Pancreatology xxx (2017) 1–7

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Is surgery the best treatment for sporadic small (≤2 cm) non-functioning pancreatic neuroendocrine tumours? A single centre experience

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ARTICLE INFO

Article history:
Received 7 December 2016
Received in revised form
31 January 2017
Accepted 12 March 2017
Available online xxx

Keywords:
Pancreatic endocrine neoplasm
Surgery
Surveillance
Tumor size

ABSTRACT

Backgound: There is currently there is substantial controversy regarding the best management of non-functioning pancreatic neuroendocrine tumours ≤2 cm.
Methods: Retrospective study involving 102 surgically treated patients affected by non-functioning pancreatic neuroendocrine tumours. Patients having small tumours (≤2 cm) (Group A) and those having large tumours (>2 cm) (Group B) were compared regarding demographics, clinical and pathological factors with the aim of evaluating the risk of malignancy and survival times.
Results: The small tumours were T3-4 in 11% and G2-3 in 36.6% of cases; lymph node and distant metastases were present in 31% and 8% of the cases, respectively. When small and large tumours were compared, significant differences were found in relation to the presence of symptoms ($P = 0.012$), tumour status ($P > 0.001$), grading ($P > 0.001$) and years lost due to disability ($P = 0.002$). Multivariate analysis of the factors predicting malignancy and survival times showed that tumour size was related only to grading ($P < 0.001$). The years of life lost and disability adjusted life years were influenced by age at of diagnosis, the presence of symptoms and years lost due to disability only by grading.
Conclusions: Tumour size alone did not seem to be reliable in predicting malignancy because, first, small tumours (≤2 cm) could present lymph node or distant metastases, and could be G2-3 in a non-negligible percentage of cases and second, their risk of malignancy and survival time are similar to large tumours. Additional parameters have to be considered in order to establish the proper management of small tumours, such as age at diagnosis, presence of symptoms and grading.

1. Introduction

It is generally accepted that non-functioning pancreatic neuroendocrine tumours (NF-PNETs) >2 cm have to be resected when found in patients who are otherwise fit for surgery [1–3]. On the contrary, there is substantial controversy regarding the best management of NF-PNETs smaller than 2 cm. Some authors and the National Comprehensive Cancer Network (NCCN) guidelines [2] have advocated surgical management as the best curative option because it allowed an overall survival advantage for avoiding progression of the disease [4–7]; other authors and the European Neuroendocrine Tumour Society (ENETS) guidelines [1] have emphasised that a conservative approach seems to be safe as the majority of the tumours observed did not show any significant changes during follow-up having an overall favorable prognosis [8–11]. However, the proper treatment of these tumours should be determined by balancing, on the one hand, the safety of the non-operative management expressed by tumour growth, natural history and prognosis, and, on the other hand, the estimated surgical

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http://dx.doi.org/10.1016/j.pan.2017.03.004
1424-3903/

risk calculated considering postoperative morbidity and mortality, and exocrine and endocrine insufficiency due to an aggressive surgical policy. In this setting, the main question is: "Does small size preclude malignant behaviour, therefore making pancreatic resection unnecessary"?

In attempting to answer this question, we hypothesized that small NF-PNETs (≤2 cm) and large ones (>2 cm) have the same risk of malignancy, with the aim of evaluating whether the surgical approach was the best treatment for sporadic, small NF-PNETs.

2. Methods

2.1. Study design

This was a retrospective study of a prospective database, approved by the Ethic Committee of S.Orsola-Malpighi Hospital with patient informed consent, regarding 196 consecutive patients having sporadic PNETs, surgically treated in our Institute from January 1990 to December 2015. The inclusion criteria were: patients 1) with non-functioning PNETs, 2) with R0/1 resection, 3) with KI-67 available and 4) with at least six months of follow-up.

For these reasons, patients with functioning tumours (n = 46), who had an R2 resection (n = 10) and those without any information regarding the KI-67 value (n = 38) were excluded. The remaining 102 patients were divided into two groups based on tumour size: Group A (n = 36) which included patients with small NF-PNETs (≤2 cm) and Group B (n = 66) which included patients with large NF-PNETs (>2 cm) (Fig. 1).

