Onco-surgical Strategies in Pancreatic Ductal Adenocarcinoma

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ABSTRACT

Pancreatic ductal adenocarcinoma (PDAC) is an important healthcare problem because is a leading cause of death by cancer. PDAC is a highly lethal disease with a very dismal prognosis. Most patients present advanced disease at diagnosis. The management of a patient diagnosed with PDAC should be discussed in a multidisciplinary team in high-volume centers. Pancreatectomy represents the single hope of long-term survival for a patient with PDAC but the resectability rate is less than 20% of the cases. Several progresses were observed in the last years regarding the surgical and oncological approach for PDAC. The aim of the paper is to make a brief review of the current onco-surgical strategies available for patients with PDAC.

Key words: pancreatic ductal adenocarcinoma, pancreatectomy, adjuvant chemotherapy, neoadjuvant therapy, survival

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal disease and has a very dismal prognosis. Thus, in 2017 in the United States, although PDAC is not in top 5 the most frequent types of cancer, however, PDAC is the fourth leading cause of death by cancer both in men and women (1). Similar data were reported in the European Union in 2017 (2).

The 5-year overall survival rate for all stages of PDAC is less than 8% (1) and most patients will die within one year of diagnosis (3). Surgery (i.e., pancreatectomy) represents the single hope for a long-term survival in a patient diagnosed with PDAC (4,5).

One reason for the grim prognosis of a PDAC is related to the fact that most patients are diagnosed in advanced stages. Thus, 52% of the patients with PDAC have distant metastases at presentation, 29% have regional disease and only 9% have localized disease (1).

Another reason for the dismal prognosis of PDAC is that no consistent progress has been made in the management of these patients. Thus, the advances in developing effective treatment for PDAC are by far too modest and the treatment still remains largely palliative(3). In the last years some

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improvements were observed for the surgical technique used to treat PDAC (5-7), combined with new chemotherapy schemes. However, a recent study has shown that most new cancer drugs developed on the European market failed to deliver any clinically meaningful benefit (8).

Nevertheless, it appears that the overall 5-year survival rate of patients diagnosed with PDAC has increased with time (from 3% in 1975 to 7% in 2010), probably due to increasing availability of medical therapies (9).

The management of a patient diagnosed with PDAC should be discussed in a multidisciplinary team including the oncologist, surgeon, radiologist, pathologist, gastroenterologist etc.

The aim of the paper is to make a brief review of the current onco-surgical strategies available for patients with PDAC.

Resectable PDAC

A resectable PDAC is defined as a localized, non-metastatic tumor, without the involvement of the main veins or arteries (i.e., stage I/II)(4). The imaging method of choice for the assessment of resectability in a patient with PDAC is the thoraco-abdomino-pelvic multiple detector-computed tomography with thin sections, non-enhanced, late arterial and portal venous phases and reconstructions (so called "pancreas protocol") (10). The computed tomography of a localized, resectable PDAC should demonstrate no distant metastases, no evidence of superior mesenteric vein/portal vein abutment, distortion, tumor thrombus or venous encasement and clear fat planes around the celiac trunk, hepatic artery and superior mesenteric artery (11).

The current standard strategy for a patient with resectable PDAC is resection (i.e., pancreatectomy) followed by adjuvant chemotherapy (10). For resectable PDAC, pancreatectomy was associated with a statistically significant increase in survival, compared with any other therapy (12).

Unfortunately, resection is feasible in a limited number of patients with PDAC (15 – 20%)(10,13). A recent study has shown that even with resection the number of patients with PDAC who survived more than 5 years is very low (10.1%)(14). A 5-year survival rate of 10.1% after resection for PDAC is by far much better than the 5-year survival rate of 0.5% for unresectable localized PDAC or the 5-year survival rate of 0.1% for unresectable metastatic PDAC (14). The reported 5-year survival rates after pancreatectomies for PDAC vary between 8% and 36% (15).

Improvements of surgery for resectable PDAC were observed in the last years. Thus, the postoperative mortality after pancreatectomies has dramatically decreased from more than 25% before 1980 to less than 5% in the recent years (16). High hospital volume is strongly correlated with low mortality rates (17). Furthermore, a high volume surgeon is associated with low mortality rates after pancreatic resections (18,19). It is worth to mention however that even nowadays the mortality after pancreatectomies is not nil, particularly after pancreatoduodenectomies. Thus, Swanson and co-workers have shown that the 90-day mortality after pancreatic resections for cancer is double the 30-day mortality (7.4% vs. 3.7%)(20).

