



Heterogeneity in the management of patients with locally advanced pancreatic cancer: current surgeons' perspective and lessons for the future

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Abstract

The management of patients with locally advanced pancreatic cancer (LAPC) in the era of promising neoadjuvant treatments and “conversion” surgery remains challenging. This survey sought to register the current practices and perspectives of recognized pancreatic surgeons and provide valuable insights for future research. An online survey consisting of 18 questions on real-life challenging clinical situations was conducted using Google Forms. Participants were asked about their approach in the management of a 60-year-old patient with LAPC after 8 weeks of neoadjuvant chemotherapy in different settings of response to the neoadjuvant treatments and of intraoperative findings. Seventy-three respondents from 19 different countries completed the survey. 74% (54/73) of the respondents declared working at centers performing more than 50 pancreatic resections per year. Overall, the answers among participants were very heterogeneous. There was no consensus regarding the optimal duration of neoadjuvant chemotherapy, nor on the appropriate timing and indications for regimen modification. Similarly, the criteria for surgical exploration, the intraoperative strategies in case of venous or arterial involvement, and the role of perivascular frozen-section analysis in guiding intraoperative decisions remained debated among the participating surgeons. Here, the lack of knowledge in the current literature on these issues and the subsequent reliance on individual expertise may account for this heterogeneity. Further research efforts are required to address existing knowledge gaps and to advance and standardize the management of patients with LAPC.

Keywords Pancreatic surgery · Pancreatic cancer · Arterial resection

Introduction

Recent promising oncological treatments and reduced morbidity and mortality of pancreatic surgery in high-volume centers have changed the profile of surgically resectable pancreatic cancers. In the last years, the definition of resectability has evolved, from the concept of purely anatomical resectability to a new concept including biological and conditional resectability, until the recent emerging “prognosis-based resectability” [1–3]. Neoadjuvant treatments and the feasibility of complex arterial resections/divestments by expert pancreatic surgeons have reduced the distance between resectable, borderline, and locally advanced pancreatic cancers in terms of negative margins and survival outcomes [4, 5]. Promising results have become achievable also in patients with LAPC after neoadjuvant chemotherapy and/or neoadjuvant chemoradiation followed by surgical

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resection, also known as “conversion surgery” [2, 6]. As a result, the definition of resectability is no longer based on the initial anatomical extent of the disease, but on the tumor biology and the expected prognosis [1, 6]. A very recent study has shown that patients with a borderline or LAPC who underwent surgery after a favorable response to neoadjuvant or primary oncologic therapy and were selected according to the “prognosis-based resectability” concept, experienced a significant long-term survival benefit compared with those who received continued nonsurgical oncologic treatment [7]. The definition of “conversion surgery” and the management of LAPC were discussed at the joint meeting of the International Association of Pancreatology (IAP) & Japan Pancreas Society (JPS) in 2022, resulting in a position paper in which several questions remained unanswered [6]. Very recently, the REDISCOVER Guidelines have also endorsed this evolving concept of resectability in the management of patients with LAPC. These guidelines proposed 34 validated recommendations and an algorithm to guide the decision-making process in patients with LAPC, although supported by low level of evidence. Moreover, several other recommendations failed to gain approval, and many issues remained unresolved, highlighting the urgent need for further investigations in this field. In this context, there are still significant regional and institutional discrepancies in the management of LAPC, and clinical practice remains challenging [3, 8].

Therefore, we asked experts in the field to share their habits, experiences, and personal opinions in real-life challenging clinical scenarios in patients with LAPC, with the aim of providing valuable insights for the daily practice of pancreatic surgeons worldwide and for further investigations.

Methods

An online survey was designed using Google Forms (<http://docs.google.com/forms>; Google LLC, Menlo Park 120 California, USA) and, with the purpose of providing insights and guidance for pancreatic surgeons worldwide, was submitted to a selected panel of internationally recognized pancreatic surgeons. The panel included surgeons working in internationally renowned referral centers for pancreatic surgery, as well as the co-authors of the REDISCOVER Guidelines. The survey was conducted from November 22 to December 31, 2024, and consisted of 18 questions on the management of patients with LAPC (Supplementary Content 1).

