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Recent Developments in the Treatment of Pancreatic Cancer

Desenvolvimentos Recentes no Tratamento do Cancro do Pâncreas

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ABSTRACT

Pancreatic duct adenocarcinoma is currently the sixth-leading cause of cancer death worldwide and the fourth in Europe, with a continuous increase in annual lethality in Portugal during the last two decades. Surgical *en-bloc* resection of the tumor with microscopic-negative margins and an adequate lymphadenectomy is the only possibility of long-term survival. As this type of cancer is a systemic disease, there is a high rate of recurrence even after curative resection, turning systemic therapy the core of its management, mostly based on chemotherapy. Neoadjuvant strategies for nonmetastatic disease showed significant improvement in overall survival compared with upfront surgery, namely in borderline resectable disease. Moreover, these strategies provided downstaging in several situations allowing R0 resections. Under these new oncologic strategies, several recent surgical issues were introduced, namely more aggressive vascular resections and even tumor resections in oligometastatic disease. This review revisits the state-of-the-art of surgical and oncological interventions in pancreatic duct adenocarcinoma and highlights recent advances in the field aiming to achieve higher survival rates.
Keywords: Carcinoma, Pancreatic Ductal/drug therapy; Carcinoma, Pancreatic Ductal/surgery; Carcinoma, Pancreatic Ductal/therapy; Pancreatic Neoplasms/drug therapy; Pancreatic Neoplasms/surgery; Pancreatic Neoplasms/therapy

RESUMO

O adenocarcinoma ductal é atualmente a sexta causa de morte oncológica a nível mundial, e a quarta na Europa, com um aumento contínuo da letalidade anual em Portugal nas duas últimas décadas. A ressecção cirúrgica em bloco do tumor com margens microscopicamente negativas e com uma linfadenectomia adequada é a única possibilidade de sobrevida a longo prazo. Como o adenocarcinoma ductal é uma doença sistémica tem uma alta taxa de recidiva, mesmo depois de uma ressecção curativa, tornando a terapêutica sistémica o centro da sua abordagem, baseada sobretudo em quimioterapia. As estratégias neoadjuvantes para a doença não metastizada demonstraram uma melhoria significativa na sobrevida global em comparação com a cirurgia direta, nomeadamente em doença tangencialmente ressecável. Além disso, estas estratégias possibilitaram um re-estadiamento inferior em várias situações, permitindo ressecções R0. Sob essas novas estratégias oncológicas, foram introduzidas várias modalidades cirúrgicas recentes, nomeadamente ressecções vasculares mais agressivas e mesmo ressecções tumorais na doença oligometastática. Esta revisão aborda o estado da arte das intervenções cirúrgicas e oncológicas no adenocarcinoma ductal pancreático e destaca os avanços recentes na área visando alcançar maiores taxas de sobrevida.
Palavras-chave: Carcinoma Ductal Pancreático/cirurgia; Carcinoma Ductal Pancreático /tratamento; Carcinoma Ductal Pancreático/tratamento farmacológico; Neoplasias Pancreáticas/cirurgia; Neoplasias Pancreáticas/tratamento; Neoplasias Pancreáticas/tratamento farmacológico

INTRODUCTION

Despite its much lower incidence than other malignancies such as lung, breast, colorectal, or prostate, pancreatic ductal adenocarcinoma (PDAC) is the sixth-leading cause of cancer death worldwide and the fourth in Europe and in the United States.[1,2]

In Portugal, PDAC-associated deaths doubled from 1991 to 2015, reflecting a mean annual increase of around 3%, predicting a 51% increase in annual deaths during the next two decades: generating more awareness concerning PDAC is highly pertinent in the near future.[3]

Pancreatic cancer primarily consists of adenocarcinomas originating from the exocrine portion of the pancreas. However, a smaller proportion comprises neuroendocrine tumors derived from the endocrine pancreas. In most cases, PDAC develops through a series of cumulative genetic alterations starting from precursor lesions known as pancreatic intraepithelial neoplasia (PanIN). These PanIN lesions are microscopic in size (< 5 mm) and arise from the pancreatic ducts. Low grade PanIN represents ductal cells with mucinous differentiation and minimal atypia, while high grade PanIN corresponds to carcinoma in situ, indicating a more advanced stage. The average time between the progression from low to high grade PanIN1 is estimated to be approximately 11.7 years.[4,5]

