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Review

Squamous cell carcinoma of the pancreas: A systematic review and pooled survival analysis

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Abstract The diagnosis and treatment of squamous cell carcinoma of the pancreas pose dilemmas in the clinical practice. The present study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Eligible articles were sought in MEDLINE up to 30th April 2016. A pooled Cox regression analysis was performed to evaluate factors potentially associated with overall survival (OS) and relapse-free survival (RFS). Fifty-four cases of pure squamous cell pancreatic carcinomas were identified in total. The mean age was 61.9 years, and most patients were males (61.1%). The median OS was 7 months. Resectability ($p = 0.003$) and more recent publication year ($p < 0.001$) were associated with better OS, as was low/intermediate tumour grade ($p = 0.032$) with RFS. Despite its poor prognosis, survival rates of pancreatic squamous cell carcinoma seem improved during the recent years; resectability and low/intermediate grade emerged as favourable prognostic factors. Collaborative epidemiological studies are deemed necessary to further validate the results stemming from the published case reports of this rare entity.

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1. Introduction

Pancreatic cancer is among the five leading causes of cancer-related deaths both in Europe and the United States of America, although the incidence of pancreatic carcinomas is relatively low; survival rates remain dismal for all cancer stages [1,2]. In addition, death rates slightly increase over the years, indicating the poor response to the available therapeutic regimens, whereas the new therapies are of limited efficacy [1].

Regarding the histological classification of pancreatic neoplasms, the majority are non-endocrine tumours with ductal adenocarcinoma representing the most common entity (85–90%) [1]. Primary pure squamous cell carcinoma of the pancreas accounts for 0.5–5% of all exocrine neoplasms and is viewed as an aggressive subtype with poor prognosis [3]. The pathogenesis of pure squamous cell carcinoma of the pancreas remains elusive. Several theories have been proposed such as the transformation of squamous metaplasia to malignancy or transition of pre-existent adenocarcinoma to squamous cell carcinoma, or even the emergence from a precursor progenitor cell [3–5]. Due to the fact that squamous cells do not normally exist in the pancreatic parenchyma, an extensive workup for another primary squamous cancer site including imaging modalities and endoscopic series is necessary in order to exclude any possibility of metastatic origin [4,6,7].

The present systematic review and pooled analysis aims to describe the characteristics of this rare entity and provide insight into factors potentially modifying its survival, including patients' features (sex and age), tumour features (location in the pancreas, grade, size, nodal status, presence of metastasis and resectability) and time trends (expressed as publication year). To our knowledge, this is the first systematic review and pooled analysis to synthesise all relevant data in this field.

2. Materials and methods

2.1. Search strategy and eligibility of studies

This systematic review and pooled analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (PRISMA checklist in Supplemental Table 1) [8]. The study protocol was discussed and agreed upon in advance by all authors. Potentially eligible studies were retrieved in MEDLINE with the end of search date 30th April 2016, using the following search algorithm: (pancreatic OR pancreas) AND (cancer OR carcinoma OR carcinomas OR neoplasm OR neoplasms) AND squamous. Only articles written in English, French, German or Spanish were considered eligible. Moreover, a 'snowball' procedure was conducted; reference lists of the eligible articles and relevant reviews were systematically screened in order to detect relevant publications. Eligible articles included prospective and retrospective studies, along with case reports and case series, all referring to humans. Studies referring to adenosquamous carcinoma were considered irrelevant and were therefore excluded from the present review. Furthermore, one unpublished case of squamous cell pancreatic carcinoma from the Cytopathology Department, Hygeia Hospital, Athens, Greece, was included. Two independently working reviewers (INS, PK) carried out the selection of studies, and final decision was reached after team consensus in case of discrepancies.

2.2. Data extraction

The extraction of data comprised first author's name, publication year, age, sex, ethnicity or country, reported risk factors, history of cancer/other dysplasia/human papillomavirus (HPV), clinical symptoms, blood test abnormalities, diagnostic tests and description of their findings, tumour markers such as carcinoembryonic antigen (CEA) and Cancer antigen 19-9 (CA 19-9), tumour location and size, nodal status, the presence of metastasis, tumour stage and grade, perineural and vascular invasion, way of ascertainment that the squamous pancreatic cancer was primary, immunohistochemical indices, surgical treatment, postoperative hospitalization in days, postoperative complications, postoperative mortality and residual disease, revision operations and re-admission, other treatments such as chemotherapy and radiotherapy, cause of death other than squamous carcinoma of the pancreas, overall survival (OS) and finally relapse-free survival (RFS). Notably, the data regarding one case report [9] were based on those reported by Brown *et al.* [10] due to the inability of obtaining the full text of the corresponding paper. Two reviewers working separately (INS, DIT) performed the data extraction, while any discordance was resolved following consensus among all authors.

2.3. Statistical analysis

The pooled analysis (quantitative synthesis) of the eligible studies included two sets of calculations. At first, the descriptive statistics were calculated, and Kaplan–Meier survival curves were estimated for OS, separately by resectability and publication year, in order for the results to be presented graphically. Second, factors that were potentially associated with RFS and OS were evaluated by performing univariate Cox regression analyses. The examined factors were as follows: categorical variables including sex (male versus female), tumour location (head versus body/tail versus multiple), nodal status (yes versus no), metastasis (yes versus no), grade (high versus low/intermediate) and resectability (yes versus no), as well as continuous variables including age (1 year increment), publication year (1 year increment) and tumour size (1 cm increment).