Original Article

Outcome of head compared to body and tail pancreatic cancer: a systematic review and meta-analysis of 93 studies

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Background: Even when resectable pancreatic cancer (PC) is associated with a dismal prognosis. Initial presentation varies according with primary tumor location. Aim of this systematic review and meta-analysis was to evaluate the prognosis associated with site (head versus body/tail) in patients with PC.

Methods: We searched PubMed, Cochrane Library, SCOPUS, Web of Science, EMBASE, Google Scholar, LILACS, and CINAHL databases from inception to March 2018. Studies reporting information on the independent prognostic role of site in PC and comparing overall survival (OS) in head versus body/tail tumors were selected. Data were aggregated using hazard ratios (HRs) for OS of head versus body/tail PC according to fixed- or random-effect model.

Results: A total of 93 studies including 254,429 patients were identified. Long-term prognosis of head was better than body/tail cancers (HR =0.96, 95% CI: 0.92–0.99; P=0.02). A pooled HR of 0.95 (95% CI: 0.92–0.99, P=0.02) from multivariate analysis only (n=77 publications) showed that head site was an independent prognostic factor for survival.

Conclusions: Primary tumor location in the head of the pancreas at the time of diagnosis is a predictor of better survival. Such indicator should be acknowledged when designing future studies, in particular in the operable and neoadjuvant setting.

Keywords: Pancreatic cancer (PC); head; tail; survival; meta-analysis

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Introduction

Pancreatic cancer (PC) is a very lethal disease associated with very poor 5-year survival rates generally not exceeding 10 percent (1). Ductal adenocarcinoma is by far the most common histologic subtype, accounting for about 85 percent of all pancreatic tumors.

Surgery is the only potentially curative option, with adjuvant chemotherapy adding a modest survival benefit (2). However, relapse after pancreatectomy is frequent and has a dramatic impact on final outcome.

According to primary tumor location initial presentation may vary. The vast majority of PCs involve the head of the organ, while 20 to 25 percent are located in the body/tail (3). Therefore, patients with tumors originating in the head often present with jaundice whereas pain and weight loss are typical symptoms of body/tail cancers. Pancreatic head tumors usually cause progressive jaundice with secondary

hyperbilirubinemia due to the obstruction of the common bile duct. Accompanying symptoms are represented by pruritus, dark urine, and pale stools. Hyperbilirubinemia is characteristically of the cholestatic type, with a predominant increase in its conjugated fraction.

Several studies have suggested that the anatomic location of pancreatic tumors represent a potential determinant of survival (4-6). Thus, we performed a systematic review of the literature currently published on this topic and a meta-analysis of the available studies with the aim to demonstrate possible clinically meaningful differences in outcome of PCs located in the head, compared with those of the body and tail.

Methods

This systematic review was conducted according to PRISMA guidelines and the Cochrane Handbook for Systematic Reviews of Interventions. Due to the nature of the study, it did not require any ethics approval.

Search strategy

An electronic search of PubMed, the Cochrane Library, SCOPUS, Web of Science, EMBASE, LILACS, and CINAHL from inception to April 2018 was performed in order to identify all the eligible publications. Searches used the following keywords: ("Pancreatic Neoplasms"[Mesh] OR "pancreatic cancer" OR "pancreatic carcinoma" OR "adenocarcinoma of the pancreas") AND (head and tail) AND survival. Additionally, a manual selection of any potential eligible studies was carried out with the related articles function. The references of all selected articles were analyzed to identify other relevant publications.

Study selection and data extraction

The following criteria for eligibility among studies were identified for selecting the articles: (I) site of PC was reported (head *vs.* tail or vs body/tail if site was not splitted); (II) survival information [overall survival (OS), progression-free survival (PFS) or disease-free survival (DFS)] at specific follow-up was reported in the article as hazard ratio (HR) according to univariate or multivariate Cox regression analysis, after primary tumor location was significantly associated with outcome in univariate analysis; (III) articles were written in English language; (IV) when several articles were published by the same authors or group, the most updated article was considered. Exclusion criteria were: (I) no information on OS or PFS provided; (II) letters to editor/commentary, reviews, and articles published in a book or papers published in a non-English language; (III) clinical studies presenting odds ratios or risk ratios as measure of effect; and (IV) studies including non-adenocarcinoma histologies or other gastrointestinal carcinomas.