The survey could be filled out only once, and, to avoid missing data, all responses were mandatory. No reward was offered for participation. Participants were asked to enter their names and affiliations to acknowledge them as

contributors. General information about the participants and their expertise in pancreatic surgery was also asked, such as the number of pancreatic resections performed annually, personally, and at their institution. A clinical case of a 60-year-old patient with LAPC and good health status who underwent the first restaging after 8 weeks of neoadjuvant chemotherapy was considered for the survey. Then, the management in different preoperative and intraoperative situations was questioned. For each question, we offered an open-ended response option to also collect personal opinions not represented by the proposed answers.

In this survey, particular attention was paid to the preferred intraoperative approach in cases of arterial infiltration, namely arterial resection or arterial divestment. Arterial divestment refers to the circumferential dissection of tumor tissue from a major artery along the arterial adventitial plane, allowing preservation of the artery without the need for arterial resection or reconstruction.

The data were collected and analyzed anonymously using Microsoft Excel 2024 (Microsoft, Redmond, USA). Data on categorical variables were reported as frequencies with percentages.

Results

Participants

A total of 73 out of 156 surgeons (47%) from 19 different countries on five different continents completed the online survey. General information regarding the participants is shown in Table 1. At the time of the survey, 74% (54/73) of the respondents declared to work at a center in which more than 50 pancreatic resections are performed per year. Of these, 28 (38%) and 14 (19%) reported working in a hospital with more than 100 and 200 pancreatic resections per year, respectively. Moreover, most respondents work in university hospitals (85%, 62/73). Sixty-one surgeons (84%) declared to personally perform more than 20 pancreatic resections per year, while 12% (9/73) of the total personally execute more than 100 annually.

Surgeons' perspective at the first restaging after neoadjuvant chemotherapy

The first 3 questions of the survey sought to investigate the usual approach of the participants in the case of a 60-year-old patient with LAPC and a good health status undergoing the first restaging after 8 weeks of neoadjuvant chemotherapy with different responses to the treatment (Fig. 1).

In the case of radiologically stable disease and absence of distant metastases but an increase of serum Ca19-9 from

Table 1 General information regarding survey's participants

	N (%)
<i>Countries</i>	73
Germany	7 (10)
Italy	30 (41)
Spain	1 (1,4)
Portugal	1 (1,4)
Austria	1 (1,4)
Nederland	1 (1,4)
Sweden	2 (3)
France	4 (5)
Norway	1 (1,4)
Serbia	1 (1,4)
England	3 (4)
Turkey	3 (4)
Russia	2 (3)
U.S.A.	9 (12)
Japan	3 (4)
South Africa	1 (1,4)
Australia	1 (1,4)
India	1 (1,4)
China	1 (1,4)
<i>Type of Hospital</i>	
University Hospital	62 (85)
Not University Hospital	11 (15)
<i>N° pancreatic resection at the institution/year</i>	
<20/year	3 (4)
20–50/year	16 (22)
50–100/year	12 (16)
100–200/year	28 (39)
>250/year	14 (19)
<i>N° pancreatic resections personally performed/year</i>	
<10/year	7 (10)
10–20/year	5 (7)
20–50/year	30 (41)
50–100/year	22 (30)
100/year	9 (12)

100 to 300 U/ml, 78% of the participants (57/73) declared to favor a switch in the chemotherapy protocol, while 3% to prolong the current chemotherapy. In contrast, 9.5% (7/73) suggested surgical exploration, and another 9.5% (7/73) advised radio(chemo)therapy.

Surgeon's opinions were more heterogeneous in case of radiologically regressive disease and no distant metastases, but an increase of serum Ca19-9 from 100 to 300 U/ml. Here, 40% (29/73) of the respondents declared to continue the current chemotherapy regimen, 30% (22/73) to switch chemotherapy, and 5% (4/73) to consider the use of radiotherapy, while 22% (16/73) supported the need for surgical exploration or diagnostic laparoscopy. One colleague suggested checking the patency of the biliary stent, and another suggested performing FDG-PET to better stage the patient.