Epidemiological studies have identified several modifiable risk factors associated with PDAC. These factors include overweight and obesity,[6,7] physical inactivity,[8] smoking,[9,10] alcohol consumption[11] and diabetes mellitus.[12] Additionally, there are non-modifiable risk factors such as age,[13] chronic pancreatitis,[11] and genetic factors/family history of PDAC.[14]

Pancreatic duct adenocarcinoma is usually diagnosed at advanced stages, with 53% of the patients having metastasis at the time of diagnosis. The prognosis remains very poor, with a 5-year survival rate of 2.9% for metastatic disease and just 20% for resectable disease.[1] Therefore,

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identifying high-risk individuals for early detection is a rising strategy, using new diagnostic and therapeutic tools.

About 10% of PDAC cases harbor inherited factors or associated germline pathogenic variants, and a smaller number of these will have a therapeutically actionable gene change. Among these, one of the most common molecular abnormalities are mutations in the breast cancer susceptibility genes (BRCA 1/2), making these cells particularly sensitive to platinum-based chemotherapy and olaparib as maintenance therapy.[15,16]

The only potentially curative treatment is surgical resection with negative margins (R0), and this statement has remained accurate for more than 20 years.[17,18] Local radicality (R0) in oncological pancreatic surgery includes *en-bloc* resection of the tumor with clear margins in combination with an adequate extent of lymphadenectomy, which follows the same principles of any digestive cancer.[19]

Local radicality is more difficult to achieve in PDAC compared to other gastrointestinal cancers, due to the pancreatic anatomical relationships (with the major visceral blood vessels), and to PDAC biology (with its predisposition for perineural invasion and growth towards these main structures).

Radicality is defined by the resection margin (R−) status and by the distance to it.[20]

The R-status has considerable impact on survival outcomes if all relevant margins (including transection and circumferential) are thoroughly evaluated according to current standards. If a pancreatic head cancer was resected with a minimum safety margin of 1 mm, this is associated with a median survival of 42 months and a 38% five-year survival rate. For left-sided pancreatic cancers the median survival and five-year survival associated with a minimum safety margin of 1 mm are even more favorable, with 62 months and 53%, respectively.

Surgical resection will remain the cornerstone of treatment for localized PDAC, and its indication will even be extended.[21] Despite more active systemic therapy combinations for PDAC, cure remains elusive and is feasible only with localized, operable disease.[22]

Based on whether a distant organ is involved, PDAC is divided into metastatic or nonmetastatic diseases. In surgical terms, resectability status for the nonmetastatic group is defined by the probability of obtaining a negative margin, assessing circumferential degrees of contact between the tumor and the arterial (superior mesenteric artery, SMA, celiac axis, CA, and common hepatic artery, CHA) and venous (portal vein, PV, or superior mesenteric vein, SMV) structures: the so-called vascular margins. For nonmetastatic disease, that status can further be classified as resectable (RPC), borderline resectable (BRPC) and unresectable/locally advanced (LAPC) disease.[23] The concept of resectability itself is currently a point of debate, considering the context of neoadjuvant therapy (treatment given as a first step to shrink a tumor before the main treatment, which is usually surgery). Beyond anatomical factors, biological and conditional host-related factors should be evaluated before considering surgery.[24] New criteria are being proposed, including inflammatory response, liquid biopsy markers, and genomic mutations.[25]

Surgical options in the treatment of PDAC

There has been a continuous effort in order to achieve a R0 resection: surgical options aim for local radicality and should be guided towards the mesenteric and celiac arteries and at the mesenteric and portal veins.

All the techniques of PDAC surgery must be based on two closely related factors: efficacy and safety. The main parameters of safety are perioperative (90-day or in-hospital) morbidity and mortality, both mostly determined by the rate of postoperative pancreatic fistula. The efficacy of surgery is defined by two main outcome parameters: median survival time and five-year survival rates.

The efficacy is mainly determined by local radicality of the resection while its safety is mainly determined by the reconstruction.

