012, based on the November 2011 submission), the estimated 34-year limited-duration prevalence of GI carcinoid on 1 January 2009 is 6549 (localized: 4454; regional: 1088; distant: 471; unstaged: 536), with a population at prevalence date of 28 893 550. We projected this prevalence into the US standard population and matched by sex, race and age: the resulting estimated 34-year limited-duration prevalence in the United States is 21.6 per 100 000. As the prevalence of all GI cancers is 401 per 100 000, GI carcinoid represents about 5% of all prevalent GI cancers.

GI carcinoid presents at diagnosis as an advanced/metastatic disease in a high proportion of cases (43.2%), 23.8% of patients harboring distant metastatic disease: interestingly, the latter figure is almost identical to that found for all GI cancers (23.6%).

In the majority of cases (75.5%), GI carcinoid is the only tumor patients develop during their lifetime, and in subjects with two or more primary tumors GI carcinoid is the first tumor in most subjects (83.9%). Notably, patients with GI carcinoid present an incidence of further primary cancers (any site) significantly higher than expected (that is when compared with the general population), the SIR being 1.15 (95% CI 1.10–1.21). As shown in supplementary Table S2, available at Annals of Oncology online, the risk regards GI sites (e.g. small bowel, stomach, SIR = 2.33, 95% CI 1.77–3.02) as well as extra-intestinal sites (e.g. thyroid, SIR = 2.28, 95% CI 1.51–3.29; kidney, SIR = 1.71, 95% CI 1.28–2.24). Of note, having a GI carcinoid is also associated with a significantly lower risk of developing skin melanoma (SIR = 0.64, 95% CI 0.41–0.95).

**Survival analysis**

After a mean follow-up (among survivors) of 70 months (range: 3–442 months), 2379 of 25 531 patients (9.3%) died of disease, the 5-year, 10-year and 20-year disease-specific survival rates being 91.3%, 86.1% and 77.1%, respectively (for all GI cancers, the 5-year disease-specific survival rate is 53.1%).

Considering only patients who died of disease ($n = 2379$), the 5-year, 10-year and 20-year uncensored survival rates are 28.5%, 10.1% and 1.8%, respectively (median survival for all patients: 30 months; for patients with distant metastatic disease: 23 months). For comparison purposes, according to the SEER data, the 5-year uncensored survival rate of patients dying of any type of GI cancer is 8.4%.

As regards the other causes of death, 3621 subjects died of nonmalignant diseases (mainly cardiovascular diseases) and 1711 subjects died of cancer other than GI carcinoid, which makes GI carcinoid the second cause of death in the overall cohort of patients.

The age-adjusted mortality rate of GI carcinoid has been significantly increasing over time (supplementary Figure S2, available at Annals of Oncology online), with an APC of 3.5 (95% CI 3.0–4.0) and an average of 1.0 deaths per 100 000 per year over the 2000–2009 decade. For comparison purposes, we recall that—based on SEER data—the mortality rate for all cancers and for all GI cancers is, respectively, 288 and 52 per 100 000 per year over the same decade.

At univariate analysis, race, year at diagnosis, GI site, disease stage, age, number of lymph nodes excised and examined and primary tumor size were significantly associated with patient survival (supplementary Table S3, available at Annals of Oncology online).

At multivariate analysis, the final Cox model showed that being diagnosed in the last decade (years 2000–2009), more limited disease diffusion (tumor stage) at presentation, GI site other than small bowel, younger age and smaller primary tumor size are significantly and independently associated with a better prognosis (supplementary Table S2 and Figures S5–S7, available at Annals of Oncology online). The model showed a high accuracy (C-index = 0.78, 95% CI 0.77–0.80), which well compared with that of a model based on disease stage plus primary tumor size (C-index = 0.58, 95% CI 0.57–0.59). The comparison between observed and predicted survival rates demonstrated a good model calibration (supplementary Figure S8, available at Annals of Oncology online).

On the basis of these covariates, a nomogram for the prediction of patient disease-specific survival was created (supplementary Figure S9, available at Annals of Oncology online).

The 5-year relative survival rate of patients with GI carcinoid resulted 87.4% (95% CI 86.7–88.1), which well compared with the 5-year relative survival of SEER patients with GI cancer in general (53.0%, 95% CI 52.8–53.1). GI carcinoid 5-year relative survival estimates varied remarkably according to disease stages, that is localized (95.6%, 95% CI 94.8–96.2), regional (86.5%, 95% CI 84.7–88.2) and distant (52.4%, 95% CI 50.1–54.6).

Finally, conditional survival analysis revealed that patients who have already survived 5 years after diagnosis of GI carcinoid have a high probability of surviving additional 5 years (94.3%) not only when the disease is localized (98.2%) or regionally confined (89.8%) but also when distant spread is present (73.5%).

**Discussion**

Our analysis of SEER data showed that GI carcinoid is the most frequent type of carcinoid, accounting for about 70% of these tumors. GI carcinoid—which occurs evenly in males and females—is more frequent in whites, although over the last decade the highest incidence is recorded among blacks. As regards the GI site, the carcinoid occurs most frequently in the small bowel and rectum, although the topology might be changing because the trend is most increasing for gastric and rectal carcinoids.