In the third scenario with radiologically regressive disease without distant metastases and with a decrease of serum

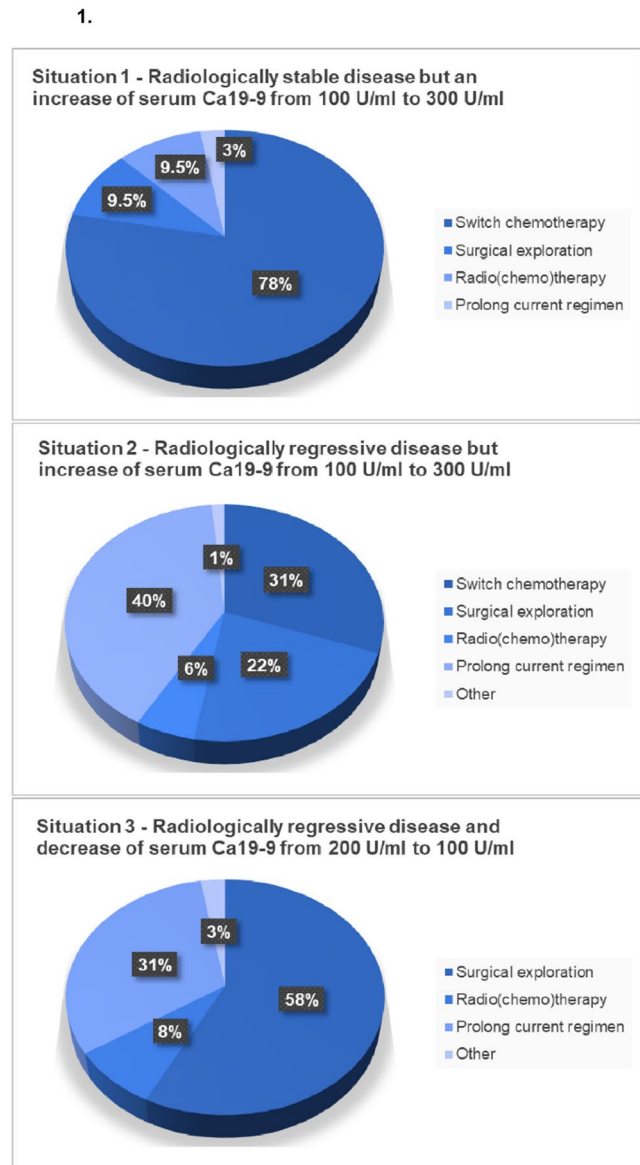


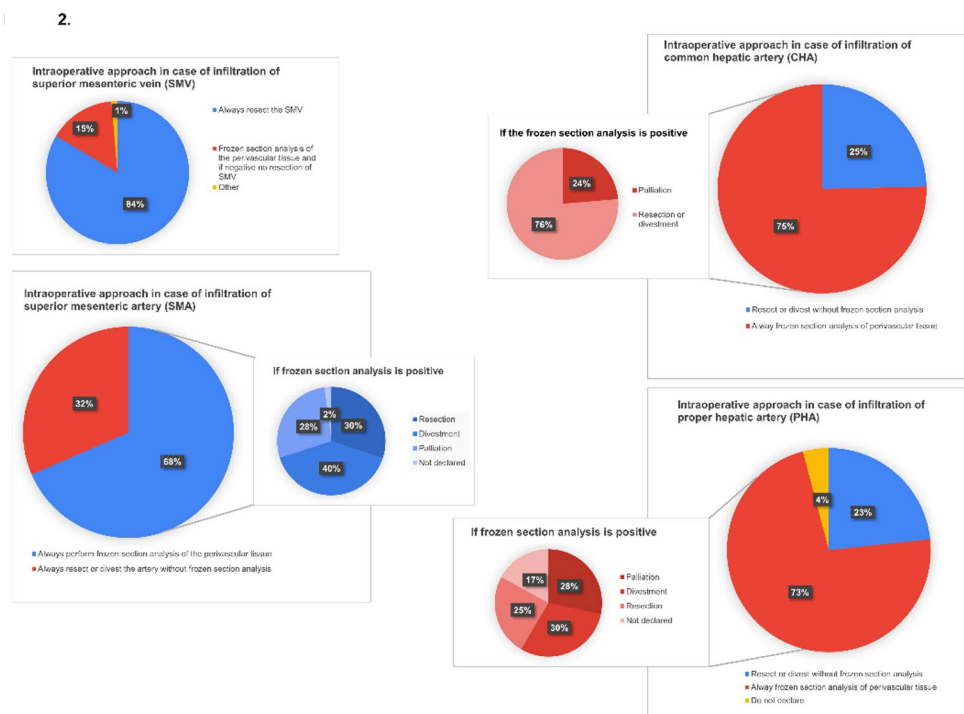
Fig. 1 Surgeons' perspective at the first restaging after neoadjuvant chemotherapy. (8 weeks) in a 60-year-old patient with LAPC and a good health status in 3 situations showing different response to the treatment