Two authors (FP and GT) conducted the search and independently identified the relevant studies, and the selection of an article was reached by consensus with a third author (MG). The following information was extracted from each article by the two authors: author/year of publication, country, patient number, type of study, stages (I–III *vs.* IV), adjuvant or palliative chemotherapy exposure (rate), survival data [reported as HRs with 95% confidence interval (95% CI)].

Statistical analysis

For analysis of OS and PFS, HRs were aggregated to provide a pooled value. In this analysis, all HRs with 95% CIs obtained from uni- or multi-variate analysis, and available in the articles were combined, to obtain a prognostic information on the location of the primary tumor (cancers of the head vs the tail of pancreas), independent of other clinicopathological covariates. Sensitivity analysis was performed according to race (Asian *vs.* non-Asian origin participants), the number of patients > *vs.* < of the median number), stage (I–III *vs.* IV), year of publication (<2006 *vs.* 2006–2016), quality (high *vs.* low-quality papers) and type of study (retrospective *vs.* prospective). To explore the impact of inter-study variability in the inclusion of different stages of PCs, we also conducted a multivariate random-effect model meta-regression of OS adjusted for the proportion of patients that received surgery. Data were entered into the Comprehensive Meta-Analysis software v 3.3.070 (November 20th, 2014) and RevMan v 5.3. The Cochran's test was used to assess the heterogeneity of included studies. For heterogeneity tests, P value <0.05 was considered to indicate significance. If the test of heterogeneity was significant (P<0.05 or I^2 >50%), the random-effect model was used to pool the estimate across studies with the Der Simonian-Laird method. Otherwise, the fixed-effect model was used. By convention, an observed HR of <1 implied better survival for the pancreatic head cancers.

We used the Newcastle-Ottawa Scale (NOS) for risk of bias assessment (7). Studies with scores of at least 7 were

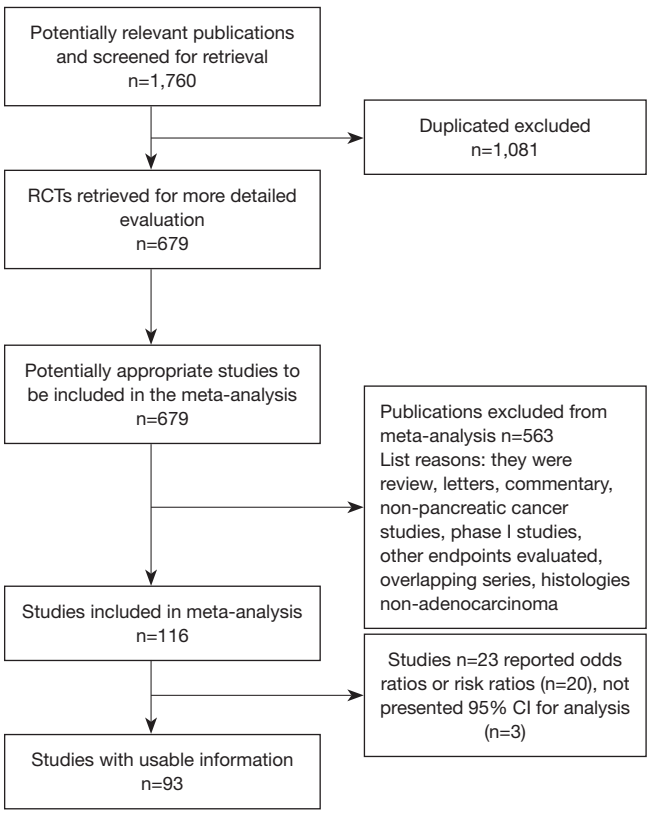

Figure 1 Overview of trials search and selection.

considered as having a low risk of bias. We assessed that follow-up was adequate if the median length was more than 5 years for early stages PC and more than 3 years for stage IV PC.

