



Research Paper

Geographic variation in attitudes regarding management of locally advanced pancreatic cancer[☆]



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ABSTRACT

Background: Recent literature suggests wide variations exist in the international management of locally advanced pancreatic cancer. This study sought to evaluate how geography contributes to variations in management of locally advanced pancreatic cancer.

Methods: An electronic survey investigating preferences for the evaluation and management of locally advanced pancreatic cancer was distributed to an international cohort of pancreatic surgeons. Surgeons were classified according to geographic location of practice, and survey responses were compared across locations.

Results: A total of 153 eligible responses were received from 4 continents: North and South America (n = 94, 61.4%), Europe (n = 25, 16.3%), and Asia (n = 34, 22.2%). Preferences for the use and duration of neoadjuvant chemotherapy and radiotherapy varied widely. For example, participants in Asia commonly preferred 2 months of neoadjuvant chemotherapy (61.8%), whereas North and South American participants preferred 4 months (52.1%), and responses in Europe were mixed (P = .006). Participants in Asia were less likely to consider isolated liver or lung metastases contraindications to exploration and consequently had a greater propensity to consider exploration in a vignette of oligometastatic disease (56.7% vs North and South America: 25.6%, Europe: 43.5%; P = .007).

Conclusion: In an international survey of pancreatic surgeons, attitudes regarding locally advanced pancreatic cancer and metastatic disease management varied widely across geographic locations. Better evidence is needed to define optimal management of locally advanced pancreatic cancer.

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is expected to become the second leading cause of cancer-related mortality by 2030 [1], and therapeutic advances remain slow. This is particularly true for the approximately 30% of patients who present with locally advanced pancreatic cancer (LAPC) that extensively involves the surrounding vasculature and makes curative-intent resection more challenging. Although a multitude of retrospective studies report encouraging survival after neoadjuvant therapy and resection in selected patients with LAPC

[2–4], there remains a lack of consensus for the optimal multidisciplinary management of this complex patient cohort. Recent studies have highlighted wide variations among institutions and providers regarding critical aspects of LAPC care, including preferences for evaluation and management, attitudes regarding treatment contraindications, classifications of resectability, and eligibility for exploration [5–7]. These inconsistencies in self-reported attitudes and practice persist even among the highest-volume pancreatic surgeons internationally [8].

Although numerous studies have reported wide variations in LAPC management, few studies have investigated provider characteristics associated with the observed variations [8]. Geographic location of practice is one such characteristic that has been identified as a major contributor to wide variations observed in both medical [9] and surgical treatments [10] and a broad range of health care services [11–13]. In addition, geographic variations have been reported to influence cancer care at all levels of analysis, from global variations among continents to local variations at the levels of county, zip code, or hospital referral region [9,14–16]. These regional differences persist across a diverse range of malignancies, including breast [17–20], colon [10], prostate [21,22], endometrial [23], and liver [24] cancers, among others. In some circumstances, geographic variations have been shown to impact health outcomes [25,26]. However, the extent to which geography is associated with management of LAPC is unclear.

In this context, we sought to better understand how geographic location of practice contributes to variations observed in the multidisciplinary management of LAPC. To do this, we leveraged data from a previously published international survey [5] of pancreatic cancer surgeons to examine the association between geographic location of practice (by continent) and self-reported attitudes regarding the evaluation and management of LAPC, contraindications to surgery, and the propensity to consider exploration. Although causes of variation in complex multidisciplinary management are no doubt multifactorial, studies of associated provider characteristics could offer insight into factors contributing to practice variation and may inform the development and implementation of interventions to reduce unwarranted variations in practice and potentially improve outcomes.

METHODS

Study Design and Participants. This study used data from a recently published international survey distributed to pancreatic surgeons via web-based survey platform (Qualtrics, Provo, UT) [5]. Potential respondents were identified using a PubMed literature search and publicly available lists from various pancreatic cancer-focused organizations and were distributed within multiple international surgical societies and the Americas Hepato-Pancreato-Biliary Association. Responses from surgeons that have operated on PDAC within the last 5 years were included for final analysis, whereas surveys with <50% of items completed or those completed by medical students, surgical residents, or surgeons involved in survey creation were excluded. This study was determined to be exempt by the Johns Hopkins Medicine institutional review board.

Survey Content and Methodology. The survey tool was developed using a previously published tool of similar scope and content [27] and was iteratively refined over 3 months. The full survey is available as an appendix to the original article [5]. The final survey consisted of 5 sections. The first section evaluated practice characteristics such as geographic location, years in practice, clinical focus, and availability of PDAC specialists. The second investigated clinical volumes and preferences for the initial evaluation of LAPC patients. The third section explored preferences for LAPC management, whereas the fourth examined attitudes regarding contraindications to surgery following neoadjuvant therapy. The fifth section investigated the propensity to consider exploration in 6 clinical vignettes of LAPC or oligometastatic disease with good response to neoadjuvant therapy (accompanied by

videos of post-neoadjuvant arterial- and venous-phase computed tomography imaging) and the rationale for recommendations chosen [5]. In all clinical vignettes, the post-neoadjuvant imaging showed no evidence of progression or metastases. All 6 cases were based on actual patients that underwent R0 resection, although respondents were unaware of resection status at the time of survey completion.

