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ORIGINAL ARTICLE

A cure model survival analysis of patients affected by small intestinal neuroendocrine neoplasms: the Bologna ENETS center experience

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Abstracts

Purpose The primary end-point was to evaluate the cure fraction. Secondary end-points were to investigate the time to cure, the excess of death risk, the probability of cure and the factors related to these parameters.

Methods Retrospective study of an ENETS database regarding patients affected by Si-NENs. For each patients, clinical, pathological and follow-up data were collected. The survival analysis was made using a novel approach: the cure model approach.

Results The cure fraction was 92.1%. The death risk, time to cure and the probability of cure were 6/1000 person-years, 3.6 years and 98.2%, respectively. The independent factors influencing these parameters were the grading and the R status ($P = 0.041$ and $P = 0.017$, respectively). Patients affected by Si-NENs G2 increased the death risk and time to cure respect to Si-NENs G1 (51 versus 6 per 1000 person-years and 5.1 versus 3.6 years, respectively) as well as patients not operated respect to those radically resected (R0/1) (66 versus 1 per 1000 person-years and 4.8 versus 0.4 years, respectively). The probability of cure decreased (88.1 versus 97.8% and 80.4 versus 99.7%, respectively). R2 resection shows better results than no resection.

Conclusions A large portion of patients affected by Si-NENs can be cured. The highest probability of cure regards patients with Si-NENs G1 who underwent to R0/R1 resection; the lower, those with Si-NENs G2 and no resection. R2 resection seems to be preferred respect to no resection.

Keywords Small intestine · Neuroendocrine neoplasms · Cure model

Introduction

The small intestinal neuroendocrine neoplasms (Si-NENs) represent an increasing incidence disease [1] with an indolent behavior and a good prognosis. In addition, the ENETS guidelines [2] suggested a therapeutic algorithm including localized, regional, and distant disease. However, to our knowledge, no articles reported data about the cure of patients affected by Si-NENs and factors capable to influence the course of the disease or its cure. The term "cure" usually explains the impact of cancer treatment on survival. Briefly, for an individual, the aim of cancer treatment is to eliminate any cancer disease that can accelerate the mortality. When the death of the patients is not related to cancer, the individual is usually considered cured. In addition, the concept of "statistical cure" is based on the statistical analysis of long-term survival data and refers to a portion of patients who are highly unlikely to die from cancer. The present study aimed to investigate how many and which patients affected by Si-NENs were cured or not cured, well-defining the natural history and the proper management of

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the Si-NENs. To obtain these aims, a novel survival approach, the cure model survival analysis, of patients affected by Si-NENs, operated and non operated, was carried out. The cure model analysis introduced the concept of "statistical cure" and represents a very useful tool capable to predict the percentage of patients cured for a specific disease (cure fraction), the time to cure, the probability of cure and the excess of death risk [3–5].

Methods

Study design

This is a retrospective study of an ENETS prospectively maintained database regarding 258 consecutive patients affected by Si-NENs, operated and non operated, observed from January 1998 to December 2017; it was approved by the Ethics Committee of S.Orsola-Malpighi Hospital (RAC 164/2017/O/Oss), with patients giving informed consent. The inclusion criteria were: (1) patients with adequate follow-up (at least 1 year from diagnosis); (2) patients with Ki-67 available. For this reason, patients who had a short follow-up ($n = 11$) and those without any information regarding the value of Ki-67-positive cells ($n = 47$) were excluded. The remaining 201 patients were potentially available for the analysis, but 5 patients were unmatched with the general population for age, gender, and year of diagnosis. Thus, 196 patients affected by Si-NENs, operated and non operated, were analyzed. The selection process is shown in Fig. 1. For each patients, clinical, pathological and follow-up data were collected. The details about these data are reported in supplementary file sMethods.