We finally investigated the publication bias for OS meta-analysis with funnel plots and with the Begg-Mazumdar Kendall's tau and Egger's bias test (8,9). Finally, in the presence of publication bias for the primary analysis, we conducted a trim-and-fill-adjusted analysis to remove the most extreme small studies from the positive side of the funnel plot, and recalculated the effect size at each iteration, until the funnel plot was symmetric about the (new) effect size.

Results

A total of 1,760 potentially relevant citations were reviewed (*Figure 1*). Among them, 23 reported OS data as risk ratios, odds ratio, or did not report 95% CI for inclusion in the final analysis. Ultimately, 93 studies (5,6,10-32) published from 1996 to 2018 (33-57), that reported the prognostic value of PC site were analyzed (58-82). The total number of patients included was 254,429 ranging from 25 to 52,759 patients per study (median, 209) (82-100). The major characteristics are shown in online table: http://jgo.amegroups.com/public/system/jgo/supp-jgo.2018.12.08.pdf.

In n=80 publications, a retrospective analysis of PC patients was presented; n=12 papers reported a prospective cohort series and one was a case-control study. According to race, the majority of patients were of Asian origin (n=55); the remaining n=38 publications included Caucasian subjects. Stages were mixed (I–IV) with n=11 studies including only locally advanced or metastatic disease. Surgery rate ranged from 0 to 100% (median 64%) with data not available in n=2 publications. Data about adjuvant chemotherapy was available in n=39 papers (median delivery rate 42%). In n=15 publications data about chemotherapy was not provided, in n=15 it was offered for advanced disease. The quality of paper expressed by the NOS scale ranged from 5 to 8, with 56% including studies of sufficient to high quality (mean NOS scale scores: 5.77).

Meta-analysis of OS

Because the heterogeneity test showed a high level of heterogeneity (I^2 =68%, P<0.001) between the studies, a random-effects model was used for the analysis. Overall prognosis of head was better than body/tail cancers (HR =0.96, 95% CI: 0.92–0.99; P=0.02; *Figure 2*). A pooled HR of 0.95 (95% CI: 0.92–0.99, P=0.02) from multivariate analysis only (n=77 publications) showed that head site was an independent prognostic factor for survival.

Meta-analysis of PFS

Data of PFS was available in n=13 studies with high heterogeneity (I^2 =64%, P<0.001), so a random-effects model was used for the analysis. PC of the head was associated with a similar PFS of tail cancers (HR =0.99; 95% CI: 0.84–1.16; P=0.91) (*Figure 3*).

Subgroup analysis

The subgroup analysis performed according to the number of patients (> or < of the calculated median number), showed that in largest studies (>182 subjects), the effect size was similar to general population: HR =0.93 (95% CI: 0.87–0.99; P=0.03) but different from smallest studies were effect size was not significant (HR =0.97, 95% CI: 0.91–1.04;