Ca19-9 from 200 to 100 U/ml, 42 (58%) participants agreed to perform a surgical exploration and 23 (32%) to continue the current chemotherapy regimen. Six other respondents (8%) declared to perform radio(chemo)therapy, one colleague to consider all 3 previous options, and another to try a total neoadjuvant chemotherapy.

Initial intraoperative approach in LAPC after neoadjuvant chemotherapy

Subsequently, participants were asked to share their intraoperative approach in the case that the 60-year-old patient with

Fig. 2 Intraoperative approach in case of vascular infiltration (SMV, SMA, CHA, PHA)



LAPC, after 8 weeks of neoadjuvant chemotherapy, without metastasis and with a decrease in serum Ca19-9 from 200 to 100 U/ml in the preoperative reassessment, underwent surgical exploration. Here, 32% (23/73) of the surgeons declared to always perform an explorative laparoscopy to start, another 34% (25/73) only sometimes, whereas 32% (23/73) affirmed to prefer an open exploration from the beginning. Two participants (3%) affirmed to usually perform a staging laparoscopy before starting the neoadjuvant chemotherapy in patients with LAPC.

In case of suspected infiltration of the superior mesenteric artery (SMA) by a pancreatic head tumor, 19 (26%) respondents declared to approach the SMA dorsally after Kocher manoeuvre, 6 (8%) surgeons starting from the medial border of the ligament of Treitz and 42 (58%) using a combination of these two methods. In addition, 3 colleagues (4%) declared to decide how to approach the SMA case by case, depending on the location of the tumor infiltration and the patient-specific anatomy, while other 3 respondents (4%) other respondents usually prefer a mesenteric approach.

Intraoperative approach in case of infiltration of superior mesenteric vein (SMV)

In case of suspected persistent infiltration of the superior mesenteric vein (SMV), most of the participants (61/73, 84%) always resect the vein (Fig. 2). In contrast, 15% of the respondents (11/73) usually perform a frozen section from the infiltrated site of the vein and omit vein resection if the frozen section is negative. One colleague declared

to perform no vein resection at all, even if an R1 status is expected.

Intraoperative approach in case of infiltration of the superior mesenteric artery (SMA)

The surgical approach in case of suspected short-segmental (max 1 cm) arterial infiltration of the proximal SMA seems to be much more variable and personalized to the specific situation and patient (Fig. 2). 68% (50/73) of the respondents declared to perform a frozen section analysis of the tissue around the SMA. If the frozen section analysis is positive, according to patient and tumor characteristics, 27% (20/73) of the surgeons declared to divest the artery, while 21% (15/73) affirmed to resect and reconstruct it. In contrast, 20% of the colleagues (14/73) would abort the planned resection and prefer palliative treatments. In contrast, 23 (32%) respondents affirmed to resect or divest the SMA without performing a frozen section analysis. Additional opinions were also recorded: several colleagues declared to always try a divestment of the artery at first, right away, or even if the frozen section analysis is negative. When the divestment is not feasible, they proceed to resect the SMA after considering technical feasibility and subsequent morbidity. Others affirmed to perform an arterial divestment only if the frozen section is negative and to prefer palliative procedures in all other cases. Interestingly, another colleague declared to perform irreversible electroporation and then resection of the SMA.