Improvements of surgical and oncological results for PDAC are strongly correlated with hospital volume and surgeon case load (4). Centralization of pancreatic cancer surgery in high-volume centers has been associated with improved resection rates and better survival rates (21).

A systematic review of the literature performed in 2008 by Garcea and co-workers did not identify any significant improvements regarding the median overall survival time after resection for PDAC over the years (16). However, a more recent study from the United States has shown that the median survival time after resection for PDAC has significantly increased from 14 months in the years 1992 – 1997 to 18 months in the years 2004 – 2010 (9). Interestingly, in this study of Luberic and co-workers it was observed that the number of patients resected for PDAC who survived more than 5 years did not change over the years (9). Nevertheless, the prognosis of a patient resected for PDAC is mainly determined by tumor-related factors such as tumor diameter, lymph nodes involvement, differentiation grade, resection margins status and completion of adjuvant therapy (10).

An extended lymph nodes dissection in PDAC has been demonstrated to have no survival benefit but only potential added complications and is not currently recommended as the routine (22).

Several technical refinements such as "artery-first" approaches were developed aiming to improve the surgical results after PDAC resection (6,23-25). Furthermore, the role of total mesopancreas excision was emphasized to better resect the patients with PDAC (13,23,26). The real benefit of these technical refinements for the long-term survival in patients with pancreatectomies for PDAC remains a matter of debate (27).

Adjuvant chemotherapy in PDAC brings an added survival benefit of several months. Adjuvant therapy

improves survival for all resected PDAC, including patients with early stages (i.e., stage I)(28).

Chemotherapy with fluorouracil or gemcitabine is the optimum adjuvant treatment after resection for PDAC (29). Gemcitabine is standard of care for patients with resected PDAC; association with a targeted therapy such as erlotinib appears to have no benefit (30). However, association of gemcitabine with capecitabine appears to bring a significant survival benefit for patients resected for PDAC (31). Ongoing clinical trials are evaluating the potential benefit of FOLFIRINOX or gemcitabine plus nab-paclitaxel over gemcitabine for adjuvant treatment in patients resected for PDAC (32).

The role of adjuvant radiotherapy after resection for PDAC remains controversial; geographical disparities were observed regarding the radiation as adjuvant treatment for PDAC, with low use in European patients (32).

In conclusion, the current standard strategy for a patient with resectable PDAC is pancreatectomy followed by adjuvant chemotherapy. These complex surgical procedures should be performed in high volume surgical centers by high case load surgeons.

Re-exploration and resection after initial diagnosis of unresectable PDAC

Nowadays, a number of patients with PDAC are operated in non-specialized surgical centers for pancreatic surgery. Assessment of resectability for PDAC in these centers is sometimes unclear and palliative bypass is often performed. Re-exploration of these latest patients with PDAC in high-volume centers allowed a pancreatic resection in up to 81% of the cases, without a negative impact on both early and late outcomes, compared with patients with upfront pancreatectomy (33-37). Thus, pancreatectomies in patients with PDAC initially assessed as unresectable can be safely performed in a group of patients by surgeons with expertise in pancreatic surgery, in referral surgical centers (33-36). Neoadjuvant therapy prior to re-exploration and resection for initially deemed unresectable PDAC has been recently demonstrated to have a survival benefit (38).

In conclusion, re-exploration and pancreatectomy for a selected group of patients initially considered as unresectable PDAC is feasible, safe and with a survival benefit in experienced surgical hands in high volume surgical centers.

Borderline resectable PDAC

A borderline resectable PDAC is defined as a tumor without distant metastases with portal vein/ superior

mesenteric vein involvement that allows safe resection and reconstruction and/or gastro-duodenal artery encasement up to the hepatic artery, without extension to the celiac trunk and/ or tumor abutment of the superior mesenteric artery less than 180 degrees of the circumference (39).

Invasion of the portal vein/ superior mesenteric vein in PDAC where safe resection and reconstruction are feasible is no longer a contraindication for resection in PDAC. Actually, this type of patients represents the largest part of patients with borderline resectable PDAC.

Initially, a venous resection was not found to have a negative effect on postoperative morbidity and mortality rates after pancreatectomies for PDAC (40). However, more recent data have shown that a venous resection during pancreatic resections for PDAC is associated with increased rates of complications (41-44). A posterior or a mesenteric approach appears to facilitate a venous resection and reconstruction during pancreatoco-duodenectomies for PDAC (7,27,45,46).