The objectives were to assess the risk of malignancy and survival time in the two groups with the aim of establishing whether the surgical approach represented the best treatment for sporadic, small NF-PNETs (≤ 2 cm). (See Fig. 2)

The baseline characteristics of the patients (age, gender, co-morbidities, symptoms), the presence of tumours (site, number of lesions), surgical data (type of resection, postoperative results-mortality, morbidity and length of hospital stay), pathological features (tumour (T) status according to ENETS, node (N) status, lymph node ratio (LNR), metastasis (M) status, staging according to ENETS [12], grading according to the World Health Organization (WHO) 2010 [13] and resection (R) status) and survival times (median follow-up, overall survival, disease-free survival, years of life lost, years lost to disability and disability adjusted life years) were recorded and compared between the two groups. In addition, multivariate analyses were carried out to evaluate which of the demographics, and clinical and pathological factors (including size ≤ 2 cm or > 2 cm) previously described were related to the risk of malignancy and survival.

2.2. Definitions

The term "malignant" regarding pancreatic NF-PNETs has not always been well defined [14] but, in the literature, the tumours with risk of malignancy were considered to be those with lymph node or distant metastasis, and tumour grading G2-G3 or only G3 [15–18].

Postoperative mortality was defined as the number of deaths occurring during hospitalisation or within 90 days after surgery. The postoperative morbidity rate included all complications following surgery up to the day of discharge; they were classified according to the Clavien-Dindo classification [19]. Atypical resections included enucleation; typical resections included pancreaticoduodenectomies, and left, central and total pancreatectomies [20]. Overall survival (OS) was defined as the time from surgery to death or the last follow-up. Disease-free survival (DFS) was defined as the length of time after primary treatment that the patient survived without any signs or symptoms of that cancer. Years of Life Lost (YLL) measures the YLL due to a specific cause as a proportion of the total YLL lost in the population due to premature mortality. Years of Life Lost (YLL) is calculated from the number of deaths multiplied by a standard life expectancy at the age at which death occurs according the following formula: YLL= N x L where N represents the number of deaths and L the standard life expectancy at the age of death in years. The survival of the general population was obtained from the Italian National Institute of Statistics [21]d.

Years Lost due to Disability (YLD) measures the years lived with disability and is calculated assuming that, from the time of the recurrence to the time of death, the quality of life was reduced; the number of years lived with the disease was obtained from the study population. This data was adjusted using the disability weight (DW), that is, a weight factor which reflects the severity of the disease on a scale from 0 (perfect health) to 1 (equivalent to death). For this calculation the DWs suggested by the WHO [22] were used. For pancreatic cancer, the WHO provided a specific DW (0.20). Therefore, estimated YLD for the study cohort was obtained using the following formula: YLD = P x DWs where P represented the number of prevalent cases and DW the disability weight.

Finally, Disability Adjusted Life Years (DALY) can be thought of as one lost year of "healthy" life and is obtained by the sum of YLLs and YLDs using the following formula [23]: DALY = YLL + YLD.

2.3. Statistical analysis

Continuous data are reported as mean and standard deviation (SD), and categorical data as frequencies and percentages. The Fischer's exact test, the Student's *t*-test and the Pearson chi-square test were used to analyse the two groups. Multivariate analyses were carried out using logistic regression.

Data regarding survival were derived from the standardised follow-up examinations previously described [16]. Overall survival and disease-free-survival were obtained using the Kaplan-Meier method and were plotted. Comparison between the two groups was carried out using the log-rank test. The YLL was calculated as the difference in area between the overall survival curve in the referent cohort and that in the study population. The YLD corresponds to the difference in area between the overall survival curve in the referent cohort and disease-free survival in the study population. The estimated YLLs, YLDs and DALYs were described as means and 95% confidence intervals (CIs). Two hundred bootstrap samples were used to obtain the 95% CI of the means. The comparison between the two group was carried out using the analysis of variance(ANOVA) test. Finally, multivariate analysis was carried out using backward linear regression. The influence of the covariate was reported as effect in years (B value) positive or negative and a 95% CI. A negative B value meant that the covariate reduced the YLL, YLD or DALY while a positive value meant that the covariate increased these parameters.

For all the analyses, two-tailed P values less than 0.05 were considered statistically significant. All statistical analyses were carried out using STATA™ 12.0 software (Stata Corporation, College Station, Texas, USA). For the flexible parametric survival models, the stmp2 module was used [24].

3. Results

The characteristics of the patients, tumours and surgery are summarised in Table 1. The two groups were comparable for gender, age and co-morbidities. Patients with small tumours were more frequently asymptomatic (72.2% vs. 45.5%; P = 0.012) than those with larger ones at the time of diagnosis while the two

Please cite this article in press as: Ricci C, et al., Is surgery the best treatment for sporadic small (≤2 cm) non-functioning pancreatic neuroendocrine tumours? A single centre experience, Pancreatology (2017), http://dx.doi.org/10.1016/j.pan.2017.03.004