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Is radical surgery always curative in pancreatic neuroendocrine tumors? A cure model survival analysis

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ABSTRACT

Background: Adjuvant therapy after curative surgery for sporadic pancreatic neuroendocrine tumor (pNETs) is not currently recommended, assuming that all patients could be cured by a radical resection. The aim of our study is to establish how many and which kind of patients remained uncured after radical resection of pNET.

Methods: Retrospective study involving 143 resected sporadic pNETs. The survival analysis was carried out using the cure model, describing the cure fraction and the excess of risk recurrence. Multivariate analyses were made in order to evaluate the non negligible effect of demographics, clinical and pathological factors on survival parameters. The results were reported as percentages, fractions, ORs and HRs with 95% confidence interval (95 CI %).

Results: The cure fraction and the excess of hazard rate of the whole population were 57.1% (37.4–74.6, 95% CI) and 0.06 (0.03–0.07, 95% CI), respectively. Two independent factors were related to the cure fraction: TNM stage (OR 0.27 ± 0.17; $P = 0.002$) and grading (OR 0.11 ± 0.18; $P = 0.004$). Considering the excess of hazard rate, only two independent factors were related to an increased risk of recurrence: TNM stage (HR 3.49 ± 1.12; $P = 0.004$) and grading (HR 4.93 ± 1.82; $P < 0.001$).

Conclusion: The radical surgery has a high probability of cure in stages I-II or in grading 1 while, in stages III-IV or in grading 3 tumors, surgery alone failed to achieve a "cure". A multimodal treatment should be employed in order to avoid a recurrence of the disease.

Introduction

A "well-known" axiom in pancreatic surgery is that "radical surgery is the only chance of cure for patients having functioning or non-functioning sporadic pancreatic neuroendocrine tumors (pNETs)" [1,2]. Nevertheless, it is well known that a certain quota of patients experienced a recurrence of the disease during the follow-up [3–5]. In addition, in the recent years, some new types of drugs [6–9] and/or complementary treatments [10] have demonstrated a certain degree of efficacy as the first or second lines of treatment for unresectable, locally advanced or metastatic pNETs. However, no clinical trials have been conducted in order to verify the efficacy of the adjuvant treatment in preventing recurrences after radical surgery. Thus, the main question is:" how many and which patients remain uncured after radical surgery?"

In order to provide an answer to this question, the present study carried out a cure model analysis on a population of radically resected pNETs. Briefly, the cure model is a well-accepted special survival analysis [11,12] which estimates the proportion of patients really "cured" for a specific disease, relying on the concept of the statistical plausibility of cure. The primary endpoint of the present study was to establish the cure fraction, the time to cure and the excess of risk recurrence. The secondary endpoint was to identify the demographic, clinical and pathological factors significantly related to these measures.

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Methods

This was a retrospective study of a prospectively maintained database regarding 199 consecutive patients affected by sporadic pancreatic NETs, surgically treated from January 1990 to December 2016. The inclusion criteria were: 1) patients with R0/R1 resection, 2) patients with KI-67 available and 3) patients with almost 6 months of follow-up. For this reason, patients who had an R2 resection (n = 21) and those without any information regarding the value of KI-67-positive cells (n = 35) were excluded. The remaining 143 patients were included in the analysis. The selection process shown in Supplementary Fig. 1. The details about the clinical pathological and follow-up data are reported in supplementary file sMethods.

Survival and statistical analysis

The survival analysis was carried out using the cure model [13–15] Relative survival curves (recurrence free survival and smoothed hazard function) were reported for both the "whole" population and the "uncured" group. Two models were built: Model 1 which represented the cure fraction and Model 2 which represented the excess of hazard rate. Post-estimation data about cure fraction, time to cure and excess of risk recurrence were calculated and reported with 95 %CI. Univariate and multivariate analyses were carried out in order to define the covariates influencing the cure fraction, time to cure and excess of risk recurrence. The statistical analyses were computed using STATA software (StataCorp. 2011. College Station, TX: StataCorp LP). The cure model was computed using the *strsnmix* package; the *weibull distribution* option was used for all the analyses while the *logistic* and *loglog* link functions were used to calculate the odds ratios (ORs) and hazard ratios (HRs), respectively. All details about survival and statistical analysis were described in supplementary file sMethods.

Results

The baseline characteristics and postoperative course of the 143 patients included in the analysis are reported in Supplementary Tables 1 and 2, and the detailed results are described in the supplementary file, sResults. The median follow-up of the entire sample was 5 years (0.5–25), with an OS and an RFS of 4.1 (0.5–25.1) and 3.3 (0.5–25.1) years, respectively. The 3, 5 and 10-year RFS rates were 78.3% ± 0.1, 67.5% ± 0.1 and 61.1% ± 0.1, respectively. Forty (27.9%) patients experienced recurrence of the disease during the follow-up. In particular, in 8 patients the recurrence was in the abdominal lymph nodes, in 12, it was in the liver and, in the remaining 20, it was in both sites. All patients had recurrences within 11.2 (2.6–36.4) years. The median relative survival of the whole population was not computable because more than half of the patients were cancer-free at the end of the observation period. The mean relative survival of the whole population at the 99th percentile of the "uncured" patients (namely when all patients had recurrences) was 21 years (6.8–25, 95% CI). The median relative survival of the uncured patients was 3.9 years (1.7–6.8, 95% CI) (Fig. 1).