When we asked participants specifically, what they do if the frozen section analysis of the proximal SMA is negative, 50 (69%) respondents declared to divest the artery, 15 (20.5%) to leave the tissue as it is because the frozen section analysis was negative and 4 (5%) to perform a short arterial resection with reconstruction. On top of them, one respondent added to try a divestment and, if the tissue is not divestible, to proceed with the resection, while another to perform a frozen section analysis of the divested tissue and, if this is positive, to resect the SMA. Of note, a participant also highlighted that he performed around 1.250 vascular resections without performing a frozen section analysis in any of these cases, stressing the uselessness of the procedure for two reasons: (1) its limited diagnostic value due to sampling error and (2) the scarce evidence that positive perivascular frozen section analysis carries a negative prognostic value. Accordingly, the colleague affirmed that, if the intraoperative assessment suggests that an attempting divestment may result in an R1 resection, he performs directly an en bloc arterial resection. Similarly, another surgeon affirmed to base and personalize his decision exclusively on the clinical suspicion.

Intraoperative approach in case of infiltration of the common hepatic artery (CHA)

As above, in a patient with suspected short-segmental (max 1 cm) arterial infiltration of the common hepatic artery (CHA) proximally to the gastroduodenal artery (GDA), the approach advised by the participants was very diversified (Fig. 2). 25% (18/73) of the respondents resect or divest the CHA without performing a frozen section analysis. By contrast, most surgeons (55/73, 75%) reported performing a frozen section of the tissue around CHA. Of them, if this is positive, 13 (13/73, 18%) participants prefer not to continue with resection but undertake a palliative approach. Whereas the remaining participants declared to divest the artery or to resect it, according to the patient and the feasibility of the procedure. Two colleagues globally affirmed to consider an Appleby procedure in this situation.

In the case of negative frozen section analysis, the opinions were less heterogeneous. Forty-six respondents (63%) declared to divest the artery, 12 (9%) to perform a short segmental resection and reconstruction, and 17 (23%) to leave the periarterial tissue, as the frozen section is negative, and carry on the tumor resection. One surgeon affirmed to decide on a case-by-case basis, depending on the clinical circumstances.

Intraoperative approach in case of infiltration of the proper hepatic artery (PHA)

Same as above, in the case of suspected short-segmental (max 1 cm) arterial infiltration of the PHA right after or distally to GDA, the answers were very heterogeneous (Fig. 2). Most of the surgeons (53/73, 73%) declared to perform a frozen section analysis of the periarterial tissue. The other 17 remaining participants (23%) affirmed to divest or resect the PHA depending on the clinical suspicion and the patient's conditions, without resorting to the frozen section analysis, while 3 (4%) did not declare if they perform a frozen section analysis before arterial divestment or resection. In case of positive frozen section analysis, 21% of the participants (15/73) affirmed to interrupt the tumor resection, 22% (16/73) to divest the artery, 19% (13/73) to resect it (of note, one of them after preoperative embolization), and 12% (9/73) did not specify the preferred approach. If the frozen section analysis of the periarterial tissue is negative, like above, most of the surgeons (44/73, 60%) declared to divest the artery, 23% (17/73) to leave the tissue, while 12% (11/73) affirmed to preponderate for the segmental resection and reconstruction anyway. Another surgeon declared to perform a frozen section analysis of the divested tissue and to proceed with resection in case of positivity.

We also asked respondents what they would do if the divestment of the periarterial tissue is not feasible and the resection of the artery seems too risky, but the frozen section analysis is negative. 77% (56/73) declared to leave it as it is and to continue the tumor resection, while 12% (9/73) do not proceed with the resection. Seven colleagues (7/73, 9.5%) would try a resection of the artery anyway, depending on the longitudinal extension of the infiltration and eventually performing a microvascular reconstruction or seeking help from vascular surgeons. Of note, one participant responded by pointing out that a surgeon with no experience in arterial resections should not even undertake divestment, as resection might be necessary in any case.

