Review Article on Surgery for Locally Advanced Pancreatic Cancer

Selecting surgical candidates with locally advanced pancreatic cancer: a review for modern pancreatology

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Abstract: Pancreatic cancer (PC) is likely to become the second leading cause of malignancy-associated mortality within the next 10 years and surgery remains the best hope for cure. The introduction of effective neoadjuvant treatment (NAT) has increased the resection rate of PC in the era of contemporary pancreatology. This review summarizes the surgical selection criteria for locally advanced PC (LAPC), by focusing on the commonly used predictors for resectability and better overall survival outcome. Based on the currently available evidence, the role of change in carbohydrate antigen 19-9 (CA 19-9) and patient's tumor response to NAT are critical in surgical candidacy selection. Although, consensus on surgical candidacy selection for LAPC still needs to be made, several data have shown that surgery provides the most optimistic chance of cure for PC. Surgery is, therefore, recommended whenever the benefits of pancreatectomy outweigh surgical complications, and the chance of local or distant metastases in the postoperative setting is low. This review also provided our insight for and experience in selecting surgical candidates by focusing on optimizing the overall survival of LAPC patients. Nevertheless, a collaborative approach to formulating standardized criteria for surgical candidate selection and treatment guidelines for LAPC is a common goal that pancreatologists worldwide should focus on.

Keywords: Locally advanced pancreatic cancer (LAPC); borderline resectable pancreatic cancer (borderline resectable PC); neoadjuvant treatment (NAT); resectability; carbohydrate antigen 19-9 (CA 19-9)

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Introduction

Management of pancreatic cancer (PC) remains a formidable challenge. Despite our constant effort in investigating the biology of PC and improving our therapeutic approaches (1), PC is very likely to become the second main cause of malignancy-associated mortality within the next 10 years (2). Since the identification of population at risk for early cancer detection and prevention remains difficult, only approximately 20% of the patients are candidates for pancreatectomy at the moment of

diagnosis (3). The difficulty in the management of PC lies in the selection of surgical candidates from the population with borderline resectable or locally advanced PC (LAPC). There is no consensus on the selection of surgical candidacy for LAPC, despite the general effort in maximizing survival with available treatment methods. The time point to perform surgery is also debatable. In general, surgeons need to operate when recurrence chances are low.

According to National Comprehensive Cancer Network (NCCN) guideline on pancreatic adenocarcinoma (version 1, 2020), LAPC is defined as a tumor with >180° contact with celiac and/or superior mesenteric artery, invasion/occlusion that results in unreconstructable portal and superior mesenteric vein, or invasion of celiac artery with aortic involvement (4). Thanks to the introduction of more effective chemotherapy, including FOLFIRINOX and gemcitabine-nab-paclitaxel (GnP), within the last 10 years, patients with LAPC have higher chances of being operable after receiving neoadjuvant treatment (NAT) (5,6). Considering that conventional cross-sectional imaging cannot discriminate the difference between cancer tissue and post-neoadjuvant scar tissue, the absence of radiological evidence of tumor progression after NAT should be regarded as a possible effective treatment response (7,8). Recently published series have shown improvements in the long-term survival of patients who underwent aggressive surgery for LAPC after NAT. It is evident that NAT has revitalized the role of vascular resections in pancreatic surgery, and has made new and more innovative techniques like artery divestment more achievable (9,10).

Studies have presented factors that predict resectability in cases of LAPC. Pre- and post-neoadjuvant carbohydrate antigen 19-9 (CA 19-9) serum levels have often been compared for their ability to predict chances of successful resection and overall survival. Similarly, tumor responses to the neoadjuvant chemotherapy based on cross-sectional imaging findings, following the Response Evaluation Criteria in Solid Tumors (RECIST) (11), have often been described and debated as an important reference for deciding surgical candidacy. It is important to emphasize that conventional radiology cannot accurately determine the extent of true tumor involvement after NAT (8).

This review paper describes existing approaches in selecting LAPC patients for tumor resection based on the currently available evidence. In conjunction with the summary of recent publications, our group also provided our insight for and experience of selecting surgical candidates focusing on optimizing the overall survival of LAPC patients. A collaborative approach on formulating a standardized criterion for surgical candidate selection and treatment guidelines for LAPC is a common goal that pancreatologists worldwide should focus on.