Perioperative morbidity, especially pancreatic fistula and other septic complications have considerable impact on the possible delay in the administration of adjuvant therapy, which in turn is closely associated with survival. On the opposite, increase in local radicality (extended lymph node dissection, vascular/multivisceral resections, and total pancreatectomy) increases the risk of morbidity.[26]

Resection phase: efficacy issues

Lymphadenectomy

Pancreatic duct adenocarcinoma spreads rapidly to the regional lymph nodes with a high number of metastatic lymph nodes found even in early cancers, which is considered an important prognostic factor. Recent data highlights the importance of peripancreatic lymphatics in the progression and metastases and their potential as a predictor of patient outcomes and a therapeutic target.[27,28]

Due to the prognostic importance of lymph node involvement, lymphadenectomy is considered an essential step of any resection technique, and should be removed with the specimen whenever possible. Standard lymphadenectomy is a guide for surgeons when operating on patients with resectable tumors, and according to literature, extended lymphadenectomy does not benefit long-term survival and might lead to higher levels of morbidity.[29]

Comparable to the setting of pancreatic head resection, more extended lymphadenectomy is not recommended in distal resections, as this is associated with increased

morbidity without proven oncological benefit.

The volume of lymph node dissection in total pancreatectomy comprises standard lymph- adenectomy in pancreaticoduodenectomy and distal pancreatectomy.[30]

Artery-first approaches

The rates of R1 resection (removal of all macroscopic disease, but microscopic margins are positive for tumor) remain high with most patients, who develop recurrence either locally (mainly along the SMA margin) or liver metastases within the first two years.

The increasing use of neoadjuvant therapy for BRPC and LAPC has created the added challenge of local staging predominantly along the SMA. Starting surgical resection by the dissection of the SMA (artery-first approach) has a potential role allowing trial dissection and frozen sections along the SMA at an earlier stage of pancreatoduodenectomy before irreversible steps are taken to identify tumor regression along this margin.[31]

Recent studies suggest that there is only a marginal improvement in R0 resection status with an artery-first approach, and that therefore evidence is lacking to support its routine use.[32]

Oligometastatic PDAC

It defines an intermediate stage between limited and metastatic disease, being characterized by the presence of fewer than five metastases.[33] These include para-aortic lymph-nodes, liver, and pulmonary metastases.

According to currently valid guidelines, local resection procedures are not recommended in the metastatic stage of PDAC.[34]

There is increasing data suggesting that there may be subgroups within stage IV patients that might benefit from primary tumor and metastatic resection, especially in the setting of modern multimodal therapy regimens. No data are currently available so far, and therefore the oncological benefit cannot be assessed beyond individual experiences and individual case reports.

Vascular resections

Experience with vein resections has increased and is now accepted as a standard approach for selected patients in most institutions.[35] The need to perform a venous resection must be considered whenever required to get negative resection margins.

Surgical outcomes show that pancreatectomy with venous resection requires longer operative time and increases blood loss compared to standard resections, even if postoperative morbidity is similar.[36]

Based on the lower R0 rates and more positive lymph nodes, overall survival rates can be lower,[37] even though this remains controversial as a recent analysis showed similar survival in pancreaticoduodenectomy with venous resection compared to standard pancreaticoduodenectomy after adjustment for baseline characteristics.[38]

In contrast with the wide acceptance of vein resection in treating PDAC, performing pancreatectomy with artery resection remains debatable, since there are only a few publications that show favorable long-term survival results.

Traditional resectability criteria are currently challenged by the development of new and more powerful systemic treatments. In fact, recent literature has demonstrated that there are survival advantages associated with arterial resections compared to palliative procedures.[39]

There is evidence that overall prognosis and survival outcomes are more associated with the biological characteristics of the tumor rather than the vessels involved. Therefore, factors such as the aggressiveness of tumor development and its response to systemic therapy should be taken into consideration prior to performing surgical treatment.[40]

There are three main modalities of radical pancreatectomies with arterial resection that are described in the literature:

- Pancreaticoduodenectomy with superior mesenteric artery resection[41];
- Distal pancreatectomy with *en-bloc* celiac axis resection (modified Appleby Operation)[42];
- Pancreatoduodenectomy with common hepatic artery resection and reconstruction.[43]

These complex arterial resections should be reserved for high volume centers as they require experience beyond pancreatic surgery and entail skills in vascular and transplant surgery.

