

REVIEW ARTICLE

A systematic review of the role of periadventitial dissection of the superior mesenteric artery in affecting margin status after pancreatoduodenectomy for pancreatic adenocarcinoma

James R. Butler¹, Syed A. Ahmad², Matthew H. Katz³, Jessica L. Cioffi¹ & Nicholas J. Zyromski¹

¹Indiana University School of Medicine, Department of Surgery, Indianapolis IN, ²The University of Cincinnati Cancer Institute, Cincinnati OH, and ³Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Abstract

Background: Resectable pancreatic ductal adenocarcinoma continues to carry a poor prognosis. Of the controllable clinical variables known to affect outcome, margin status is paramount. Though the importance of a R0 resection is generally accepted, not all margins are easily managed. The superior mesenteric artery [SMA] in particular is the most challenging to clear. The aim of this study was to systematically review the literature with specific focus on the role of a SMA periadventitial dissection during PD and its effect on margin status in pancreatic adenocarcinoma.

Study design: The MEDLINE, EMBASE and Cochrane databases were searched for abstracts that addressed the effect of margin status on survival and recurrence following pancreaticoduodenectomy [PD]. Quantitative analysis was performed.

Results: The overall incidence of a R1 resection ranged from 16% to 79%. The margin that was most often positive following PD was the SMA margin, which was positive in 15–45% of resected specimens. Most studies suggested that a positive margin was associated with decreased survival. No consistent definition of R0 resection was observed.

Conclusions: Margin positivity in resectable pancreatic adenocarcinoma is associated with poor survival. Inability to clear the SMA margin is the most common cause of incomplete resection. More complete and consistently reported data are needed to evaluate the potential effect of periadventitial SMA dissection on margin status, local recurrence, or survival.

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Correspondence

Nicholas J. Zyromski, MD, Indiana University School of Medicine, Department of Surgery, 545 Barnhill Dr., Emerson Hall 519, Indianapolis, IN 46202, USA. Tel: +1 317 274 5012. E-mail: nzyromsk@iupui.edu

Introduction

Among patients who undergo pancreatoduodenectomy (PD) for pancreatic adenocarcinoma (PDA), multiple clinical variables have been determined to be associated with postoperative prognosis.^{1,2} Of these, margin status appears to be one of the most important.³ The American Joint Committee on Cancer staging guidelines have attempted to standardize the pathologic evaluation of PD specimens to facilitate margin assessment.⁴ According to these guidelines, PD specimen margins that should be evaluated by the pathologist include the pancreatic

neck, bile duct, duodenum, stomach, as well as the superior mesenteric artery margin. The last of these margins, referred to as the SMA- or uncinete-margin, is specifically emphasized. Recent work by Verbeke *et al.*, has illustrated that standardization of the histopathological examination of PD specimens can allow for a tighter correlation between histological staging and outcomes.^{5,6}

The SMA margin comprises the tissue that connects the uncinete process to the right lateral border of the proximal 3–4 cm of the SMA (Fig. 1). PDA has a propensity to spread through this tissue along the perineural autonomic plexus that surrounds the

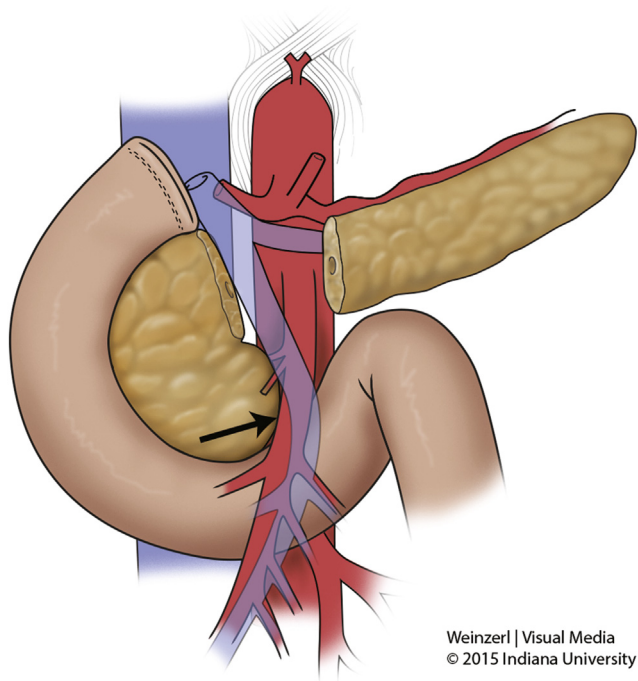


Figure 1 Superior mesenteric artery margin. Negative resection margin in the uncinate process is complicated by its proximity to the superior mesenteric artery

artery. The SMA margin is similar to the mesorectal margin emphasized during rectal surgery. However, the SMA cannot be removed and reconstructed at surgery in the absence of considerable morbidity. Many surgeons therefore strongly recommend that a periadventitial dissection of the SMA be performed at PD to skeletonize the right lateral aspect of the vessel from the uncinate process and adjacent tissues, to maximize the likelihood of obtaining a negative margin in the retroperitoneum.

