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REVIEW ARTICLE

Surveillance strategy for small asymptomatic non-functional pancreatic neuroendocrine tumors – a systematic review and meta-analysis

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Abstract

Background: Non-functional pancreatic neuroendocrine tumors (NF-PNET) are rare neoplasms being increasingly diagnosed. Surgical treatment or expectant management are both suggested for small NF-PNETs. The aim of this study was to evaluate the outcome of surveillance strategy for small NF-PNETs.

Methods: A systematic search was performed up to March 2016 in MEDLINE, EMBASE and the Cochrane Library according to the PRISMA guidelines. Data was pooled using the random-effects model.

Results: Nine articles including 344 patients with sporadic and 64 patients with MEN1 related NF-PNET were selected. Tumor growth was observed in 22% and 52%, development of metastases were reported on 0% and 9%, and rate of secondary surgical resection was 12% and 25% in patients with sporadic or MEN1 related NF-PNETs, respectively. All metastases (1 distant, 4 nodal) were reported by a single study in patients with MEN1. Reason for secondary surgery was tumor growth in half of patients undergoing surgery.

Discussion: Expectant management of small asymptomatic, sporadic, NF-PNETs could be a reasonable option in highly selected patients. However, the level of evidence is low and longer follow-up is needed to identify patients could benefit from upfront surgery instead of expectant treatment.

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Introduction

Pancreatic neuroendocrine tumors (PNET) are rare neoplasms with highly variable prognosis that is mainly influenced by tumor size, secretion, histological grade, and stage at the time of diagnosis.[1] Large, high-grade tumors tend to have a poor prognosis, whereas smaller and lower grade tumors can be curatively treated.[2–5] Advances in modern imaging technology have contributed to widespread use of computed tomography (CT) and magnetic resonance imaging (MRI). This has resulted in increased incidence of multiple diseases and possibly led to overtreatment of patients.[6] PNET is one such finding that has become more common in the era of modern imaging technology.[7,8]

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There is a consensus that patients with symptomatic or large (>2 cm) PNETs should undergo pancreatic resection.[9,10] However, controversy exists whether to resect small (≤2 cm), asymptomatic, and non-functional PNETs (NF-PNET). Some authors advocate surgery for all PNETs,[11–13] while recently others suggest that small, asymptomatic NF-PNETs are safe candidates for surveillance.[14–17] Similarly, some guidelines recommend upfront surgery,[18] while others acknowledge surveillance as an option.[19–21]

The aim of this study was to systematically review the current literature reporting results of surveillance of small NF-PNETs.

Methods

Search strategy

A systematic review of literature published in PubMed, EMBASE, and Cochrane Database from January 2000 to 3rd March 2016 was performed. The following search strategy for the MESH and non-MESH heading was used: ("neuroendocrine tumor*" or carcinoid or ((neuroendocrine or "neuro-endocrine") AND (cancer* or carcinom* or malignan* or neoplas* or tumor* or tumour*))) AND (pancrea* AND (cancer* or carcinom* or malignan* or neoplas* or tumor* or tumour*) OR ("pancreas tumor*" or pnet*)). Filters were used to exclude animal studies and non-English articles. Only relevant studies were selected via search terms for specific studies (epidemiology studies, cohort studies, clinical trials, retrospective/prospective studies, case–control studies).

Eligibility criteria and data collection

Titles and abstracts of found articles were independently screened by three reviewers. Unpublished data, abstracts, and duplicate publications were excluded. Original clinical studies of any level of evidence in English language were considered. Article full-texts of putatively relevant articles were retrieved and further screened for articles dealing with surveillance of PNETs. These articles were read and analyzed for eligibility by two reviewers (SV, LLTYS) independently. Disagreement was settled with discussion and/or participation of a third reviewer in the discussion (GS). Only studies were included in the final analyses, which defined non-operative expectant management for small NF-PNETs that had no metastases at the time of diagnosis. Studies were excluded if i) the study reported less than 10 patients with expectant management, ii) median follow-up was less than 18 months or not reported, iii) expectant management included specific treatment (such as somatostatin analogs), iv) observation group included patients with metastatic disease, and if non-metastatic tumors were not reported separately, v) the study did not report non-functional and functional PNETs separately, vi) the study did not report patient characteristics of patients undergoing expectant management separately from patients undergoing upfront surgery, or vii) the study did not report the sizes of the tumors accurately or did not report small and large tumor separately.

Data extraction

Patients with sporadic and MEN1 related NF-PNETs are reported separately. Outcomes measured were proportion of patients with growth of tumor in follow-up, the need for pancreatic resection, and the development of metastases (lymph node or distant). Standardized forms were used by two independent researchers (SV, LLTYS) to extract the data. Data regarding basic patient characteristics, tumor characteristics, type of diagnostic work-up, follow-up, tumor growth, surgery during surveillance, development of metastases during surveillance, reason for expectant management, and follow-up protocol were extracted. Quality of the studies was assessed using the Methodological Index for Non-Randomized Studies (MINORS)[22] by two independent reviewers (SV, LLTYS). Each study was assessed for eight MINORS items specifically designed for non-comparative studies with 0–2 points given each (total score 0–16). This article is reported in accordance with the guidelines set out by the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) statement.[23]

Statistics

Fixed and Random effect models of pooled proportions were performed using DerSimonian and Laird approach (Freeman-Tukey double arcsine transformation) by using R (R Foundation for Statistical Computing, Vienna, Austria). Ninety-five percent confidence intervals are presented for each effect measure. Heterogeneity was assessed by using the I^2 statistic. Funnel plots for proportion were used as an analytic tool to identify potential presence of publication bias using a Web-based software tool developed by APHO (Association of Public Health Observatories, www.apho.org.uk).

Results

Literature search

Literature search yielded 5440 articles, of which 107 full-texts were analyzed and finally 9 studies were included in the analyzes (Fig. 1). Eleven studies dealing with expectant management were excluded (Supplementary Table 1).

Characteristic of the studies

The nine included studies reported a total of 408 patients including 344 with a sporadic PNET and 64 with MEN-1 related PNET (Tables 1,2, Supplementatry Table 2). Median age ranged from 32 to 68 years undergoing expectant management of small NF-PNETs. Patients with MEN1-related tumors were younger (median age ranging 32–42) than patients with sporadic tumors (median age ranging 56–68) (Supplementary Table 2).

Six were single center studies, two included patients from two centers,[15,24] and one from four tertiary centers.[25] Study inclusion period varied between 11 and 32 years. Rationale for expectant management was disclosed in three studies (n = 76) and included the following reasons: small incidental tumor, patients' personal

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