Study Exposure and Statistical Analysis. To evaluate the relationship between survey responses and geographic location of practice, in this study, surgeons were categorized into 3 groups according to the continent in which they practice: North or South America, Europe, and Asia. For the primary analysis, surgeon characteristics, preferences for the evaluation and management, and the propensity to consider exploration and resection for 6 clinical vignettes were compared across geographic categories. Descriptive statistics are presented as number (percent) or median (interquartile range) for parametric and nonparametric data, respectively. Missing data, when present, are included in the analysis, resulting in some values that equal less than 100%. For all statistical tests, *P* values are 2 tailed, and α is set at .05. All analyses were performed using STATA version 16.1 (StataCorp, College Station, TX) [5].

RESULTS

Between July and December of 2018, 177 participants completed the survey, yielding an estimated response rate of 10.6% [5]. Nine surgeons reported not having operated on a patient with PDAC within 5 years, 3 participants identified as surgical residents, and 3 identified as medical students. An additional 9 partially completed surveys were excluded, leaving 153 eligible responses.

The characteristics of respondents according to geographic location of practice are shown in Table 1. A majority of respondents reported practicing in North and South America (NSA, $n = 94$, 61.4%), whereas 16.3% ($n = 25$) practice in Europe and 22.2% ($n = 34$) practice in Asia. The self-reported focus of surgical practice for a majority of respondents from the Americas was surgical oncology (40, 42.6%), while a majority of those in Europe (19, 76%) and Asia (27, 79.4%) identified their primary focus as hepato-pancreato-biliary (HPB) surgery ($P = .01$). Surgeons practicing in the Americas reported fewer years in practice (median 10 years, IQR [5–17]) as compared to those in Europe and Asia (14, IQR [6–25] and 15, IQR [9–20], $P = .02$). When *high volume* thresholds were defined as > 10 cases/year for surgeons and > 25 cases/year for hospitals, fewer surgeons in Asia reported practicing in high-volume hospitals (77% vs 92% for NSA and 96% for EUR, $P = .03$) (Table 1). However, when thresholds > 25 cases/year for surgeons and > 50/year for hospitals were used, no statistically significant differences were identified in respondents' reported case volumes.

The preferences for the evaluation of LAPC according to geographic location of practice are also shown in Table 1. Compared to respondents in the Americas and Europe, surgeons in Asia were more likely to use magnetic resonance imaging, positron emission tomography/computed tomography, and abdominal ultrasound in the initial evaluation. The criteria used to define resectability also varied by geography. Although the National Comprehensive Cancer Network (NCCN) criteria were used frequently across all regions, the Americas Hepato-Pancreato-Biliary Foundation (AHPBA) criteria were more often used by respondents in the Americas, the Dutch Pancreatic Cancer Group criteria were more often used by respondents in Europe, and the Japan Pancreas Society criteria were more often used by respondents in Asia.

As shown in Table 2, geographic area of practice influenced neoadjuvant treatment preferences for LAPC in multiple areas. Respondents in the Americas (77, 81.9%) and Europe (17, 68.0%) were more likely to always recommend neoadjuvant therapy to patients with advanced PDAC compared to surgeons in Asia (16, 47.1%; $P = .001$). In addition, surgeons in both the Americas (65, 69.2%) and Europe (19, 76.0%) were more

Table 1
Characteristics and evaluation preferences of participating surgeons by geographic location. Numbers represent count (%) unless stated otherwise.