Importantly, GI carcinoid—though rare (it represents about 4% of all GI cancers)—is increasing in incidence (APC = 4.4, 95% CI 4.0–4.8). Remarkably, according to the SEER data, the pace of this increase is greater than that observed for other tumors whose incidence has been reported to be augmenting [37, 38], such as liver (APC = 3.5, 95% CI 3.2–3.7) and thyroid cancer (APC = 3.5, 3.1–4.0), extranodal Hodgkin disease (APC = 3.2, 95% CI 2.2–4.2), non-Hodgkin lymphomas (APC = 3.1, 95% CI 2.6–3.7), malignant melanoma of the skin (APC = 3.0, 95% CI 2.8–3.2) and lung cancer in females (APC = 1.8, 95% CI 1.4–2.2), and is only slightly lower than esophageal adenocarcinoma (APC = 4.8, 95% CI 4.2–5.6).
The reasons for this increasing trend, which contrasts with that of GI cancers in general (APC = −0.8, 95% CI −1.0 to −0.7), is unknown. Interestingly, small bowel and rectal carcinoids are occurring at a rate higher than that of carcinoids originating from other GI sites. While the biological/environmental causes of these phenomena are basically obscure, it appears reasonable to hypothesize that the growing diffusion of endoscopic procedures might be (at least in part) responsible for an increased diagnosis of GI carcinoid. However, while this hypothesis is reasonable for carcinoid of the rectum (endoscopy for anorectal and colonic diseases is very commonly carried out), this does not appear to be the case for the other GI site mostly involved by this incidence trend, that is, small bowel. To make things more complicated, we found that the incidence of appendix carcinoid—once often reported as the most frequent among GI carcinoids—is instead decreasing, although this might be due to misclassification as carcinoid of the cecum or ascending colon.

Overall, we found evidence that the increased incidence of GI carcinoids is real: in fact, the mortality rate is also increasing, which confutes the hypothesis that the putative increase is sustained by a recently increased tendency to diagnose tumors that would remain otherwise clinically silent. Again, the mortality trend (APC = 3.5, 95% CI 3.0–4.0)—which does not differ much from the incidence trend (APC = 4.4, 95% CI 4.0–4.8)—is in contrast with that of all GI cancers that has remained basically unchanged over time (APC = 0, 95% CI −0.3 to 0.4), suggesting an ongoing epidemiological dichotomization within tumors of the GI tract.

As widely known, GI carcinoid is a slow-growing tumor with an overall favorable prognosis, as confirmed by the high survival rates even 20 years after diagnosis, as well as by the relative survival rate (87.4%), which far exceeds the corresponding rate for GI cancers in general (53.0%). This evidence remains substantially true also considering patients diagnosed with locally advanced or metastatic disease: for instance, the 5-year survival rate is 89.4% and 59.4% for regional and distant stage GI carcinoid, respectively, whereas for all GI cancers, the rates drop to 56.3% and 8.8%, respectively. Therefore, despite the fact that at diagnosis GI carcinoid presents with a proportion of metastatic disease almost identical to that of GI cancers (23.8% versus 23.6%, respectively), patients with GI carcinoid have a relatively good life expectancy, which may explain why patients developing this tumor often develop also other primary malignancies. Intriguingly, GI carcinoid is also associated with a lower incidence of skin melanoma: although the molecular biology underlying this observation is completely unexplored, this finding is in line with other similar epidemiological data (e.g. patients with melanoma have a lower incidence of GI cancers [39]) and with some recently emerging genetic data (e.g. germline polymorphisms of cancer-related genes such as telomerase are risk factors for some tumors but at the same time are associated with protection against others [40]).

Despite these considerations, it should be noted that people who die of GI carcinoid have a median survival of 30 months, which is not improving over time (data not shown) and goes down to 23 months in case of distant metastatic disease. Therefore, while most patients with GI carcinoid survive this disease, most of those who are not cured by medical interventions (including surgery, chemotherapy or both) die of disease within roughly 3 years. Furthermore, although the prognosis of all patients diagnosed with GI carcinoid has significantly improved over the three time spans considered (1973–1989, 1990–1999 and 2000–2009), the mortality rate has increased over time, which suggests that early diagnosis and therapeutic management are not fully counterbalancing the increased incidence.

Finally, we must acknowledge the limitations of this study. While presenting the results, we are aware of the fact that, although the SEER database provides investigators with a unique opportunity of generating and testing medical hypotheses on an unprecedentedly large series of patients, underreporting is a potential limit of this databank. Moreover, missing data—which for some variables exceeded 50% of cases—generate the possibility of selection bias and the evolving definition of GI carcinoid could be the basis for misreporting. Yet, the substantial lack of therapy information has precluded any analysis of the impact of medical interventions on the natural history of this disease.

Depicting the epidemiology and the clinical course of GI carcinoid, our findings represent a solid reference for the clinical management of this disease and prompt further research to develop more effective therapeutic strategies against this slow-growing but chemoresistant tumor.

Acknowledgements
We truly thank Marta Briarava (Department of Surgery Oncology and Gastroenterology, University of Padova, Italy) for setting up and managing the large database we used for statistical analysis purposes.

Disclosure
The authors have declared no conflicts of interest.

References