Minimally invasive (laparoscopically and robotic) surgery

As pancreatic surgery implies intricate dissections and complex sutured anastomoses, open surgery remains standard practice. Minimally invasive surgery practice among pancreatic surgeons is significantly lower than in other surgical specialties, largely due to a considerable learning curve for laparoscopic pancreaticoduodenectomy (PD). The LEOPARD-2 trial comparing laparoscopic versus open PD was terminated early due to a higher mortality directly related to the laparoscopic group of patients.[44]

As robotic pancreatic surgery is a new technology, there is still an absence of robust and established evidence to justify its use despite the perceived advantages.[45]

Reconstruction phase: safety issues

Post-operative pancreatic fistula and hemorrhage

Post-operative pancreatic fistula (POPF) is a serious

complication and a major cause of morbidity and mortality in pancreatic surgery. It is the main complication after cephalic pancreaticoduodenectomy, a procedure with a constantly high morbidity (30% - 50%) for the last 20 years.[46]

Post-operative pancreatic fistula are responsible for and/or associated with 70% of deaths due to septic and/or hemorrhagic complications.

The diagnosis of POPF has been based on the definition of the International Study Group for Pancreatic Fistula, namely a level of amylase in drained fluid greater than three times the upper limit of blood amylase from D3 postoperatively, associated with a significant change in postoperative course or management.[47]

According to the classification, post-operative hemorrhage is divided by time of onset:

- Early (within the first 24 hours after operation),
- Delayed (beyond 24 hours).

Based on the intensity, events of bleeding are classified into:

- Mild (hemoglobin decrease less than 3 g/dL and no need for surgical or interventional angiographic procedures),
- Severe (hemoglobin decrease more than 3 g/dL, life-threatening, invasive procedures are necessary).

Grade A consists of all episodes of early mild bleeding and Grade C of all late severe events. Grade B contains the early severe and late mild bleeding occurrences.

The most common bleeding sources are the stump of the gastroduodenal artery, followed by the common and proper hepatic artery, superior mesenteric artery, and other bleeding sites.[48,49]

Since 2003, it has been shown that radiological interventions, mainly for intraabdominal fluid collections due to undrained postoperative pancreatic fistulas but also for control of post pancreatectomy hemorrhage, can prevent the need for re-operation in a high proportion of patients postoperatively and reduce associated morbidity/mortality.[50]

Delayed gastric emptying

Delayed gastric emptying (DGE) is a frequent complication of pancreaticoduodenectomy, accounting for 14% - 30% of patients post-operatively. Delayed gastric emptying, or gastroparesis, occurs due to the impaired motor function of the stomach to empty its contents.

The International Study Group on Pancreatic Surgery (ISGPS) suggested as definition “the inability to progress to a standard diet by the end of the first post-operative week” and includes prolonged nasogastric intubation.[51]

It is possible that there is an association with several risk factors such as sepsis, intra-abdominal collections, POPF and respiratory complications. Management of these complications is mandatory. The type of digestive anastomosis makes no difference in the incidence of DGE.[52]

Patience from the surgeon is crucial. Reoperation is not indicated in the absence of any mechanical obstruction and can aggravate the problem.

Adjuvant therapy

Adjuvant therapy is the additional treatment given after the primary treatment to lower the risk that the cancer will come back.

After diagnosis, only 10% to 20% of cases are resectable.[18] Pancreatic duct adenocarcinoma is a systemic disease, with a 70% - 80% recurrence rate, even after curative resection, turning systemic therapy the mainstay of its management, largely based on cytotoxic agents.[53] It has been demonstrated that there are epithelial to mesenchymal transition (EMT) cells in mouse models seeding the liver at pancreatic intraepithelial neoplasia (PanIN) stage.[54] Circulating tumor cells (CTC) have been found in all stages of PDAC even in precursor lesions.[55] This is probably the reason why surgery alone does not enable long-term survival in these patients, with median survival times of around eight to 10 months and early tumor relapse in most of them.[56,57] Adjuvant chemotherapy has thus been developed during the last decades with improvement in overall survival (OS).