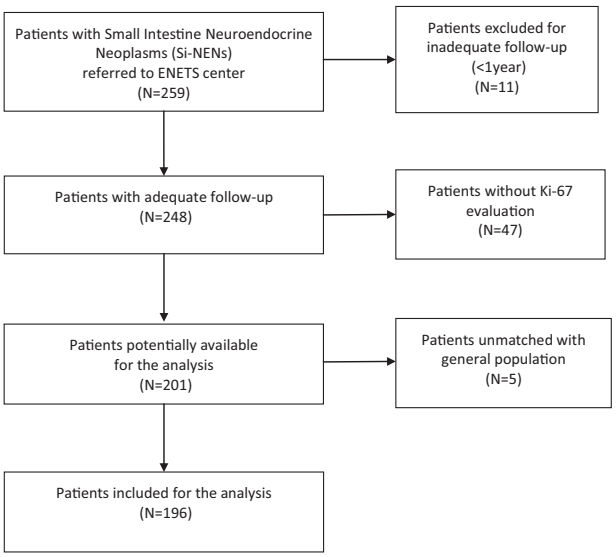

Fig. 1 Flow chart of patients selection for the analysis

Survival analysis

The survival analysis was made using the cure model approach [3]. Briefly, we start from the assumption that patients receiving a diagnosis of Si-NENs could experienced a reduction of lifespan. This life lost were measured using the relative survival (RS): it is calculated by dividing the percentage of patients with a disease (Si-NENs) who are still alive at the end of the period of time with the percentage of people in the general population of the same sex and age who are alive at the end of the same time period [5]. The first step consist in the calculation of the two survival (expected and observed). The expected survival of the general population is derived from survival tables obtained from the Italian National Institute of Statistics, matched for age, gender and year of diagnosis with patients affected by Si-NENs [6]. The observed survival used was computed in Si-NENs population as overall survival (OS): it was calculated from the date at diagnosis to the date of the last follow-up or death for any cause. The second step is to verify the statistical plausibility of the cure model [7]. In fact, if there is a subgroup of patients with a significant reduction of lifespan (excess of death risk) with respect to the general population, the RS curve would tend to a plateau on the y-axis. The statistical plausibility is graphical observed and mathematically tested. In the third step, uni- and multivariate model were used to identify the covariates related to the excess of death risk [8]. The primary end-point of the present study was to evaluate the cure fraction, that is the portion of patients affected by Si-NENs cured (highly unlikely to die from cancer) and not cured (premature death related to cancer). Secondary end-points were to investigate the excess of death risk, the time to cure, the probability of cure and the factors related to these parameters. The excess of death risk was defined as the number of death per 1000 person-years during 20 years of follow-up. The time to cure was defined as the estimated years at which the probability of premature death was < 1%. The probability of cure was defined as the probability of normal lifespan as function of 20 years follow-up.

Statistical analysis

Frequencies with percentages were used to describe the discrete variables. The continuous value and survival data were reported as medians and 95% confidence interval (95% CI). Relative survival curves (RS) and OS were also plotted for both the "whole" population and the patients with reduced lifespan group. The plausibility of the models was statistically measured by the presence of a P-value < 0.05 using the Pearson Chi-square test. The effect of the covariates on the excess of hazard rate (HR) was identified by reporting the HR ratio ± SE. Thus, when the HR was >1,

the positive change in the value of the covariates corresponded to an increase of HR (death risk). On the contrary, an HR < 1 indicated a reduction in the death risk with positive change of the covariate values. In multivariate model only co-variables with P value = 0.10 at univariate are included. A non negligible independent effect of the covariates is identified by a *P*-value < 0.05. The post-estimation values of independently and statistically significant covariates are reported using three different measures: (1) excess of HR with 95% confidence interval (95% CI) that represent the excess of death risk per 1000 person-years during 25 years of follow-up; (2) the time to cure with 95% CI namely the esteemed years at which the probability of premature (not equal to those expected for age, sex, and years of diagnosis) death was <to 1%; (3) the probability of cure that means the probability of normal lifespan (equal to those expected for age, sex, and years of diagnosis) as function of 25 years follow-up. The statistical analyses were computed using STATA software (StataCorp. 2011. College Station, TX: StataCorp LP). The cure model was computed using the *strsmix* package; the *weibull distribution* option was used for all the analyses while the *loglog* link functions were used to calculate the HRs.