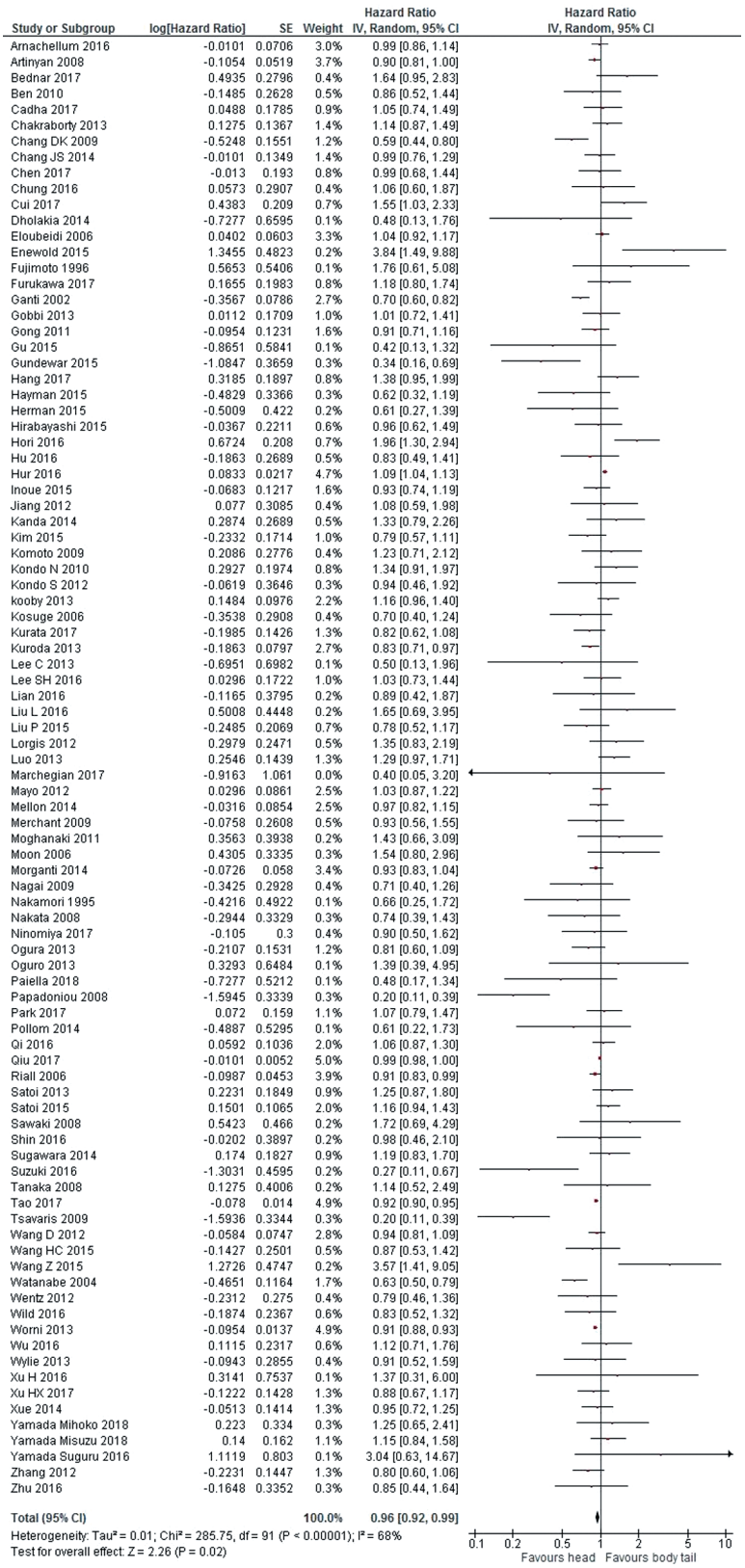

Figure 2 Overall survival according to site of pancreatic cancer.