	Americas n = 94	Europe n = 25	Asia n = 34	P value
Practice type				NS
Independently practicing surgeon	89 (94.7)	24 (96.0)	30 (88.2)	
Surgical fellow	5 (5.3)	1 (4.0)	4 (11.7)	
Focus of surgical practice				.01
General surgery	4 (4.3)	2 (8.0)	1 (2.9)	
Surgical oncology	40 (42.6)	4 (16.0)	4 (11.8)	
HPB surgery	47 (50.0)	19 (76.0)	27 (79.4)	
Other*	3 (3.2)	0 (0)	2 (5.9)	
Years in practice (median [IQR])	10 (5–17)	14 (6–25)	15 (9–20)	.02
Practice setting†				
Community practice	4 (4.3)	1 (4.0)	0 (0)	NS
Teaching	17 (18.1)	6 (24.0)	1 (2.9)	NS
University	69 (73.4)	19 (76.0)	30 (88.2)	NS
Government	6 (6.4)	2 (8.0)	10 (29.4)	.001
Urban	14 (14.9)	2 (8.0)	11 (32.4)	.03
Rural	1 (1.1)	0 (0)	0 (0)	NS
Practice in multiple hospitals	4 (4.3)	1 (4.0)	0 (0)	NS
Available specialists†				
Medical oncologist specialized in PDAC	85 (90.4)	25 (100.0)	33 (97.1)	NS
Radiation oncologist specialized in PDAC	77 (81.9)	23 (92.0)	25 (73.5)	NS
Interventional radiology-biliary procedures	85 (90.4)	25 (100.0)	34 (100.0)	NS
Gastroenterology-advanced endoscopy	87 (92.6)	25 (100.0)	30 (88.2)	NS
None	4 (4.3)	0 (0)	0 (0)	NS
Institution offers PDAC clinical trials	84 (89.4)	24 (96.0)	27 (79.4)	NS
Roughly how many pancreatectomies do you typically perform for PDAC annually?				
> 10	83 (88.3)	23 (92.0)	26 (76.5)	NS
> 25	54 (57.5)	18 (72.0)	17 (50.0)	NS
Roughly how many pancreatectomies are typically performed for PDAC annually at your institution?				
> 25	86 (91.5)	24 (96.0)	26 (76.5)	.03
> 50	65 (69.2)	18 (72.0)	19 (55.9)	NS
High-volume surgeon (10/y) at high-volume hospital (25/y)	79 (84.0)	22 (88.0)	21 (61.8)	.01
High-volume surgeon (25/y) at high-volume hospital (50/y)	48 (51.1)	15 (60.0)	11 (32.4)	NS
Preferred diagnostic tests for initial staging				
Pancreatic protocol CT scan	91 (96.8)	25 (100.0)	34 (100.0)	NS
CA 19-9	91 (96.8)	23 (92.0)	29 (85.3)	NS
Liver function tests	71 (75.5)	14 (56.0)	15 (44.1)	.002
Endoscopic ultrasound	60 (63.8)	11 (44.0)	23 (67.6)	NS
CEA	33 (35.1)	8 (32.0)	18 (52.9)	NS
MRI	22 (23.4)	8 (32.0)	23 (67.6)	<.001
Diagnostic laparoscopy	21 (22.3)	7 (28.0)	4 (11.8)	NS
PET/CT	8 (8.5)	4 (16.0)	15 (44.1)	<.001
Abdominal ultrasound	4 (4.3)	6 (24.0)	12 (35.3)	<.001
Participate in multidisciplinary conference	91 (96.8)	25 (100.0)	34 (100.0)	NS
What criteria do you use to define resectability?†				
AHPBA	63 (67.0)	6 (24.0)	9 (26.5)	<.001
NCCN	39 (41.5)	13 (52.0)	24 (70.6)	.01
MD Anderson Cancer Center	25 (26.6)	3 (12.0)	3 (8.8)	.046
Intergroup (Alliance)	10 (10.6)	0 (0)	1 (2.9)	NS
Japan Pancreas Society	0 (0)	0 (0)	9 (26.5)	<.001
Dutch Pancreatic Cancer Group	0 (0)	6 (24.0)	0 (0)	<.001

AHPBA, The Americas Hepato-Pancreato-Biliary Association; CEA, carcinoembryonic antigen; CT, computed tomography; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; PET, positron emission tomography.

* Pancreas surgery only (3), transplant surgery (2).

† Participants could select all that apply.

likely to recommend FOLFIRINOX for neoadjuvant systemic therapy compared to surgeons in Asia (12, 35.3%; $P < .001$), who instead preferred gemcitabine-based combination chemotherapy regimens (15 [44.1%] vs 6 [6.4%] in the Americas and 1 [4.0%] from Europe, $P < .001$). The preferred duration of therapy also varied, with surgeons in the Americas more often recommending a longer duration of therapy (4 months: 49, 52.1%) than counterparts in Asia (2 months: 21, 61.8%) ($P = .006$). Similar wide variations were observed in respondent's perceived utility of radiotherapy. In particular, 49 (52.1%) of surgeons in the Americas always or often recommend neoadjuvant radiation therapy to patients with advanced PDAC compared to 4 (16%) and 10 (29.4%) in Europe and Asia, respectively ($P < .001$). Although details on specific operative techniques

were limited by the nature of the survey, surgeons in Asia (18, 52.9%) were more likely to offer a minimally invasive pancreaticoduodenectomy for PDAC compared to those in the Americas (25, 26.6%) and Europe (8, 32%, $P = .02$). However, among respondents offering a minimally invasive approach, utilization of a robotic approach was more commonly reported by surgeons in the Americas and Europe compared to surgeons in Asia. Use of diagnostic laparoscopy also differed among the 3 cohorts.