The ESPAC-1 trial showed for the first time that a fluorouracil-based adjuvant chemotherapy significantly increased survival, compared to surgery alone (median OS: 20.1 *vs* 15.5 months, respectively). A detrimental effect on survival by using concomitant chemoradiotherapy compared to chemotherapy was also shown.[58]

The CONKO-001 trial compared adjuvant gemcitabine in monotherapy versus observation in resectable PDAC, with a statistically significant improvement in disease-free survival (DFS) (13.4 *vs* 6.9 months, respectively), and an OS comparable between the gemcitabine and the control group (22.1 *vs* 20.2 months, respectively).[59]

The ESPAC-3 trial compared the two regimens fluorouracil and gemcitabine-based chemotherapy used in the ESPAC-1 and in CONKO-001 trials and showed no significant differences between the two (median OS 23.0 *vs* 23.6 months respectively) with a more acceptable safety profile in the gemcitabine arm (grade 3 - 4 toxicities: 7.5% *vs* 14.0% in the fluorouracil arm).[60]

In 2017, the ESPAC-4 trial demonstrated a superior OS of gemcitabine plus capecitabine *versus* gemcitabine alone in patients with R0 resection, of 28 months to the experimental arm and 25.5 months for the control arm (gemcitabine alone). No relapse free survival (RFS) was seen.[61]

The PRODIGE 24 trial (2018), compared modified mFOLFIRINOX (5-FU+irinotecan+oxalplatin) and gemcitabine: the toxicity was higher in the experimental arm

with grade 3 - 4 toxicities of 75.5% *vs* 51.1%.[62]

According to current guidelines, FOLFIRINOX (5-FU+irinotecan+oxalplatin) is now the first choice for fit selected patients.

New strategies are being implemented like the addition of immunotherapy -algenpantucel-L to standard adjuvant therapy, with a 12-month DFS of 62% and OS of 86%. A multi-institutional phase 3 trial is ongoing.[63]

At the American Society of Clinical Oncology (ASCO) in 2022 a phase I trial of adjuvant autogene cevumeran, an mRNA neoantigen vaccine identified from resected PDAC, concomitant with atezolizumab and FOLFIRINOX, was presented. The vaccine induced neoantigen-specific immunity with responders performing a long RFS versus non responders (median not reached versus 13.7 months). Further clinical trials are necessary.[64]

The role of radiotherapy in the adjuvant setting has contradictory data, as shown in the ESPAC1 and EORTC trials with no benefit, even in R1 resected patients. However, more recent studies with data reported from two different cancer database registries, showed potential benefit, particularly in node positive and R1 resection.[57,65-67]

Neoadjuvant therapy

Neoadjuvant/induction strategies (treatment given as a first step to shrink a tumor before the main treatment, usually surgery) result from the evidence of many trials with different entities (LAPC, BRPC, even RPC).

A meta-analysis of neoadjuvant versus upfront surgery, using six prospective randomized trials for RPC and BRPC, with 850 patients, significantly improved OS in an intention to treat approach for neoadjuvant treatment. All neoadjuvant chemotherapy were gemcitabine based, and none used associations with Nab-paclitaxel nor FOLFIRINOX.[68]

Neoadjuvant therapy seems consensual, but the best regimen to use is not well established.

The intention to treat results from a meta-analysis of 20 studies, representing 283 patients with BRPC who received neoadjuvant FOLFIRINOX, showed an OS of 22.2 months, 67.8% underwent a curative resection with a R0 rate of 89.1%. Toxicity with severe adverse events was more frequent with neutropenia 17.5%, diarrhea 11.1% and fatigue 10.8%.[69]

Similar results have been reported in a meta-analysis published in 2017 including eleven non-randomized studies (315 patients) with LAPC with a median PFS of 15 months and an OS of 24.2 months, which is identical to that reported in the ESPAC- 3 trial (patients in stage I-II that underwent resection followed by adjuvant therapy with gemcitabine).[70]