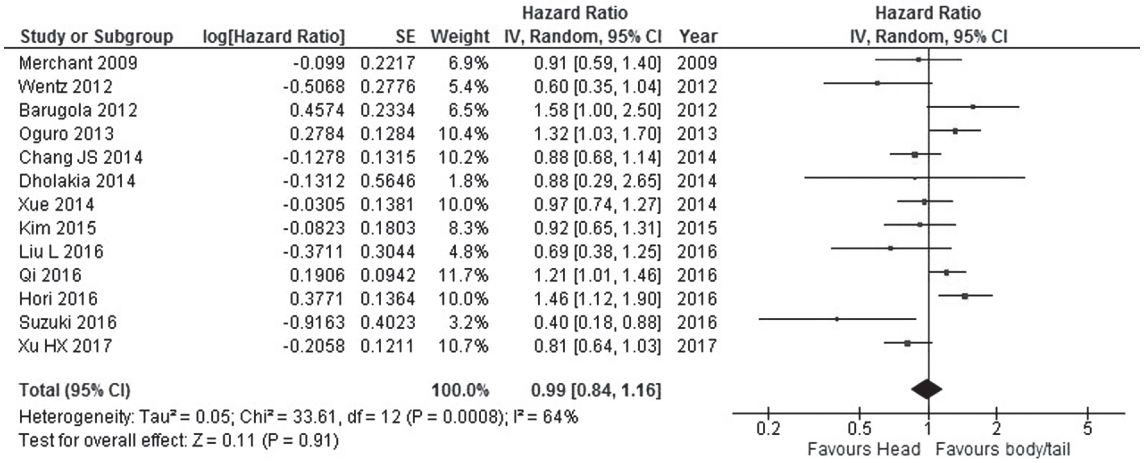

Figure 3 Disease-free survival according to site of pancreatic cancer.

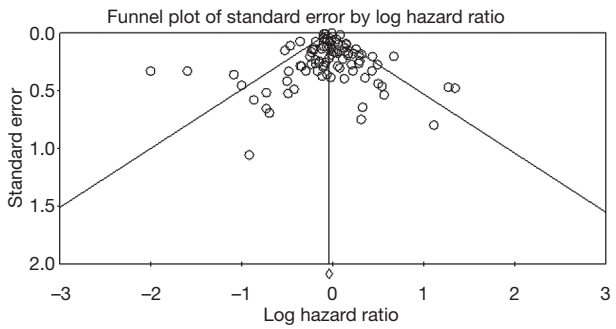

Figure 4 Funnel plot for publication bias.

P=0.5).

Analysis according to race (Asian *vs.* non-Asian) led to a similar effect on OS for head cancer (HR =0.92, 95% CI: 0.81–1.04 and HR =0.96, 95% CI: 0.90–1.02, P=0.2).

Both studies with prospective (HR =1.00; 95% CI: 0.94–1.09; P=0.6) and retrospective design (HR =0.95, 95% CI: 0.90–1.00; P=0.05) gave similar results. Results were instead different according to quality of the study, with significant results for those with NOS score ≥7 *vs.* <7 (HR =0.91; 95% CI: 0.88–0.93 and HR =0.93; 95% CI: 0.84–1.00, P<0.001 and P=0.2, respectively).

Results remained significant only considering studies published from 2007 and 2018 (HR =0.95, 95% CI: 0.91–0.99; P=0.02); conversely, in older studies, the prognostic effect of site was not significant. Studies that included only stage IV or locally advanced inoperable patients (n=13) showed a similar mortality of head and body/tail PCs (HR =1.01, 95% CI: 0.91–1.12). In studies where disease stages I–III were at least 90%, PC of the head had a trend to better OS than body/tail (HR =0.91; 95% CI: 0.82–1.00; P=0.07).

The funnel plot (P=0.45; *Figure 4*) and Egger test (P=0.19) did not indicate the existence of obvious publication bias.

Discussion

Treatment of PC is one of the biggest challenges in oncology. Surgical resection is the only chance for cure, but unfortunately, because of the late presentation of the disease, only 15 to 20 percent of patients are candidates for pancreatectomy. As a result, even after surgery, long-term prognosis remains very disappointing, with 5-year survival rates of about 30% after margin-negative (R0) pancreaticoduodenectomy for node-negative and 10% for node-positive disease (101).

Recent studies and meta-analyses have reported in tumors different from pancreas (e.g., colorectal and gastric) that the anatomic site of origin may have a significant impact on prognosis (102,103). This meta-analysis aimed at investigating possible differences in outcome between PCs arising in the head compared to body and tail.