Results

The baseline characteristics of the 196 patients included in the analysis are reported in Table 1 and the detailed results are described in the supplementary file, sResults. The median follow-up of the sample was 4 years (0.6–14.3 95% CI), with a median overall survival (OS) of 14.4 years (12.8 to impossible to calculate for % survivor >50, 95% CI). Relative survival was 92.1% (91.5–99.9, 95% CI) as shown in Fig. 2 by the plateau of the blue line. Thus, only a 7.9% (0.01–8.5, 95% CI) of patients (red line) with Si-NENs experience a reduction of lifespan than those expected for age, gender and date of diagnosis. The cure model based on excess of hazard rate was statistically plausible for the whole population (*P*-value <0.001). The univariate analysis showed that the excess of HR was significantly increased in patients with carcinoid syndrome (8.62 ± 10.38; $P = 0.073$), liver or extra-hepatic lesions (2.57 ± 1.24; $P = 0.050$), in those who did not undergo to surgery (0.29 ± 0.18; $P = 0.051$), with G2 tumors (6.27 ± 4.42; $P = 0.009$) and in patients with different R status (starting from a radical resection-R0/R1-through R2 resection versus no surgical therapy)(3.62 ± 1.64; $P = 0.005$). Sex, gender, age, primary occult lesions, ENETS stage did not influence the excess of death risk. At multivariate analysis, the only independent factors were the grading according to 2017 WHO and the R status. Patients with Si-NENs G2 had a significant increased of death risk respect to Si-NENs G1 (4.23 ± 2.99; $P = 0.041$) as well as those who did not underwent to surgery respect to patients who underwent to radical resection (R0/R1) (2.94 ± 1.33; $P = 0.017$) (Table 2). Post-estimation values obtained are shown in Table 3. The entire population had an excess of death/HR of 6 (0–32, 95% CI) per 1000 person-years with respect to the general population. The median time to consider the patients at risk of premature death was 3.6 years (2.1–6.1). The probability that a patient with Si-NENs, experienced a normal lifespan in 20 years

Table 1 Baseline characteristics of 196 patients included in the analysis

Baseline characteristics	Total patients $n = 196$ (%)
Sex	
M	113 (57.6)
F	83 (42.4)
Age	
≤65 years	111 (56.6)
>65 years	85 (43.4)
Symptoms	
No	66 (33.7)
Yes	130 (66.3)
Carcinoid syndrome	
No	153 (78.1)
Yes	43 (21.9)
Distant metastasis at the end of preoperative staging	
No	90 (45.9)
Liver only	60 (30.6)
Extra-hepatic ± Liver	46 (23.5)
Primary occult lesion at the at the end of preoperative staging	
No	140 (71.4)
Yes	56 (28.6)
Surgery	
No	23 (11.7)
Intestinal resection	121 (61.7)
Intestinal plus liver resection	52 (26.6)
ENETS TNM	
I	4 (2.1)
IIa-IIb	12 (6.1)
IIIa-IIIb	73 (37.2)
IV	107 (54.6)
Grading according to the WHO 2017	
NET G1	170 (86.7)
NET G2	26 (13.3)
R Status	
R0/R1	107 (54.6)
R2	66 (33.7)
Not applicable	23 (11.7)

ENETS European Neuro-Endocrine Tumor Society, *WHO* World Health Organization, *NET* Neuro-Endocrine Tumor

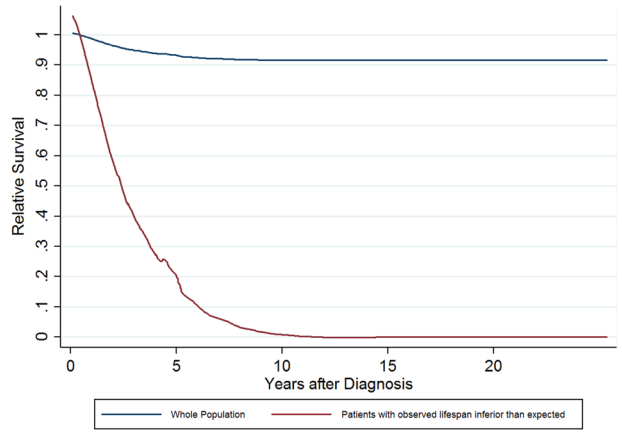

Fig. 2 Relative survival of the whole population (blue line) and the "not cured" population (red line) (patients with observed lifespan inferior than expected)

was 98.2% (91.6–100%). The excess of death risk increased in patients affected by Si-NENs G2, counting 51 excess of death risk per 1000 person-years. The time to cure was 3.6 and 5.1 years, for Si-NENs G1 and G2, respectively. The probability of cure during the observation period was 97.8% for Si-NENs G1 versus 88.1% for G2 ones. Considering the R status, post-estimation data showed that both R2 resection and no resection were associated to an excess death quantifiable in 19 and 66 excess of death for 1000 person-years. On the contrary, the excess of death/HR for R0/1 resection was proximal to the 0% value (HR = 0.001; 0–0.001 95% CI). The related time to cure for R0/1, R2 and no surgery were 0.4, 3.9, and 4.8 years, respectively. The probability of cure was near to 100% for patients R0/1 resected (99.7%), decrease to 94.7% for those R2 resected and 80.4% for those patients who did not undergo to surgical resection.