Intraoperative approach in high-volume centers

The treatment decisions of surgeons working in centers performing more than 250 pancreatic resections annually are broadly comparable to those of their colleagues, except in cases of arterial infiltration, where they are markedly less likely to opt for palliative treatment (SMA: 14% vs. 20%; CHA: 0% vs. 22%; PHA: 7% vs. 24%) and more inclined to attempt arterial resection or divestment.

Discussion

As many questions in the management of patients with LAPC remain unanswered [3, 6, 8] and neoadjuvant therapies increase the possibility of a surgical curative treatment in these patients, with this survey, we sought to register the habits and thoughts of internationally recognized pancreatic surgeons. A survey is certainly an imperfect and biased method. We acknowledge that real-world scenarios may be more complex than the one presented in our survey and that additional factors, not included in the questions, may influence the decision-making process. However, it is a useful tool for describing the state of the art, detecting the lack of knowledge, and measuring the weight of experience and subjectivity, as well as the distance between practice and available evidence and guidelines.

In our survey, as already pointed out by the REDISCOVER Guidelines, we found a significant variation in the clinical practice and management of patients with LAPC. Just in 5 questions, more than 70% of the participants agreed with the same answer; in most cases, the chosen approach and opinions were very diverse. From the first 3 questions, there appears to be no clear consensus on the duration and regimen of the neoadjuvant chemotherapy, the timing and utility of a surgical exploration, as well as the use of radio(chemo)therapy. Several reports suggested that the level of CA19-9 predicts more accurately the presence of occult micrometastasis, the biology of the tumor, and the global prognosis compared to the local extent of pancreatic tumor and radiological downstaging [9–11]. Ferrone et al. also showed that in the case of radiology-predicted persistent unresectability, 92% of these patients had an R0 resection and a significantly improved prognosis. In our survey, in case of increased CA19-9 after neoadjuvant treatment, the radiological response influenced the treatment choice significantly. In case of increased CA19-9 and radiologically stable disease, most surgeons (77%) were inclined to switch the chemotherapy regimen. By contrast, in the case of increased CA19-9 and radiologically regressive disease, only 30% of surgeons agreed to switch the chemotherapy regimen, while 40% preferred to continue with the same one, and 22% would attempt a surgical exploration. Even when the radiological and biological response agreed at the first restaging, the opinions were heterogeneous: 60% of the surgeons would already attempt surgical exploration, while the rest were in favor of continuing neoadjuvant treatment. Our survey was designed to capture surgeons' perspectives and personal opinions and therefore may reflect a surgeon-driven viewpoint. However, the heterogeneity of the recorded responses likely reflects the lack of knowledge on this topic. Indeed, the optimal duration and regimen of the neoadjuvant treatment, as well as the benefit of

chemotherapy switch remain unresolved issues in the current literature [12–14]. In this context, we emphasize the importance of a multidisciplinary approach to determine the optimal treatment strategy for patients with LAPC.

In the case of surgical exploration, opinions on the optimal approach were also heterogeneous among respondents. Even if the use of laparoscopy has been shown to improve the staging and reduce the rate of non-therapeutic laparotomy [15–17], its use is still not considered by many colleagues. We registered that the use of explorative laparoscopy to start the operation is preferred by just one-third of the surgeons, while the other two-thirds declared to perform it not routinely or prefer an open exploration, respectively. In addition, only a few mentioned their routine use of laparoscopy before starting neoadjuvant chemotherapy.