Recent meta-analyses have shown that patients with venous resection during pancreatoco-duodenectomies for PDAC have significantly lower negative resection margins and survival rates (41,43). The histological proof of venous invasion in PDAC has a detrimental effect on survival rates after pancreatectomies with venous resection for PDAC (42,47,48). There is a correlation between radiographic appearance and pathological grade of portal vein wall invasion in PDAC (49).

Arterial resections during pancreatectomies for PDAC are feasible and safe (50-52) but appear to have no demonstrated benefit and are associated with increased complications rates (53,54). However, some surgical centers reported good outcomes after arterial resections (55), particularly for distal pancreatectomies with celiac axis resection (56,57).

The treatment of a patient with a borderline PDAC is multimodal. Currently there are two approaches to a borderline PDAC: upfront surgery and neoadjuvant therapy followed by resection. Some surgical teams prefer upfront surgery for borderline resectable PDAC (42,58,59). Furthermore, the International Study Group for Pancreatic Surgery does not recommend routine neoadjuvant therapy for patients with PDAC and venous invasion where resection and reconstruction is feasible (39). However, a recent French multicentric study has shown that neoadjuvant therapies is a better strategy for patients with borderline resectable PDAC with venous invasion, compared with the upfront surgery, in term of survivals (60). The value of neoadjuvant therapy in borderline PDAC will be discussed in

an upcoming paragraph. Nevertheless, the upfront surgery is no longer recommended for patients with borderline PDAC, particularly for patients at high risk for positive resection margins.

In conclusion, patients with portal vein/ superior mesenteric vein invasion represent the largest part of patients with a borderline resectable PDAC. The optimal therapy for borderline resectable PDAC remains a matter of debate. However, neoadjuvant chemotherapy appears to have a benefit for borderline resectable PDAC. A venous resection during pancreatectomies for PDAC can be safely performed but increased complications rates should be expected compared with patients with pancreatectomies without a venous resection.

Neoadjuvant therapies in PDAC

Neoadjuvant chemotherapy has been proposed even for resectable PDAC considering the disease as systemic from the beginning (32). The rationale of a neoadjuvant therapy in resectable PDAC is early control of the disease and potential selection of patients who might really benefit after pancreatectomies (32). Furthermore, a neoadjuvant treatment may lead to tumors downstaging and increased chances of negative resection margins. Negative resection margins operative specimen after curative-intent surgery for PDAC is of utmost importance, with significant impact for the long-term survival (61). The studies in the literature evaluating the role of neoadjuvant therapy for resectable PDAC did not reach meaningful conclusions (32). Furthermore, the proportion of patients with neoadjuvant chemotherapy who were deemed resectable at laparotomy varies between 38% and 89% (32). Nevertheless, recently Mokdad and co-workers have shown that the use of neoadjuvant chemotherapy for localized, resectable PDAC has been associated with improved survivals (62). Conversely, a recent systematic review and meta-analysis has shown no potential benefit of neoadjuvant therapy for resectable PDAC (63).

Currently most of studies addressing the issue of neoadjuvant therapy in PDAC refer to borderline PDAC. The theoretical advantages of a neoadjuvant approach in PDAC includes potential downstage of disease, increase of negative resection margins rates, early treatment for micrometastatic disease and identification of patients with an aggressive tumor biology in whom resection offers no survival benefits. Thus, recent studies have shown the benefit of neoadjuvant chemotherapy with FOLFIRINOX or gemcitabine and nab-paclitaxel for borderline resectable PDAC (64-67).

A recent systematic review and meta-analysis has shown the potential benefit of neoadjuvant therapy for borderline PDAC (63).

It is worth to mention also that radiologic response does not correlate to pathologic response in patients with neoadjuvant therapy for borderline PDAC (68). Thus, the decision to undergo a pancreatectomy in these patients should not rely on the local imaging appearance of the tumor. Some technical refinements might be necessary to better resect these patients (69).

A recent systematic review and meta-analysis has shown that neoadjuvant therapy is associated with a radiological response (i.e., disease control) in 88% of the patients with resectable PDAC and in 77% of patients with borderline and locally advanced PDAC (70). Furthermore, the rates of resection after neoadjuvant therapy were 76%, 69% and 26% for resectable PDAC, borderline PDAC and locally advanced PDAC, respectively (70). The median overall survival time after neoadjuvant therapy and pancreatectomy was 30 months for resectable PDAC, 27.4 months for borderline PDAC and 18.7 months for locally advanced PDAC (70). It is worth to mention that a limited number of patients in the analyzed studies included FOLFIRINOX regimens (70).