Results of our study demonstrate that, although not particularly deep, a significant difference in prognosis exists. Specifically, patients with PC located in the head have a 5% reduced risk of death as compared with subjects affected by tumors arising in the body/tail.

Major reasons for such different prognosis probably rely on the lack of early symptoms at the time of initial presentation. Because ductal adenocarcinomas involving the

body or tail of the pancreas usually do not cause obstruction of the intrapancreatic portion of the common bile duct, early diagnosis is rare, therefore the majority have locally advanced or metastatic disease at the time of first diagnosis. Moreover, painless jaundice is a relatively early sign, and tumors arising from the pancreatic head have been reported to be associated with a relatively more favorable prognosis compared with those that present with pain and obstructive jaundice (104,105). Jaundice secondary to cancers of the body/tail frequently occurs at late disease stages and may be due to the presence of liver metastases. This observation is strengthened by the results of our subgroup analysis performed according to stages. In fact, although not statistically significant, a positive trend towards a survival benefit in favor of PC of the head has been found in patients diagnosed in stages I to III.

Beyond these clear differences in clinical presentation, the two entities probably retain distinct molecular features which may be responsible for a different biological behavior.

In this regard, very recently, a retrospective study tried to shed light on molecular heterogeneity according to tumor location in the pancreas. Specifically, by performing genomic analyses (whole genome and RNA sequencing) on 421 PC cases, authors were able to demonstrate that patients with tumors of the body and tail had significantly worse survival than those with pancreatic head tumors (12.1 *vs.* 22.0 months; P=0.001) (106). Primary tumor location in the body and tail was associated with the squamous subtype of PC. Body and tail PCs were also shown to be enriched for gene programs involved in tumor invasion and epithelial-to-mesenchymal transition, as well as features of poor antitumor immune response. Such aggressive behavior may therefore explain the worse prognosis associated with body and tail tumors. It still remains to be elucidated if these molecular alterations are present from the outset or develop at definite time points during tumor progression.

Ultimately, further results coming from our subgroup analysis conducted according to the year of publication, revealed a larger and significant OS benefit for pancreatic head cancers in more recent studies (from 2007 and 2017) compared to older ones. This probably reflects a general improvement over the years in surgical skills and imaging techniques which made it possible to reduce post-operative complications and enhance the possibilities of achieving earlier diagnoses, respectively. Historically, pancreaticoduodenectomy has always represented a complex surgical procedure associated with high perioperative morbidity and mortality rates. However, perioperative mortality drastically declined over the last few decades reaching in modern series rates of less than 4 percent (107-113). The main reason for this improved outcome is probably the increase in the proportion of patients undergoing surgery at higher-volume hepatobiliary centers. Centralization of pancreatic surgery can definitely improve outcomes as reported by a recent meta-analysis of 14 studies (114) in which a significant association between hospital volume and postoperative mortality (odds ratio 0.32, 95% CI: 0.16–0.64), and between hospital volume and survival (HR =0.79, 95% CI: 0.70–0.89) was demonstrated.

Our paper has some intrinsic limitations. First, only retrospective studies were included. Thus, since the indication and outcome after surgery depend on local surgeons and center preference, morbidity and mortality after resection were not standardized. Second, while in some studies location of cancer into the body and tail were aggregated and compared to head PC, in other tail cancers only were separated and compared with head PCs. Finally, a high heterogeneity was observed and, although the random effects model takes into account such heterogeneity among studies, conclusions should be interpreted with caution.

In conclusion, our study confirms that primary tumor location in the head of the pancreas at the time of diagnosis is a significant predictor of better survival. Although prognosis of patients with PC remains poor, such indicator deserves to be acknowledged when designing future trials, particularly in the operable and neoadjuvant setting. Hopefully the constant progresses in the field of precision medicine will allow oncologists to identify the exact molecular profile of the single patient which better correlates with long-term outcome. This will be fundamental to spare patients from high morbidity surgical procedures and select those who will benefit most from adjuvant treatments.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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