Role of NAT in the selection of surgical candidates with LAPC

Surgical intervention is the only potentially curative modality of treatment for PC. The role of NAT in PC is indispensable in achieving resectability in the initially inoperable patients. In the era prior to the introduction of FOLFIRINOX and GnP, surgery after NAT with gemcitabine with or without radiotherapy (RT) of LAPC was extremely rare (12). Within the last decade, the introduction of FOLFIRINOX and GnP has played a significant role in improving the overall survival of PC patients (5,6,13), as LAPC patients would more likely become operable after undergoing more effective chemotherapy treatment (14-19). Therefore, FOLFIRINOX and GnP are currently the preferred first-line regimens in the neoadjuvant setting for patients with LAPC. Considering that PC is almost always a systemic disease at the moment of diagnosis and that PC recurrence is generally represented as distant metastasis or local recurrence in 23.7% of cases (20), the primary objective of NAT in LAPC should not be focused on tumor size reduction for achieving easier resection (21). Instead, the systemic treatment approach should focus on stratifying patients by tumors of different levels of biological aggressiveness according to response to NAT. Several attempts have been made to stratify patient prognosis based on the overall characteristics of a tumor instead of purely on anatomic features (22-24). With the improvement of oncologic therapy, studies have shown that arterial resections in well-selected cases can achieve similar long-term overall survival in experienced centers (9,25,26). The shift in this concept is critical as several reports have indicated that surgical resection after NAT for LAPC, even for metastatic PC, can give a significant increase in survival rate and even a chance for cure (16,18,19). Oba *et al.* have shown that administration of NAT and CA 19-9 levels are two of the eight prognostic factors of overall survival in the preoperative setting (21). However, there is no consensus with regards to how long NAT needs to be administered before proceeding to surgical treatment (*Table 1*). Some have indicated that ≥8 months of NAT is associated with better prognosis and resectability (17,19). Conversely, some

Table 1 Predictors for resectability

Author	Year	Period	Resection rate	CA 19-9 as predictor of resectability	Size change as predictor of resectability	Other
Satoi *et al.*	2013	2001–2009	40%	CA 19-9 does not predict resectability	PR/CR associated with better OS	≥8 months associated with better OS
Sadot *et al.*	2015	2010–2013	31%	>50% reduction	≥30% reduction	1/3 of patients will have a radiographic response after NAC/NACRT; PR (16%) typically underwent resection (15%; 15/101); SD (63%) typically underwent NACRT and 16% were resectable (16/101)
Marthey *et al.*	2015	2010–2012	36%	>30% decrease in 63 %, normalized in 35% resected cases	PR/SD underwent surgery	–
Hackert *et al.*	2016	2001–2015	51%	<400 U/mL* for good prognosis	N/A	Resection rate is 60.8% after FOLFIRINOX compared with 48.0% after gemcitabine
Michelakos *et al.*	2017	2011–2016	N/A	>100 U/mL* associated with poor DFS and OS	>3.0 cm on CT* associated with poor OS	–
Bednar *et al.*	2017	2010–2014	21%	>50% reduction	Radiologic downstaging is not common and was not analyzed	–
van Veldhuisen *et al.*	2018	2013–2015	20%	>30% reduction associated with resectability and better OS	PR/SD in combination with CA 19-9 >30% reduction predicts resectability	–
Lee *et al.*	2018	2012–2016	23%	CA 19-9 does not predict resectability[#]	PR/SD underwent surgery	Dose reduction was associated with poor resectability
Heger *et al.*	2019	2001–2017	52%	<91.8 U/mL, >40.7% reduction predicts resectability	N/A	–
Rangelova *et al.*	2019	2010–2017	49%	High CA 19-9 should not be a contraindication for surgery	PR/SD underwent surgery; RECIST criteria are not very useful because down-sizing of the tumor is unusual	Dose reduction of FOLFIRINOX was not associated with poor OS
Tanaka *et al.*[+]	2019	2011–2017	N/A	<150 U/mL* predicts resectability	≥50% reduction predicts resectability	≥8.1 months associated with resectability
Gemenetzis *et al.*	2019	2013–2017	20%	Median 72 U/mL* in resected (*vs.* 206 U/mL* in unresected) (P<0.001)	PR/SD underwent surgery	>4 months (without PD) may be eligible for surgery

*, after NAT; [#], median 43 U/mL in resected (*vs.* 197 in unresected cases) (P=0.519); [+], metastatic disease cohort. CA 19-9, carbohydrate antigen 19-9; DFS, disease-free survival; OS, overall survival; PR, partial response; CR, complete response; SD, stable disease; RECIST, Response Evaluation Criteria in Solid Tumors criteria; NAC, neoadjuvant chemotherapy; NACRT, neoadjuvant chemoradiotherapy; PD, progressive disease.

have argued that with radiological evidence showing no signs of disease progression, surgery may be warranted even after just ≥4 months of NAT (16). Although some studies have indicated that dose reduction of NAT is associated with poor resectability (27), Rangelova and colleagues have stated that this association does not apply to FOLFIRINOX (15). In fact, in the setting of successful surgical resection, dose reduction of mono-chemotherapy or other combination therapy did not seem to have a negative impact on survival (15). With resection rate reported to be as high as 51.9–61% after NAT (14,28), these results highlighted the potential synergistic effect of surgery and NAT in the treatment of LAPC.