In conclusion, for borderline PDAC neoadjuvant therapy appears to have a survival benefit, particularly when FOLFIRINOX regimens are used.

Locally advanced PDAC – conversion therapy

A locally advanced PDAC is usually considered as a primary unresectable disease and is defined by the absence of distant metastases with portal vein/ superior mesenteric vein involvement that do not allow reconstruction and/ or invasion of the aorta/ inferior vena cava and/ or superior mesenteric artery encasement more than 180 degrees (for PDAC of the pancreatic head) and/ or celiac trunk abutment (for PDAC of the pancreatic head) and/ or superior mesenteric artery encasement (for PDAC of the distal pancreas) and/ or encasement of the celiac trunk over 180 degrees (for PDAC of the distal pancreas)(10).

For locally-advanced PDAC resection has been demonstrated to be of benefit in terms of survival compared with the unresected patients (71), even for patients with microscopic positive resection margins (72).

Recent studies have shown that using a preoperative therapy with FOLFIRINOX in locally advanced PDAC allowed further resection in 60% of the patients (73), with up to 80% negative resection margins rates (74). A systematic review of the studies published in the

literature regarding the use of FOLFIRINOX in locally advanced PDAC has shown a resection rate of 28% and negative resection rate of 77%(75).

In conclusion, chemotherapy with FOLFIRINOX appears to convert to resectability an important percentage of patients with locally advanced PDAC.

Resection for M1 PDAC

Most patients with a PDAC have distant metastases at the time of presentation. Thus, a study performed in the United States has shown that more than 50% of the patients with PDAC present distant metastases at diagnosis (1). The most common sites for distant metastases in PDAC are liver, peritoneum, lung and para-aortic lymph nodes (76). Liver metastases were observed in more than 60% of the patients diagnosed with PDAC in a recent national epidemiological study performed in France (77).

The treatment of M1 PDAC usually includes symptom-directed palliative therapies with or without chemotherapy (78), with very low survival rates. It appears that for patients with M1 PDAC the quality of life is by far more important than the quantity of life (79).

A study from the United States including 32 452 patients with M1 PDAC (1988 – 2008) has shown a median survival time of only 3 months (80). However, it appears that the use of modern chemotherapy schemes was associated with improved survivals (9). Thus, the use of FOLFIRINOX or FOLFOX in M1 PDAC has significantly increased the survivals in M1 PDAC, compared with gemcitabine alone, leading to a median survival time of around 11 months (81,82). Alternation of FOLFIRI with gemcitabine also significantly increased the survival rates of patients with M1 PDAC, compared with fixed-dose rate gemcitabine, reaching also a median survival time of 11 months (83). Nevertheless, the use of nab-paclitaxel has been reported to be associated with improved survivals in M1 PDAC (84). The introduction of the above mentioned chemotherapy protocols after 2010 might explain the very low survival rates in the study of Worni and co-workers(80) where gemcitabine was the single validated chemotherapy option.

The value of resection in patients with M1 PDAC remains very controversial. However, the results of some relatively recent studies are worth to be mentioned and discussed.

The presence of inter/ para-aortical lymph nodes metastases is a M1 PDAC and was considered a long time a firm contraindication for resection (85). Nowadays it appears that this paradigm might shift.

Two systematic reviews and meta-analyses performed in 2016 have shown that patients with para-aortic lymph nodes metastases had worse survivals compared with patients without para-aortic lymph nodes involvement (86,87). However, recent studies did not identify the para-aortic lymph nodes involvement as an independent predictor of worse outcome in patients resected for PDAC (88,89). Furthermore, Hempel and co-workers showed that patients resected with para-aortic lymph nodes metastases have had significantly better survivals compared with patients with only explorative or palliative surgery (90). Thus, pancreatectomy might be of benefit in term of survivals for some patients with PDAC and para-aortic lymph nodes metastases but to clarify these aspects there is a need for further investigations (86,87).

Lung is a common site for metastases in patients with PDAC and chemotherapy is the main therapy (91). Resection for pulmonary metastases of PDAC was demonstrated to be feasible and safe but the survival benefit remains unclear (92). A recent study has shown that patients resected for metachronous lung metastases of PDAC have had significantly prolonged survivals compared with patients with only chemotherapy or observation (93). The number of reported patients resected for M1 lung PDAC in the literature is very low to draw definitive conclusions but there is a potential benefit of resection in selected patients (94).