Figure 1 illustrates respondent perceptions regarding the characteristics often or always considered a contraindication to exploration following neoadjuvant therapy, according to geographic location of practice. Compared to surgeons in Europe and Asia, surgeons in the

Table 2

LAPC management preferences of participating surgeons by geographic locations. Numbers represent count (%) unless stated otherwise.*

	Americas n = 94	Europe n = 25	Asia n = 34	P value
Do you recommend neoadjuvant systemic therapy to patients with advanced PDAC?				.001
Always	77 (81.9)	17 (68.0)	16 (47.1)	
Often	12 (12.8)	4 (16.0)	7 (20.6)	
Sometimes	5 (5.3)	4 (16.0)	11 (32.4)	
Never	0 (0)	0 (0)	0 (0)	
What neoadjuvant systemic therapy do you prefer or typically recommend?				<.001
FOLFIRINOX	65 (69.2)	19 (76.0)	12 (35.3)	
Gemcitabine & Abraxane	6 (6.4)	1 (4.0)	10 (29.4)	
Gemcitabine & Xeloda	0 (0)	0 (0)	5 (14.7)	
Gemcitabine only	0 (0)	1 (4.0)	0 (0)	
Defer to medical oncology	20 (21.3)	3 (12.0)	7 (20.6)	
What duration of neoadjuvant systemic therapy do you prefer or typically recommend?				.006
At least 2 mo	30 (31.9)	9 (36.0)	21 (61.8)	
At least 3 mo	4 (4.3)	5 (20.0)	2 (5.9)	
At least 4 mo	49 (52.1)	9 (36.0)	8 (23.5)	
At least 6 mo	11 (11.7)	2 (8.0)	3 (8.8)	
Do you recommend neoadjuvant radiation therapy to patients with advanced PDAC?				<.001
Always	24 (25.5)	2 (8.0)	9 (24.5)	
Often	25 (26.6)	2 (8.0)	1 (2.9)	
Sometimes	42 (44.7)	13 (52.0)	18 (52.9)	
Never	3 (3.2)	8 (32.0)	6 (17.6)	
When do you typically recommend neoadjuvant radiation therapy?				.005
All nonmetastatic PDACs	13 (13.8)	3 (12.0)	1 (2.9)	
Borderline resectable and locally advanced PDACs	41 (43.6)	10 (40.0)	14 (41.2)	
Locally advanced PDACs only	14 (14.9)	2 (8.0)	8 (23.5)	
Any vessel involvement	9 (9.6)	1 (4.0)	3 (8.8)	
Any arterial involvement	14 (14.9)	1 (4.0)	2 (5.9)	
What neoadjuvant radiation therapy do you prefer or typically recommend?				.002
Conventional chemoradiation over 5–6 wk	54 (57.4)	8 (32.0)	19 (55.9)	
Stereotactic body radiation therapy over 1–2 wk	29 (30.8)	8 (32.0)	6 (17.6)	
Other*	8 (8.5)	1 (4.0)	3 (8.8)	
How often do you reevaluate PDAC patients receiving neoadjuvant therapy?				.015
I defer to medical/radiation oncology, and I reevaluate after the completion of therapy	14 (14.9)	6 (24.0)	14 (41.2)	
I reevaluate the patient with medical/radiation oncology with every occurrence of imaging	67 (71.3)	17 (68.0)	14 (41.2)	
I reevaluate the patient during therapy, but less often than medical/radiation oncology	13 (13.8)	2 (8.0)	6 (17.6)	
Do you use diagnostic laparoscopy prior to resection?				.001
Routinely	39 (41.5)	5 (20.0)	2 (5.9)	
Selectively	46 (48.9)	13 (52.0)	24 (70.6)	
No	9 (9.6)	7 (28.0)	8 (23.5)	
Offers minimally invasive Whipple				.02
Laparoscopic	25 (26.6)	8 (32.0)	18 (52.9)	
Robotic	13 (52.0)	2 (25.0)	12 (66.7)	.01
Both	8 (32.0)	3 (37.5)	1 (5.5)	
Offers vascular resection and reconstruction to appropriately selected patients undergoing Whipple				.007
Venous	4 (16.0)	3 (37.5)	5 (27.8)	
Arterial	93 (98.9)	25 (100.0)	30 (88.2)	
	54 (57.4)	8 (32.0)	14 (41.2)	.04

* Other responses included "Only in trials," "Depends," "Radiotherapy over 3 weeks," and "36 Gy with Gemcitabine."

Americas were more likely to consider stable isolated liver metastases (85 [90.4%] vs 18 [72%] and 23 [67.6%], respectively; $P = .004$), stable isolated lung metastases (83 [88.3%] vs 18 [72%] and 21 [61.8%], $P = .002$), and ascites (78 [83%] vs 15 [60%] and 24 [76%], $P = .04$) a contraindication to exploration following neoadjuvant therapy. Significantly more surgeons in both the Americas and Europe considered compensated cirrhosis often or always a contraindication to exploration, whereas surgeons in Asia were more likely to consider comorbidities and older age contraindications to exploration following neoadjuvant therapy.