The utility of the intraoperative frozen section analysis was also debated in this survey. In case of suspected, persistent infiltration of the SMV, most of the participants (84%) agreed to always resect the vein, and just 15% of the respondents base their decision on the frozen section analysis and omit vein resection if this is negative. In case of arterial infiltration, many participants are used to performing frozen section analysis routinely and repeatedly during surgery and make decisions based on it, as suggested by several study groups [18, 19]. By contrast, due to the known risk of false negatives in frozen section analysis, ranging from 5 to 20% [20], several colleagues declared to decide for arterial resection, divestment, or abrupt of the resection without performing it, but based on the intraoperative evaluation of the surgical site and the preoperative clinical and radiological situation. In this setting, the intraoperative approach declared by the participants in case of suspected infiltration of the SMA, CHA, and PHA was, once again, highly heterogeneous. In case of positive frozen section analysis, around 20% of the participants (for all 3 types of arterial infiltration) declared not to proceed with tumor resection but to prefer palliative treatments, while the remaining respondents were equally divided between those who prefer arterial divestment and those who usually perform arterial resection. In case of negative frozen section analysis of the periarterial tissue, most participants affirmed to perform more favorably a divestment of the artery, while just a few respondents would perform a resection of the artery anyway, and around 20% would carry on the resection of the tumor without approaching the artery. Two reasons, in our opinion, may explain this heterogeneity among respondents. First, it is still unclear whether patients with LAPC can really benefit from arterial resections and if arterial resections offer true advantages compared to arterial divestment. Our group recently found that even if arterial resections can be performed in high-volume centers for pancreatic surgery with an acceptable morbidity, the likelihood of arterial infiltration

seems to be rather overestimated [21]. In our cohort, only in 32% of the performed arterial resections a true arterial tumor infiltration was demonstrated in the final pathology. Furthermore, we showed that tumor cells mainly affect the adventitia and the nerves around vessels, rather than the vascular wall itself. Conversely, another study showed that in patients who underwent arterial resection, a review of histology slides of 25 R0 resections showed that pursuing arterial divestment instead of arterial resection would have made 12 of these 25 resections R1, increasing the overall R1 rate by more than 25%, as cancer cells were located within 1 mm of the adventitia [22]. Therefore, to achieve the goal of R0 resection, maybe we should better understand the pattern of invasion of the arteries and then, when possible, choose less invasive techniques such as divestment. If the survival outcomes after arterial resections/divestments are due to the effectiveness of this surgical procedure itself or to the tumor biology and efficacy of neoadjuvant treatments is also something that needs to be clarified. In this context, the selection of patients to take to the operating theatre remains, for sure, the more challenging issue [23]. Further prospective studies and new biomarkers are necessary, and, hopefully, some important input will come from the REDISCOVER online registry [3]. The second reason, in our opinion, is that the expertise of pancreatic surgeons in performing vascular resections can influence the management of patients with LAPC. Even to perform a divestment, a pancreatic surgeon should be prepared to perform an arterial resection and to face arterial rupture, even without the help of vascular surgeons, in case they are not available. Arterial resection and divestment are not alternative treatments but rather complementary strategies. An arterial resection must be preferred if divestment may result in an R1 situation. Persisting in divesting solely to avoid resection is not justified and do not respect the fundamental principles of oncologic surgery. The lack of confidence of the pancreatic surgeon in these challenging technical skills may reduce treatment options in patients with LAPC and influence the outcomes. Therefore, in the era of “conversion surgery” and increasingly promising neoadjuvant treatments, it is important that the surgical training of a pancreatic surgeon includes the acquisition of these skills, and that these patients are centralized in referral centers able to offer this type of expertise.

Conclusions

In conclusion, our survey showed that habits and opinions of pancreatic surgeons worldwide in the management of patients with LAPC are very diversified. Here, the lacking evidence on one side and the influence of personal expertise on the other play an important role. Further efforts

and research are needed to address the many unresolved issues, particularly regarding the duration and regimen of neoadjuvant chemotherapy, the timing and indications for chemotherapy switch, the timing and indications for surgical exploration, and the usefulness of arterial resection or divestment. On these matters, the REDISCOVER online registry will likely provide important inputs.

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Declarations

Conflict of interest The authors have no conflicts of interest to declare.

Ethical approval This study is based on a survey about surgeons' opinions. No patients are involved or included in the study evaluation, accordingly no patient's consent was required. Participating in the survey, the colleagues gave their consent to collect data.

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