Liver is the most frequent site of metastases in PDAC and, as already mentioned above, chemotherapy is the most frequently used therapy. The feasibility and safety of combined pancreatectomies and liver resections has been already demonstrated (95). Actually most patients resected for M1 liver PDAC reported in the literature underwent wedge/atypical only liver resections (96-98).

The survival benefit of resection for M1 liver PDAC remains a matter of debate. Thus, Adam and co-workers reported a median survival of 20 months in 40 patients resected for metachronous M1 liver PDAC (99). A study performed at Johns Hopkins did not show any survival benefit for resection of M1 periampullary cancers compared with palliative surgery (100). Seelig and co-workers showed no differences of survivals between patients resected for M1 PDAC and patients resected for M0 PDAC (101). Interestingly, a recent multicentric study has shown that the overall survival is significantly higher in patients with oligometastatic M1 PDAC of the head who underwent resection, compared with bypass, while for M1 PDAC of the body and tail no differences were observed (102). Recent reviews of the literature have shown that resection for M1 liver PDAC might have a survival benefit in carefully selected patients, particularly

with metachronous metastases (96,98).

The largest reported series of patients resected for M1 PDAC is coming from Heidelberg University and was published in 2017 (103). The series included 128 patients resected for M1 PDAC, out of which 85 patients were resected for M1 liver PDAC, most patients with atypical liver resections (103). The median survival in patients resected for M1 liver PDAC was 12.3 months (103). The authors concluded that resection for M1 PDAC “should be considered as it may be superior to palliative treatment” (103). However, the conclusions of this study (103) should be regarded with caution because no comparisons were made with a similar group of patients with palliative therapy. Furthermore, comparing the survival data of the present study – 12.3 months (103), with those reported in the study with FOLFIRINOX – 11.1 months (81), the differences does not appear to be significant.

In conclusion, resection for M1 PDAC remains controversial although a survival benefit was suggested in some highly selected group of patients. The selection criteria for patients that might benefit after resection for M1 PDAC remain largely unclear. The use of modern chemotherapy regimens such as FOLFIRINOX prior to any surgical approach might potentially help in selection of patients with stable M1 PDAC disease. For this latest group of patients with M1 PDAC there is a potential survival benefit of resection but further studies are urgently needed to draw any reasonable conclusions.

Resection for recurrent PDAC

Recurrence after curative-intent surgery for PDAC is unfortunately a common feature and is encountered in more than 80% of patients (104-106). The recurrence can occur at the local site of resection and/or in the liver, peritoneum, lung or other distant sites. A local recurrence is encountered in almost 75% of the patients after curative-intent surgery for PDAC, while distant metastases were observed in 66%-83% of the patients (mainly liver and peritoneal)(76,104,105).

Since most patients resected for PDAC will have distant metastases at the time of recurrence, an isolated non-invasive local recurrence is a rare appearance after resection for PDAC (104-108). Thus, there are few data in the literature about resection for recurrent PDAC.

A group of researchers from Heidelberg University have shown that resection for isolated local recurrence of PDAC can be carried out safely and with potential survival benefits (109). Similar data were reported in Japan (110), United States (107;108) and other European countries (111). A study published in 2016 has

shown a 5-year survival rate of 40.1% after resection for recurrent (112).

In conclusion, resection for recurrent PDAC is feasible, safe and with survival benefit in a selected group of patients. How to select the patients with recurrent PDAC who might really benefit from resection remains unclear.

CONCLUSIONS

- The management of a patient diagnosed with PDAC should be made by a multidisciplinary team, including from the beginning the oncologist, surgeon, gastroenterologist, radiologist, pathologist etc
- Resection with adjuvant chemotherapy represents the single hope for long-term survival in PDAC
- Re-exploration and resection of initially deemed unresectable PDAC can be safely performed in high-volume centers by experienced surgical teams, with survival rates similar to those of primary resected PDAC
- Neoadjuvant chemotherapy appears to improve the prognosis of patients with borderline resectable PDAC
- Resectability should be the main end point of chemotherapy in locally advanced PDAC
- Chemotherapy (particularly FOLFIRINOX) may convert to resectability more than 50% of the patients with initially unresectable locally advanced PDAC
- Resection might confer a survival benefit in a selected group of patients with M1 PDAC
- Resection for recurrence of PDAC is feasible in a subgroup of patients, with a survival benefit
- The patients with PDAC should be managed in high-volume centers

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