Although this recommendation is commonly made, the association between the status of the SMA margin and oncologic outcomes is unclear. Indeed, the incidence of a positive SMA margin and any association between margin status and outcome may also reflect “tumor biology” rather than surgical approach or technical skill.^{1,7} The contribution of this specific surgical technique to postoperative outcome is therefore incompletely understood. The aim of this systematic review of the literature was to determine current reporting practices and the effect on outcomes of performing a periadventitial dissection of the SMA during PD.

Methods

The MEDLINE, EMBASE and Cochrane databases were searched for English-language articles published from January 1990 through January 2014 that addressed the effect of margin status

on survival and recurrence following PD. Search terms for “pancreas,” “retroperitoneal margin,” “pancreaticoduodenectomy,” “Whipple,” “margin,” “SMA dissection,” “mesopancreas,” “retroperitoneal dissection,” “morbidity,” and “uncinate dissection” were queried both in isolation and combination; duplicate references were removed prior to analysis.

The two investigators who performed the primary search (SAA and NJZ) independently reviewed the titles and abstracts of all returned references regardless of publication status to identify studies for inclusion in the analysis. Inclusion criteria dictated that articles selected for analysis focused on margin status following PD, and reported outcomes related to margin status. Review articles, and studies failing to document follow-up interval were excluded. All identified articles were examined using a predesigned proforma and the data collected were entered into a database for subsequent analysis. Articles selected for the analysis were specifically scrutinized for standardization of the surgical technique for SMA dissection, pathologic evaluation of the retroperitoneal margin, and margin status-related outcomes including local recurrence and overall survival. The methodological quality of studies was assessed for a minimum Oxford Center for Evidence-Based Medicine (CEBM) level of 2C.⁸

Results

The initial search yielded 520 unique articles; from these, 43 were selected for quantitative analysis. Fig. 2 documents flow of references through the systematic review. The articles selected for analysis focused specifically on pancreas cancer, commented on margin status following PD, and reported outcomes related to margin status. Of the 43 articles selected, 5 were prospective trials; the others were retrospective reviews of institutional databases (37 articles) or national registry data (1 article). The overall reported incidence of a R1 resection ranged from 16% to 79%. The margin that was most often positive following PD was the SMA margin. It was positive in 15–45% of resected specimens, and was implicated in 46–88% of R1 resections.

Retrospective studies of margin status, survival, and local recurrence

Thirty-eight retrospective studies meeting the eligibility criteria were evaluated with a minimum evidence level of 2C (Table 1). Only 16 studies reported the status of different margins individually; among these 16 studies, the SMA margin was the most frequently positive margin. None specifically evaluated the potential effect of periadventitial SMA dissection on margin status, local recurrence, or survival.

Among the 38 retrospective studies, 33 concluded that a positive resection margin (any margin) correlated with poorer overall survival, whereas 5 reported that margin positivity did not influence survival. Only 5 studies commented on the