Discussion

To our knowledge, the present study is the first that investigated a large cohort of patients affected by Si-NENs regarding its cure. In addition, to evaluate the cure of Si-NENs a novel survival approach was used: a cure model survival analysis, a new concept of "statistical cure", was carried out allowing to answer to some important questions. First, regarding the primary endpoint: "how many patients were cured? and how many not cured?", Fig. 2 shows that the majority of patients affected by Si-NENs were cured (92.1%), only few were not cured (7.9%). In addition, patients affected by Si-NENs rarely died with respect to the general population (excess of death risk = 6 out of 1000 person-years), had a short time to cure (3.6 years) and a very high probability to cure (98.2%) (Table 2). These data mean that the majority of the patients affected by Si-NENs, operated and non operated, have a lifespan similar to those of the general population: in other words in a large portion of patients the survival observed and expected was similar and the patients can be considered adequately cured. Conversely, a minority of the patients observed (7.9%) shows a lifespan inferior to that expected: these patients were considered not cured. Thus, these data seem to suggest that the management adopted in patients affected by Si-NENs has a high probability of curing the disease and to confirm that it has an indolent behavior, a prolonged survival and a good prognosis, as previously reported by several authors [9–12].

Second, regarding secondary end-points, the cure model analysis allowed to identify the factors capable to influence the cure of Si-NENs: "which patients were cured?" and which not cured?"

At multivariate analysis, only the patients with Si-NENs G2 grading according to the WHO classification and those who did not undergo to surgical resection (R0/1 or R2) seem to play a role in the cure of Si-NENs (Table 1). The post-estimation data (Table 2) show how much the presence of Si-NENs G2 increase the excess of death risk, time to cure and decrease the probability of cure respect to Si-NENs G1 as well as patients who did not undergo to surgical resection respect to those who undergo to surgical resection (R0/1 or R2). Interestingly, it is to note that either in patients affected by Si-NENs G1 than in those who underwent to surgical resection R0 the results were amazing: only few persons (6 and 1/1000 persons-years, respectively) had an excess of death risk respect to the general population, the time to cure was short (3.6 and 0.4 years, respectively) and the probability of cure very high (97.8 and 99.7%, respectively). These data suggested that quite all patients with low proliferative index (G1 = Ki 67 < 3%) who were radically treated (R0/1 resection) had a survival observed similar to that expected and they can be considered cured; only a very small part of it can be considered not cured, even if adequately treated. Furthermore, considering that the major part of the patients with Si-NENs are usually G1 (quite 90% in the present cohort of patients) and undergo R0/1 resection (>50% in the present cohort of patients), we can assume that quite all the entire sample of Si-NENs can be cured. Thus, patients affected by Si-NENs G1, radically resected represent those patients with the highest probability of cure. On the contrary, patients with Si-NENs G2 who did not undergo to surgical approach have the lowest probability of cure. However, it is to note that also these patients have an high probability of cure, being about 80% of cases. Furthermore, this datum confirms the indolent biological behavior of the disease. Another interesting datum is that patients affected by Si-NENs who underwent to R2 surgical resection presents better results than those patients in which surgery is not performed. This result seems to reinforce data reported from several authors

Table 2 Univariate analysis and stepwise multivariate analysis stratified by the baseline characteristics of 196 patients having small intestinal NETs