Similar to LAPC, borderline resectable PC has higher R0 resection rate (73% *vs.* 48%; P=0.004), 3-year overall survival (31.9 *vs.* 18.1 months; P=0.014) after undergoing NAT with GnP compared to conventional upfront surgery (29). Similar trends were witnessed in an RCT comparing neoadjuvant chemoradiotherapy (NACRT) with GnP and upfront surgery: both the 2-year survival rate (40.7% *vs.* 26.1%) and median survival (21 *vs.* 12 months) were in favor of NACRT (30). A phase 2 clinical trial indicated that FOLFIRINOX in the neoadjuvant setting allows patients to have a higher R0 resection rate and ultimately higher median progression-free and overall survival (31).

RT has been commonly incorporated in the multidisciplinary treatment of PDAC, especially in the United States (21). Several publications have compared the effects of FOLFIRINOX with or without RT. When FOLFIRINOX is given with RT, the resection rate for LAPC is 13–44% (32-36); if FOLFIRINOX is given without RT, the resection rate is 51–100% (14,15,37-39). However, it is important to keep in mind these data are derived from retrospective studies and bias could exist as patients who undergo RT could generally have more advanced tumors. A large retrospective study has indicated that there is no difference in survival in NAT with or without RT (40). It is also important to note that complications of RT including radiation-induced arteritis could hinder the execution of artery resection and reconstruction. However, when stereotactic body radiation therapy (SBRT) or intensity-modulated radiation therapy (IMRT) is performed in an experienced center, the 90-day mortality rate could be as low as 0% (41). Additional prospective studies need to be performed to verify the effectiveness of RT with chemotherapy.

CA 19-9 surgical candidacy selection

Consensus with regards to the indication of surgical resection of LAPC after NAT is still lacking. Currently available studies the focuses on using post-NAT factors as predictors of tumor are all of retrospective nature (*Table 1*). The common candidates proposed as potential predictors of resectability are change in CA 19-9 and change in tumor size on cross-sectional imaging after undergoing NAT. The predictive role of these factors is, however, very debatable. Studies have indicated that the significant change in CA 19-9 after NAT (35,42-44) or a specific CA 19-9 serum level cutoff (14,19,28) predicts resectability or good prognosis. Published data have suggested that change in CA 19-9 could reflect the efficacy of NAT (45-47) and, therefore, LAPC with reduced CA 19-9 post-NAT could be managed surgically if survival benefit is carefully weighed against the perioperative morbidity of pancreatectomy and vascular resection/reconstruction. Heger *et al.* described that absolute serum CA 19-9 of <91.8 U/mL or post-NAT/pre-NAT CA 19-9 ratio of <0.407 after FOLFIRINOX is associated with resectability and better prognosis in LAPC (28). It is important to note that in the same study, the same dynamic variables CA 19-9 ratio was not associated with resectability or better prognosis when patients were given gemcitabine alone. This highlights the importance of FOLFIRINOX and GnP in modern pancreatology (5,6). Similarly, Tanaka *et al.* and Hackert *et al.* have described that CA 19-9 serum levels of <150 and <400 U/mL can predict resectability or overall survival in LAPC and even in metastatic PCs that underwent metastasectomy (14,19,48). Preoperative reduction in CA 19-9 has also been reported to be associated with higher rates of resectability and R0 resection in PC (48,49). On the other hand, several studies have indicated the inability of factors associated with CA 19-9 to predict resectability (17,18,27). Nevertheless, in a retrospective cohort of 233 LAPC cases, surgical resection was shown to have a positive impact on survival for all CA 19-9 serum level values, despite the fact that higher CA 19-9 is associated with a worse prognosis (15). The results of this study advocate the idea that high CA 19-9 serum level should perhaps not be an absolute contraindication for resection. It is also important to note that there are around 5–10% of the population who are Lewis antigen-negative and are CA 19-9 none or low secretors. PC in this subset of populations is usually very aggressive and has

high proliferative and migratory characteristics (50). Luo *et al.* have shown that carcinoembryonic antigen (CEA) and CA-125 are associated with tumor metastasis and therapeutic response and are the two most reliable known biomarkers for Lewis antigen-negative PC with sensitivity (and specificity) of 63.8% (98%) and 51.1% (93.8%), respectively (51).