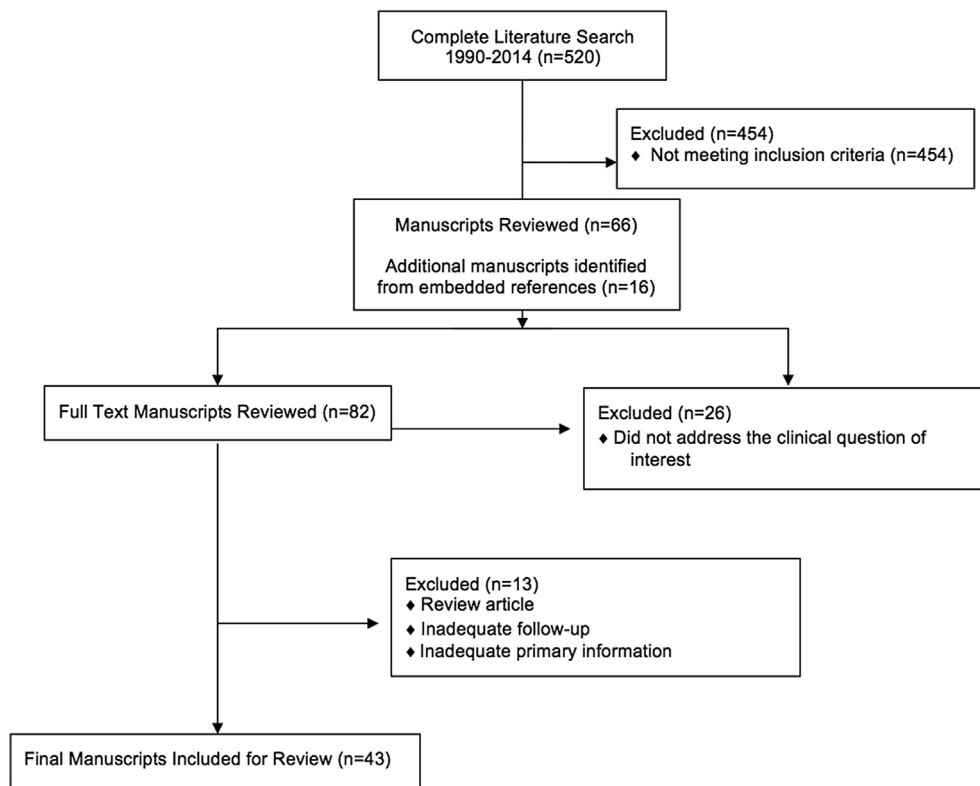


Figure 2 Flow of references through the review. The above diagram illustrates the assessment and allocation of references through the systematic review

influence of margin status on local recurrence: three studies found that margin status had no effect on the incidence of local recurrence, and 2 found that the local recurrence rates of patients with positive resection margins were higher than those of patients with negative resection margins.

Prospective studies of margin status, survival, and local recurrence

Since 1990, five prospective randomized studies (Table 2) from Europe and North America have investigated the influence of resection margins on survival and local recurrence following

Table 1 Retrospective studies on margin status after pancreatoduodenectomy

R0 definition category	n studies, (n combined patients)	R1 median%	SMA+ median%	Studies reporting observed effect of margin status on survival	Studies reporting observed effect of margin status on LR
R0 not defined ^a	16 (3674)	35% (range 16–60)	50% (range 46–73)	14 + 2 – 0 NR	1 + 0 – 15 NS
R0 = 0–1 mm ^b	14 (16,022)	28% (range 17–64)	63% (range 55–88)	11 + 3 – 0 NR	1 + 2 – 11 NR
R0 = >1 mm ^c	8 (1201)	57% (range 34–79)	47% (range 38–80)	8 + 0 – 0 NS	0 + 1 – 7 NR

Abbreviations: SMA+, superior mesenteric artery responsible for R1 designation; LR, local recurrence; NR, not reported; +, positive association; –, negative association. The grade of evidence of all papers is 2C.⁸

^a Refs. 2,3,17,18,21–32.

^b Refs. 7,16,33–44.

^c Refs. 6,45–51.

Table 2 Prospective studies on the margin status and pancreatoduodenectomy

Author, year	n	R0 definition	Patients with margin-positive resection (%)	Effect of margin status on survival	Grade of evidence
Klinkenbijn <i>et al.</i> , 1999	218	None	22	NR	2C
Neoptolemos <i>et al.</i> , 2004	289	None	18	+	2A
Regine <i>et al.</i> , 2008	451	None	34	+	2A
Oettle H <i>et al.</i> , 2013	368	None	17	+	2A
Delpero <i>et al.</i> , 2014	150	Stratified A) 0–1 mm B) 1.0–1.5 mm C) 1.5–2 mm D) >2 mm	Stratified A) 23 B) 61 C) 63 D) 71	+	2A

Abbreviations: NR, not reported. The grade of evidence was assessed by the Oxford Center for Evidence-Based Medicine (CEBM) level of 2C.⁸

PD.^{9–13} Only one of these prospective studies specifically addressed the loci of margin positivity¹³; this study found that SMA margin positivity was significantly affected by R0 definition and ranged from 23% positivity at 0–1 mm clearance to 58% positivity at >2 mm clearance. No prospective studies specifically evaluated the potential effect of periadventitial SMA dissection on margin status, local recurrence, or survival.

In addition to the variable or absent reporting of R0 definitions noted, several other causes of heterogeneity were identified across studies (Table 3). Although all 43 of the included studies utilized patient survival as a primary endpoint, margin localization, local recurrence and systemic recurrence rates were inconsistently reported. Operative technique used to address the vascular margin included documentation of a periadventitial dissection in 11/43 studies.

Discussion

Modern advancements to the surgical management of pancreatic carcinoma have centered upon improved identification and selection of operative candidates. Adjuvant therapies, evolving operative and postoperative management strategies have also had measurable effects on mortality and morbidity rates. Despite these advances, the current 5-year survival of patients undergoing operation with curative intent only approaches 25%.¹ Moving forward, better understanding the variables that affect prognosis will be paramount to optimizing surgical management

of pancreatic carcinoma. Gene mutation analysis and biomarker studies are currently promising but have yet to offer direct clinical application.^{14,15} At the tissue level, margin status, poorly differentiated histology, larger tumor size, lymph node or vascular involvement, and perineural spread have all been identified as indicators of poor prognosis.^{2,3,16–18} Although margin status has recently received considerable attention, there has been infrequent emphasis given to the *locus* of margin positivity.