Factors	Excess of death risk			
	Univariate		Multivariate	
	HR ratio ± SE	*P*-value	HR ratio ± SE	*P*-value
Sex				
M	Referent	0.438	–	–
F	1.90 ± 1.59			
Age				
≤65 years	Referent		–	–
>65 years	0.46 ± 0.62	0.565		
Symptoms				
No	Referent	0.859	–	–
Yes	1.14 ± 0.88			
Carcinoid Syndrome				
No	Referent	0.073	Referent	0.534
Yes	8.62 ± 10.38		1.62 ± 1.26	
Distant metastasis at the end of preoperative staging[a]				
No versus liver versus extra-hepatic	2.57 ± 1.24	0.050	0.74 ± 0.47	0.652
Primary occult lesion at the at the end of preoperative staging				
No	Referent		–	–
Yes	2.82 ± 1.95	0.135		
Surgery				
No versus intestinal versus intestinal plus liver	0.29 ± 0.18	0.051	1.16 ± 1.24	0.779
ENETS Stage (for each stage)[a]	$2 \times 10^6 \pm 1 \times 10^9$	0.984	–	–
Grading according to the 2017 WHO classification				
G1	Referent	0.009	Referent	0.041
G2	6.27 ± 4.42		4.23 ± 2.99	
R status				
R0/R1 vs R2 vs no surgery	3.62 ± 1.64	0.005	2.94 ± 1.33	0.017

NEN neuroendocrine neoplasm, *HR* hazard risk, *SE* standard error, *95% CI* 95% confidence interval, *M* male, *F* female, *ENETS* European Neuroendocrine Tumor Society, *WHO* World Health Organization, *R0* no microscopic residual of the disease, *R1* microscopic residual of the disease on the resection margin, *R2* gross residual of the disease, – not included in multivariate model

[a]HRs and *P*-values represent a linear trend among the categories of covariates; the referent categories were no metastasis for preoperative staging; Stage I for ENETS Stage, and R0/1 for R status

Table 3 Post-estimation data after stepwise multivariate analysis: "Excess of death", "Time to cure", "Probability of cure" and of the significant factors ($P < 0.05$)

Factors	Post-estimation data		
	Excess of death/HR (95% CI)	Time to cure (95% CI)	Probability of cure (95% CI)
Whole population	0.006 (0 to 0.032)	3.6 (2.1–6.1)	98.2% (91.6–100)
Grading according to the 2017 WHO classification			
NET G1	0.006 (0.005 to 0.007)	3.6 (1.9–6.6)	97.8% (97.5–98.2)
NET G2	0.051 (0.034 to 0.067)	5.1 (2.6–10.1)	88.1% (83.5–92.6)
R status			
R0/1	0.001 (0 to 0.001)	0.4 (0 to > 25)	99.7% (97.6–99.8)
R2	0.019 (0.015 to 0.024)	3.9 (2.1–7.6)	94.7% (93.4–95.9)
No surgery	0.066 (0.042 to 0.089)	4.8 (2.4–9.9)	80.4% (73.4–87.4)

Excess of death/HR the excess of death/hazard rate risk per 1000 person-years during 20 years of follow-up, *Time to cure* The estimated years at which the probability of premature death was < 1%, *Probability of cure* probability of normal lifespan as function of 20 years follow-up, *95% CI* confidence interval at 95%, *NET G1* small intestinal Neuro-Endocrine Tumor with Ki-67 index < 3%, *NET G2* small intestinal Neuro-Endocrine Tumor > 3%, *R0* no microscopic residual of the disease, *R1* microscopic residual of the disease on the resection margin, *R2* gross residual of the disease, *WHO* World Health Organization

regarding Si-NENs with unresectable hepatic metastases [13–15] that suggested the resection of the primary tumors (R2 resection). Thus, this surgical palliative approach allows to avoid complications but also seems to decrease

the excess of death, the time to cure and to obtain a higher probability to cure, a better prognosis respect to those patients who did not undergo to resection of the primary neoplasm.

This study has some limitations: the "statistical cure" analysis regarding recurrence, the retrospective design, in a single center, covering a long time period and regarding an over-selected population (mainly surgical cohort of patients). However, regarding the latter limitation, it can be justified by the fact that, currently, the surgical treatment represents the gold standard for the treatment of Si-NENs.

In conclusion, despite its limitations, the present study, by applying for the first time the cure model analysis to Si-NENs, operated and non operated, allowed to obtain some additional information regarding the natural history and the management of the disease. First, the possibility to cure the patients affected by Si-NENs is extremely high, being the lifespan similar to those of general population for a very large portion of patients, confirming the favorable biological behavior of the disease and the adequacy of the management adopted. Second, the patients with the highest probability of cure are those with Si-NENs G1 who underwent to curative surgical resection R0/1. Third, the patients with the lowest probability of cure are those with Si-NENs G2 and in which any surgical approach was not performed. Fourth, surgical resection of the primary tumor in patients affected by Si-NENs with unresectable liver metastases seems to be preferred respect to those patients who did not undergo to a surgical approach.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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