Radiological response to NAT for surgical candidacy selection

Aside from the utilizing serum level of CA 19-9, observing the tumor response to NAT could be a viable reference for resectability, as biologically less aggressive PC would respond more to mainstream chemotherapy. RECIST is a common reference used to assess the change in tumor burden of target lesions throughout the duration of systemic treatment of solid cancer (11). It is a common reference that pancreatologists utilize to objectively evaluate the response of PC to systemic treatment. Complete response (CR) or partial response (PR) to NAT is generally associated with a better prognosis (17). Although, cross-sectional imaging may be helpful to exclude patients with definite cancer progression from pancreatectomy, it has low accuracy in determining the viability of tumor post-NAT as existing radiologic imaging modalities cannot distinguish benign fibrosis from viable malignant tissue (8). This demonstrates that previously utilized criteria for determining resectability by cross-sectional imaging are perhaps inappropriate in patients who receive modern chemotherapy, such as FOLFIRINOX and GnP. Gemenetzis *et al.* have shown that of the 84 patients who underwent resection due to no signs of local disease progression or metastases, 77% had pathologically proven response to NAT (16). Therefore, all patients without radiologic evidence of local or systemic disease progression should be considered for surgical exploration. If evaluations rule out the possibility of R2/R1 resection or other contraindications for surgery, pancreatectomy with or without vessel resection should be considered.

LAPC resection and outcomes

Although radiologic downstaging is unusual and is reported to be approximately 28% (52), the R0 resection rate in selected LAPC patients after NAT has been reported to be >90% (8,52). Studies have correlated surgical resection of the primary tumor with significantly improved overall survival in LAPC patients, emphasizing that median survival of resected LAPC could range from 21 to 37.9 months and is significantly better than those of unresected LAPC (P<0.001) (14-17). Moreover, according to the newly developed nomogram that was recently published by our group, the LAPC-equivalent clinical T4 stage did not show a significantly worse prognosis in the resected cohort (23). Our work suggested that in the setting of undergoing modern chemotherapeutic agents, the role of local anatomic features of the tumor (including arterial involvement) has less importance than the biology of the disease and its response to chemotherapy (23).

Although radical surgery after NAT is expected to prolong survival, studies have shown that a 30% recurrence rate can be witnessed within 6 months postoperatively (53). Groot *et al.* reported that 81.8% of the 231 patients who underwent resection after NAT experienced recurrence (72.5% of which are distant metastasis) (20). The same cohort had a median postoperative recurrence-free period and median post-recurrence survival duration of 9.8 months and 8.4 months, respectively (20). Therefore, decisions for resection after NAT should be thoroughly evaluated in multi-disciplinary meetings and personalized treatment methodology that focuses on optimal timing between initial treatment and resection, accurate method of evaluating tumor remission, and patient's post-treatment quality of life should be assessed.

Due to improved surgical management, pancreatectomy has low 90-day mortality. In the modern era, this value can be as low as 2–4% when complex arterial resection is performed in an experienced center (52,54). These mortalities are caused by vascular thrombosis, liver failure, pancreatic fistulas, and sepsis-related multi-organ failure (26). These good results should be evaluated carefully. The large majority of studies on LAPC involve a small and very well selected group of patients, therefore there is a presence of selection bias. In a recent and large series published by one of the most experienced groups in the treatment of LAPC, the overall mortality rate was 8.8%, with a significant decrease to 4.8% in recent years (25).

Conclusions

Currently available NAT has significantly increased the survival in PC and have, therefore, increased the rate of resectability for patients affected by LAPC. However, a

consensus regarding the definition of resectability of PC does not exist. The majority of the current criteria is mostly anatomic-based. This approach has limitations, since we cannot accurately describe the biological response of the tumor to NAT through radiological imaging in many cases. Similar to the development of treatment for other cancers (55-57), the effectiveness of NAT for PC will improve and the surgical indications for PC will be extended so that more patients could benefit from surgical resection. Since the introduction of highly effective NAT for PC occurred only within the last decade, the majority of the available research data related to this topic are mostly of retrospective nature and, thus, have limitations related to the study type.

Future prospective randomized studies should be performed in order to investigate the algorithms for surgical candidacy selection, the adequate treatment duration of NAT, and the predictors for chemotherapy response. Future research should also focus more on the biology of PC, as anatomy-based treatment has limitations. With a better understanding of tumor biology and the emergence of more effective NAT, we should soon expect a refined definition of resectability that is more prognosis-based and is more independent of tumor anatomic involvement (23).

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