Figure 2 shows the proportion of surgeons in Asia, Europe, and the Americas willing to offer exploration following good response to neoadjuvant therapy for each of the 6 clinical vignettes. A short description of each clinical vignette is provided along with the figure. No significant differences were identified in the propensity to consider exploration in any vignette of LAPC and responses varied widely, whereas surgeons in Asia were significantly more likely to consider exploration (17, 50%) in a patient with oligometastatic liver metastases and a resectable pancreatic head lesion compared to surgeons in Europe (10, 40%) and the Americas (21, 22.3%, $P = .034$).

Figure 3 shows the cumulative alternative treatments recommended if exploration was not offered in any of the 6 clinical vignettes according to the geographic location of practice. Overall, surgeons in the Americas equally preferred continuation of the same chemotherapy regimen (33%) and consideration of a clinical trial (32%), whereas 20% recommended consideration of a new chemotherapy regimen. A majority of surgeons in Asia recommended continuation of the same chemotherapy regimen (55%), whereas 27% recommended initiation of a new chemotherapy regimen and few recommended clinical trials (9%). Recommendations of surgeons in Europe were highly variable, as continuation of the same chemotherapy regimen (25%), exploration of clinical trials (23%), initiation of a new chemotherapy regimen (17%), and active surveillance (17%) were all considered. Surgeons in the Americas and Asia infrequently recommended active surveillance, whereas referral for another surgical consultation was rarely chosen by any respondents.

DISCUSSION

This analysis of an international survey of current practice found that significant variations exist in attitudes regarding the multidisciplinary

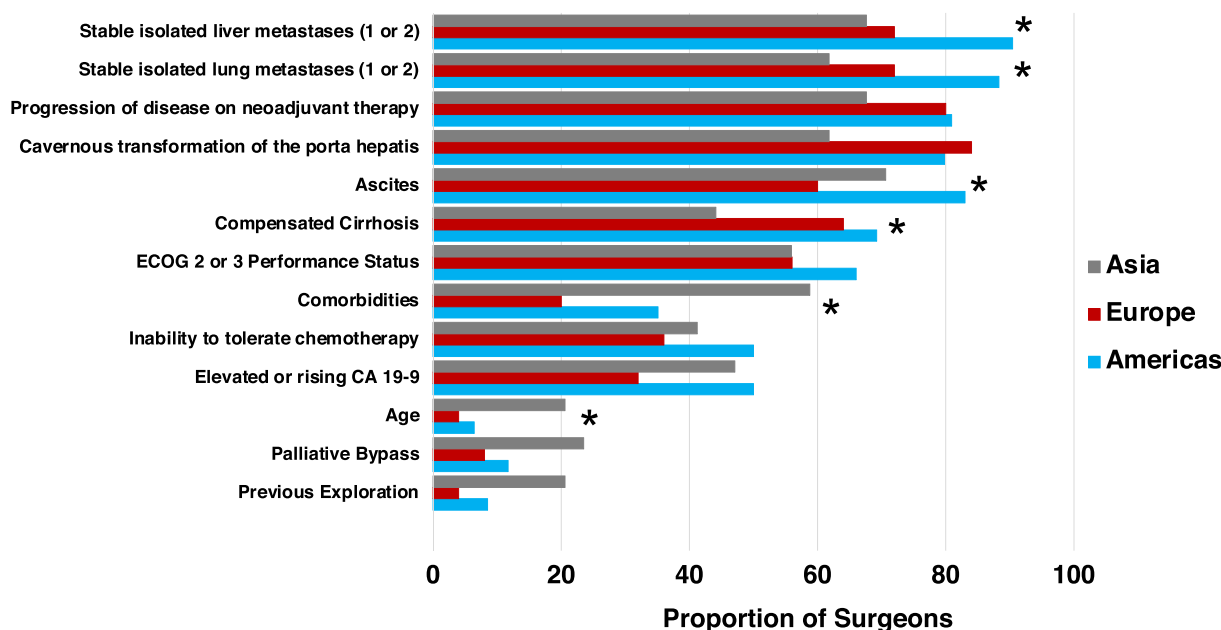


Fig 1. Characteristics often or always considered a contraindication to exploration following neoadjuvant therapy, according to geographic location of practice (ECOG: Eastern Oncology Cooperative Group; asterisk indicates significant difference $< .05$).

management of LAPC according to the geographic location of surgeon practice. These variations included differences in the preferred neoadjuvant systemic therapy recommended, the reasons for use and type of neoadjuvant radiotherapy preferred, approaches to surgical resection, perceived contraindications to exploration, and alternative treatments recommended if exploration was not pursued. Moreover, little consistency was observed across geographic locations of practice in the propensity of surgeons to consider exploration following neoadjuvant therapy for 5 clinical vignettes of LAPC. However, the decreased perception of oligometastatic disease as a contraindication to exploration among surgeons in Asia correlated with an increased propensity to consider exploration after neoadjuvant therapy in a vignette of oligometastatic liver disease with a resectable primary.