The two cure models (cure fraction and excess of hazard rate) were statistically plausible for the whole population (P value < 0.001 and P value = 0.005, respectively). The cure fraction of the whole population was 57.1% (37.4–74.6, 95% CI) after curative surgery as shown in Fig. 1 by the plateau of the blue line (dashed line). The time to cure of the whole population was 9.1 years (2.6–32.4, 95% CI). The excess of hazard rate was plotted in Fig. 2: whole and "uncured" populations had a hazard rate of 0.06 (0.03–0.07, 95% CI) and 0.21 (0.08–0.52, 95% CI), respectively. The

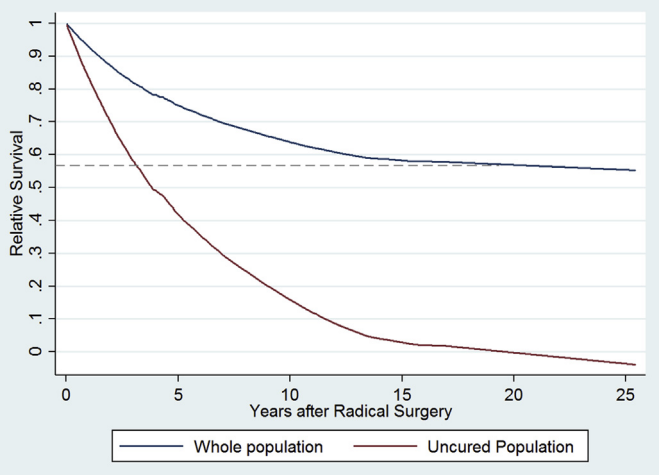

Fig. 1. Relative survival of the whole (blue line) and the uncured populations (red line). In the entire group, the survival curve reaches a plateau at 57.1% (dashed gray line) after approximately 21 years which represents the cure fraction.

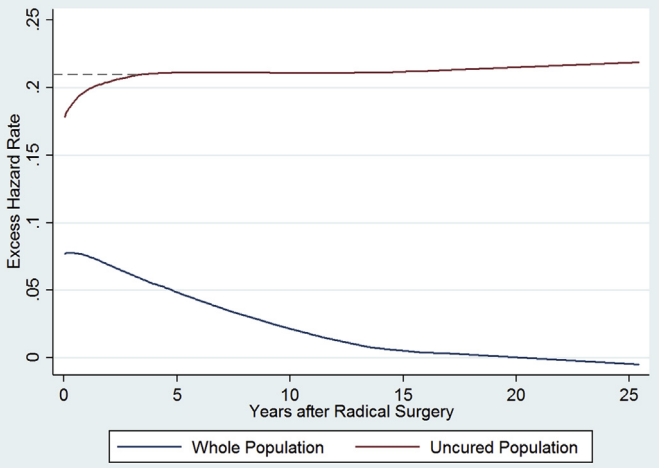

Fig. 2. The excess hazard rate of the whole (blue line) and of the uncured (red line) populations. Approximately 21 years after surgery, the excess of hazard rate tends to 0 in the whole population. Conversely, in uncured patients, the excess of hazard rate rapidly increases over time, reaching its maximum value in almost 4 years (dashed gray line) and remaining high for the entire observation period.

results of the univariate and the multivariate analyses for both models (Model 1, namely the cure fraction and Model 2, namely the excess of risk of recurrence) are reported in Table 1. Model 1 was statistically plausible for all the subgroup analyses (P values < 0.05) in univariate and multivariate analyses. In Model 1, the univariate analysis showed that age >65 years at the time of surgery increased the cure fraction (OR 1.31 ± 0.76), even if the impact did not reach statistical significance (P = 0.086). The type of surgery also seemed to influence the probability of cure after surgical treatment; when passing from typical to atypical resection, the cure fraction increased (OR 3.50 ± 2.59) even if, once again, it did not reach statistical significance (P = 0.091). The only two parameters which statistically influenced the cure fraction were the ENETS stage and grading according to the 2010 WHO classification. In fact, when the ENETS stage increased, the cure fraction significantly decreased (OR 0.15 ± 0.08, P < 0.001). Similarly, when the grading of the tumors increased, the cure fraction was reduced (OR 0.09 ± 0.06; P < 0.001). Multivariate analysis confirmed that the only

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