This study systematically reviews the literature on the topic of margin status after resection for pancreatic cancer. The SMA margin is most commonly positive in R1 resections. It is positive in up to 45% of patients undergoing operation with curative intent. This is most likely related to the close proximity of the tumor to the perineural plexus surrounding the SMA and the inability to resect additional tissue when the surgeon is confronted with a positive margin along the artery. Unfortunately the current body of literature does not support a quantitative meta-analysis. Several methodological limitations affecting the included *retrospective* studies are worthy of discussion. First, a standardized surgical technique used to clear the margins (e.g., whether a periadventitial dissection of the SMA was performed in all cases) was not routinely reported. Furthermore, the definitions of “R0” and “R1” were not applied consistently: 16 studies did not provide a specific definition of an R0 resection, 14 reports defined R0 as the microscopic absence of any tumor cells at the margin, and 8 reports, mostly from European investigators,

Table 3 Reporting practices in literature involving margin status after pancreatoduodenectomy

Margin status reported	Periadventitial dissection of SMA reported	Local recurrence rate reported	Systemic recurrence rate reported
Not localized 27/43 SMA 17/43 Pancreatic neck 15/43 Duodenum 4/43 Bile duct 11/43	Yes 11/43 No 32/43	Reported 11/43 Not reported 32/43	Reported 10/43 Not reported 33/43

Reporting practices of localized margin positivity, periadventitial SMA dissection, local recurrence, and systemic recurrence varied among studies identified within this review.

defined an R0 resection as no tumor cells >1 mm from the cut edge of the specimen (Table 1). Not surprisingly, investigators who applied more stringent definitions of R0 resection (i.e., a clear margin >1 mm) reported higher rates of R1 resection. A standardized system for naming, processing and evaluating the surgical margins was not applied consistently. Finally, many studies used both univariate and multivariate analyses to assess the association between margin status and survival. In some of these studies, the univariate analysis, but not the multivariate analysis, revealed that margin status significantly affected survival. In other studies, the effect of margin status on survival was evaluated by comparing Kaplan–Meier survival curves for margin-negative patients to those of margin-positive patients (e.g., by Cox log-rank analysis).

Although the *prospective* studies included in this review associate margin status with survival, their heterogeneity also prohibits meta-analysis. Three of the five studies did not mandate that a standard surgical technique be used or a pathologic review be performed, and only two of the studies specifically excluded patients with R2 resections. As an example, the Charité Oncology 001 study^{11,19} randomized 354 patients to surgery followed by observation or adjuvant gemcitabine. The authors reported an overall margin-positive rate of 17% and found that gemcitabine improved survival following either margin-positive or margin-negative resection but seemed to offer more benefit following margin-positive resection. However, no specific information about the SMA margin or its association with either survival or patterns of recurrence was provided. Although one prospective study reported the oncologic status of the SMA margin independently, it did not independently link arterial margin positivity to recurrence or survival outcomes. Furthermore, this study found that SMA margin positivity was significantly affected by R0 margin definition distance. This finding is not surprising as when systematically inked, tumor clearance margin was found to range from 0.2 to 30 mm, further underscoring the need for a unified R0 margin definition.¹³

In addition to pathology reporting at the SMA margin, the pancreatic neck, bile duct and duodenal margin are also important in determining outcomes. Not surprisingly, technical details of margin clearance and outcomes data (i.e. local and systemic recurrence) were quite heterogeneous as documented in Table 3. These variably reported findings further emphasize the critical need for standardized definitions and reporting of in order to accurately study outcomes of resected pancreatic cancer patients. Informed reporting will only be possible with standardized definitions.

Thus, the current literature supports the importance of a R0 resection in the surgical management of pancreatic carcinoma. The margin most often positive is the SMA margin. Both a unified definition of margin negativity and universal reporting of positive margin locus will be required to better understand outcomes for patients with tumor involvement at resected margins.

Although a periadventitial dissection of the right lateral aspect of the SMA is commonly advocated as a critical technical aspect of PD,¹⁶ no existing studies specifically address the impact of this technique on rates of margin positivity, local recurrence, or overall survival relative to a less radical resection. Similarly, “artery first” techniques have become a topic of recent interest in attempt to provide better local clearance at the SMA margin²⁰; understanding the effect of these approaches would also benefit from more complete reporting within the literature.

The SMA margin is the most commonly positive margin following PD, and most prospective and retrospective studies demonstrate improved survival when negative margins are achieved. Thus although a periadventitial SMA dissection that maximizes clearance at the arterial margin would seem to offer intuitive benefit, the heterogeneity of reported data does not support a direct appraisal of this practice.

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Conflicts of interest

None declared.

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