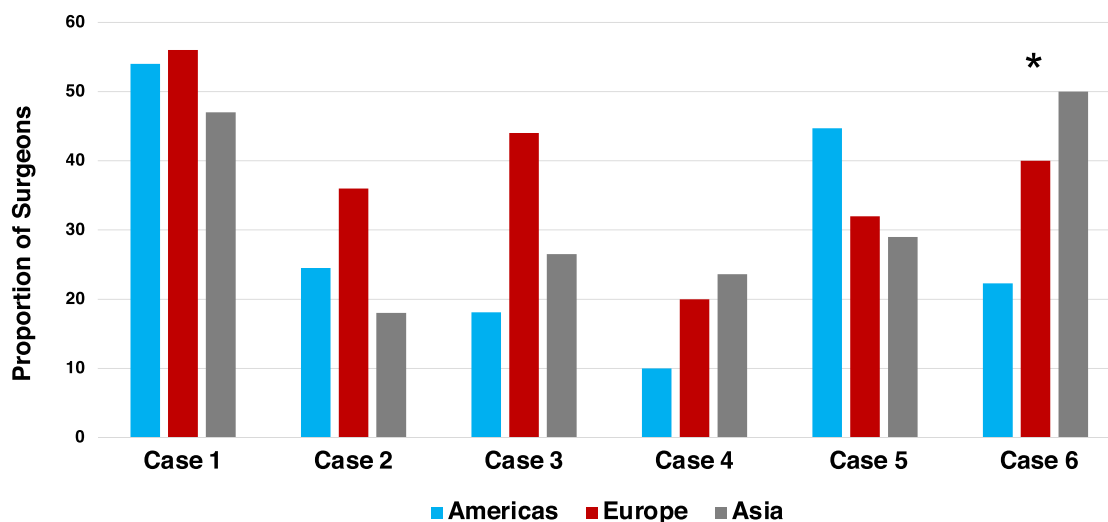
The results of this survey suggest that there are important differences in attitudes regarding the chemotherapy regimen preferred and the duration of therapy recommended across geographic locations of practice. Surgeons in both the Americas and Europe generally prefer FOLFIRINOX over gemcitabine-based regimens in the neoadjuvant setting, whereas the preferences of surgeons in Asia are reversed. Recent institutional series from high-volume centers in both the Americas and Europe corroborate these findings [2,3,28–30]. To further complicate the issue, recent LAPC management guidelines differ in preferred neoadjuvant regimens recommended. NCCN recommends either FOLFIRINOX or gemcitabine-nab paclitaxel [31], whereas the Dutch Pancreatic Cancer group guidelines recommend FOLFIRINOX for all patients with good performance status [32] and the Japanese Pancreas Society recommends gemcitabine-based regimens in patients with LAPC [33]. The differential utilization of S-1 across regions may also contribute to the variation observed herein [34–36].

Similarly, these results suggest that there is significant geographical variation in attitudes regarding reasons for use and type of neoadjuvant radiotherapy preferred for LAPC. The overall lack of consensus on neoadjuvant radiotherapy is not surprising, as its utilization in LAPC is debated and evidence evaluating its use is mixed [37–41]. Recent retrospective studies have suggested equivalent safety and outcomes in SBRT versus standard conventional therapy in LAPC patients undergoing resection [42]. However, randomized trials, such as ESPAC-1, and the recent ALLIANCE A021501 trial have failed to show survival benefit. The ALLIANCE A021501 trial, for example, was designed to compare neoadjuvant mFOLFIRINOX with or without radiation in patients with

borderline resectable PDAC against historical control. However, it was closed at interim analysis as the neoadjuvant chemoradiation arm had significantly lower R0 resection rates (25% vs 60%) and worse overall survival (OS) (47.3 vs 50% 18-month OS) compared to historical control and fared even worse when compared to the neoadjuvant chemotherapy-only arm (47.3 vs 67.9% 18-month OS) [43]. Nevertheless, among the cohort of surgeons that responded to this survey, those practicing in the Americas were more likely to recommend neoadjuvant radiation therapy than counterparts in Europe or Asia.

Differences in the use of minimally invasive (MIS) approaches among geographic locations of practice identified in this study are also supported by the current literature. Retrospective reviews and meta-analyses support the use of MIS techniques for pancreaticoduodenectomy [44–46]. Although a previously published international survey data of high-volume pancreatic surgeon did not identify significant differences in the rates of minimally invasive pancreaticoduodenectomy, that study did not compare the rates of laparoscopic versus robotic approaches among continents [47]. The present survey identified the highest rates of MIS pancreaticoduodenectomy among surgeons in Asia, yet among those offering a MIS approach, utilization of a robotic platform was more common in the Americas and Europe. These findings likely represent strong evidence supporting a laparoscopic approach within Eastern populations [46] and varying resource and financial considerations between countries. As access and experience to the robotic platform continue to expand globally, the international opinion represented by this small cohort of survey respondents is likely to evolve. An international consensus statement on robotic pancreatic surgery was recently published to inform safe practice and promote program development [48].

No consistency was observed in the propensity to consider exploration for 5 clinical vignettes of LAPC following neoadjuvant therapy across locations of practice. Although the statistical power of these analyses is limited by sample size, these findings are not surprising given the lack of strong evidence or consensus on a preferred management approach for LAPC. Moreover, these findings are corroborated by a similar analysis of the same data evaluating the association between surgeon volume and the propensity to consider exploration [8]. However, the finding of a significant geographical difference in the propensity to consider exploration in a vignette of oligometastatic pancreatic cancer is profound and is strengthened by parallel differences in the evaluation



Case	Post-Neoadjuvant Imaging Details
1	Pancreatic head mass slightly decreased in size, with encasement of the common and proper hepatic arteries, and abutment of the portal vein with mild narrowing.
2	Pancreatic head/neck mass, significantly decreased in size, encasing the celiac and common hepatic arteries and the portal vein/SMV, with venous narrowing.
3	Pancreatic head mass with encasement of the SMV and SMA, surrounded by significant stranding, and an enlarged necrotic lymph node at the root of the mesentery.
4	Pancreatic uncinate mass with encasement of the celiac axis, longitudinal encasement of the SMA, and PV/SMV abutment.
5	Vague pancreatic head mass, peripancreatic stranding, decreased SMA involvement (now just abutment), persistent long segment SMV encasement and occlusion, and prominent retroperitoneal and mesocolic collateral vessels.
6	Response in both liver metastases, decreased size of pancreatic head mass with slight abutment of the SMV without contour change.

Fig 2. Proportion of surgeons willing to consider exploration after good response to neoadjuvant therapy for each clinical vignette, according to geographic location of practice (asterisk indicates significant difference <.05), along with brief descriptions of neoadjuvant treatment response for each clinical vignette [5].

of perceived contraindications to exploration across geography. There have been growing reports of curative-intent approaches in highly selected patients with oligometastatic pancreatic cancer [49–52]. However, most guidelines recommend against exploration in the setting of metastatic disease [53,54], so the lack of consensus among surgeons in this study is anticipated. The increased self-reported propensity of surgeons from Asia to consider exploration in patients with oligometastatic disease is a unique finding and warrants further investigation, as it may represent previously undefined and evolving variations in practice and treatment philosophy. One such clinical trial (CSPAC-1) evaluating this question is actively recruiting patients [55].

This study has several important limitations. First, this study is subject to all the limitations of the original survey including a small sample size, a low survey response rate, unverifiable responses, and response bias, all of which serve to limit the generalizability of the survey findings [5]. In addition, when combined with a small sample size, the multiple geographic categories serve to further limit the sample size and generalizability of results within any individual geographic cohort and limit statistical power. However, given the international nature and the clinical complexity of the study question (evaluating international attitudes

regarding multidisciplinary management of LAPC across geographic locations), to our knowledge, these survey results are the only data available to investigate this study question. Second, geographic locations of practice are represented by continents, which themselves represent many diverse countries, cultures, health systems, institutions, and providers. For example, although responses from South America would ideally be analyzed separately, a small sample size ($n = 6$) limited statistical reliability. Although this may further limit the generalizability of these results, the geographic locations chosen for the survey instrument were left intentionally broad to ensure anonymity of responses. However, the expected heterogeneity within broad geographic categories would be expected to bias any statistical analyses toward the null hypothesis (no variation identified). Third, it remains unclear whether differences in attitudes regarding multidisciplinary management of LAPC translate into differences in outcomes for patients undergoing therapy. However, the purpose of this study is not to make inferences about best practice.

Previous reports have identified geographic variations in the surgical management of both benign [56] and malignant [10] conditions and across a wide array of operations [57–59]. Within the field of oncology,

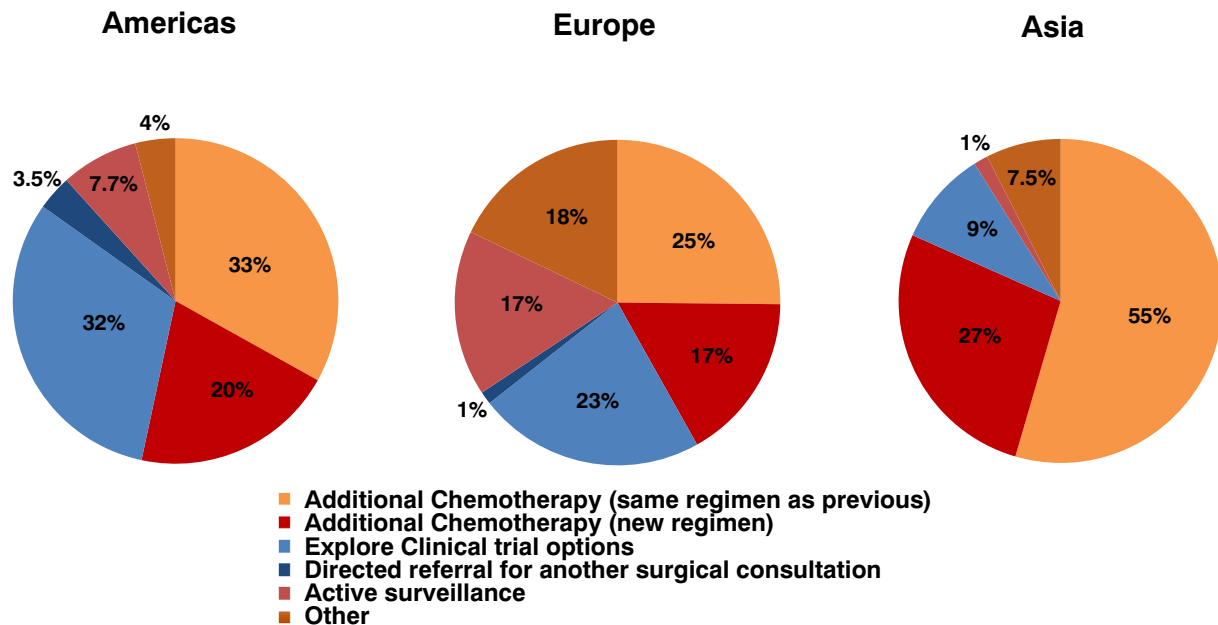


Fig 3. Cumulative recommendations for additional treatment following good response to neoadjuvant therapy for the 6 clinical vignettes if exploration is not offered, according to geographic location of practice.

geographic variation has been shown to influence the management of diverse malignancies including breast [17–20], prostate [21,22], colon [10], endometrial [23], and liver [24] cancers. For example, although no international studies have been conducted, previous national studies from the United States [17,18] and Spain [19] suggest that there is substantial geographic variation in the use of breast conservation surgery that cannot be accounted for by differences in hospital characteristics [18] or patient demographics [17] but is more likely due to regional policies and local economic status [19]. Interestingly, a more recent study by the Netherlands on the same subject found that geographic variation has decreased since the publication of detailed evidence-based national guidelines, although the generalizability of this study to countries across the globe remains questionable [20]. Similar examples are found in literature evaluating variations in the management of prostate cancer, as prior research demonstrates geographic variation in treatment patterns at the national [60,61], regional [21], and state [62] levels, again influenced by regional cultures and local income levels.

In this study, we have identified significant geographic variation in surgeon attitudes and preferences for the management of LAPC. A thorough understanding of literature evaluating the impact of geographic variation on treatment and outcomes suggests that these findings may have important implications for improving the care provided to LAPC patients. Although causes of geographic variation are no doubt multifactorial, potential contributors include mixed literature and weak evidence to support current practice; differences in patient characteristics and provider beliefs across locations [63]; national, regional, or institutional cultures; and the availability of specific technologies or therapeutics, among others.

The wide variation observed among this international cohort of high-volume pancreatic surgeons further highlights the need for stronger evidence to define the optimal management of LAPC. Although multi-institutional multimodality randomized trials are difficult to conduct, success is possible. The JCOG1407 trial evaluating use of neoadjuvant FOLFIRINOX versus gemcitabine/nab-paclitaxel in LAPC patients, for example, was recently reported but showed mixed results [64]. Additional clinical trials evaluating treatment sequencing [65], the preferred systemic therapy regimen [66,67], and use of radiotherapy [68,69] are currently under way, and results are eagerly awaited. However, until stronger evidence is available, these findings emphasize the need for improved international collaboration to better understand

best practices and define consensus guidelines for the multidisciplinary management of this complex disease.

Author Contribution

BNR, ABB, RWK, AE, VPG, GG, CLW, MJW, and JH were involved in the conception or design of this work. All authors were involved in the distribution of the survey and evaluation of the results. BNR and ABB performed statistical analysis. LRM, ABB, RWK, CZ, and BNR drafted the abstract and manuscript. All authors critically reviewed the manuscript and offered substantial edits. All authors approve the final manuscript for submission.

Conflict of Interest

All authors have no conflicts of interest to declare.

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Ethics Approval

This study was ruled exempt by the Johns Hopkins Medicine institutional review board.

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