Gemcitabine and Nab-paclitaxel have been tested prospectively in this setting, and two phase II trials should be mentioned. The Italian GAP trial tested gemcitabine plus Nab-paclitaxel versus gemcitabine alone, with a reduction of 20% in distant spread after three cycles of the combination and an advantage in PFS, of seven versus four months, OS, 12.7 *vs* 10.6 months and a response rate of 27% *vs* 5%, respectively, in the combination arm and in the gemcitabine alone arm.[71]

LAPACT was a phase II single arm trial that tested induction with Nab-paclitaxel plus gemcitabine. The trial validated the activity of Nab-paclitaxel plus gemcitabine in LAPC and the potential to convert unresectable into resectable disease.[72]

In a time of more effective chemotherapy regimens, the role of chemoradiotherapy in the treatment of LAPC and even RPC remains poorly understood.

In LAP07, a phase III randomized trial, 449 patients with LAPC were enrolled between 2008 and 2011. This trial reported no differences in OS between groups, including chemoradiotherapy *versus* CT and GEM alone or GEM/erlotinib as maintenance therapy. However, the chemoradiotherapy group experienced a decrease in local progression (32% *vs* 46%, $p = 0.03$).[73]

The SCALOP multicenter phase II study was designed to evaluate the safety and efficacy of GEM-based and CAP-based chemoradiation in 74 patients with locally advanced PDAC. The initial results suggested that the CAP-based regimen would be better than the GEM-based regimen after the induction phase, and better tolerated. However, the difference in the nine-month PFS (primary endpoint) was not statistically significant. Long-term results of the SCALOP study revealed that the CAP-based chemoradiation was superior regarding OS and PFS.[74]

The AGEO-FRENCH Group published a retrospective non-randomized study in 2019 including 203 patients with BRPC or LAPC. This study evaluated the effect of the addition of neoadjuvant chemoradiotherapy to a FOLFIRINOX induction regimen and showed an OS and DFS of 45.4 months and 16.2 months, respectively. Patients with additional CRT had higher R0 resection rate (89.2% *vs* 76.3%), ypN0 rate (no residual tumor after chemo(radio)therapy in the lymph nodes) (76.2% *vs* 48.5%), and a higher rate of pathologic major response (tumor shrinkage) (33.3% *vs* 12.9%). In the FOLFIRINOX+CRT group, patients had a lower rate of locoregional relapse (28.3% *vs* 50.7%). Patients with additional CRT had longer OS than those receiving FOLFIRINOX alone (57.8 *vs* 35.5 months), suggesting that additional chemoradiotherapy may be beneficial in the neoadjuvant setting.[75]

The ALLIANCE A021501 study randomized patients with BRPC to either mFOLFIRINOX or preoperative mFOLFIRINOX, followed by stereotactic body radiation therapy (SBRT). The results demonstrated that neoadjuvant mFOLFIRINOX was associated with favorable OS.

Moreover, mFOLFIRINOX with hypo fractionated radiation therapy (RT) did not improve OS compared with the historical data.[76]

The PREOPANC-1 was a multicenter, phase III trial, where patients with RPC and BRPC were randomly assigned (1:1) to neoadjuvant chemoradiotherapy or upfront surgery. Neoadjuvant chemoradiotherapy consisted of three cycles of gemcitabine combined with 36 Gy radiotherapy in 15 fractions during the second cycle. After restaging, patients underwent surgery followed by adjuvant gemcitabine. Patients in the upfront surgery group underwent surgery followed by adjuvant gemcitabine. The primary outcome was OS by intention-to-treat.

Two hundred and forty-six patients were enrolled between 2013 and 2017. The long-term results showed a better OS for the chemoradiotherapy arm compared with the surgery upfront arm, 15.7 months *vs* 4.3 months, the five-year OS rate was 20.5% (95% CI, 14.2 to 29.8) with neoadjuvant chemoradiotherapy and 6.5% (95% CI, 3.1 to 13.7) with upfront surgery.[77]

ESPAC-5F was a prospective four arm phase II trial with the aim of determining the feasibility and efficacy of a comparison of immediate surgery versus neoadjuvant GEMCAP or FOLFIRINOX or CRT. The resection rate was 62% for immediate surgery and 55% for neoadjuvant therapy. The R0 resection rate in resected patients was 15% and 23%, respectively. The one-year survival rate was 40% for immediate surgery and 77% for neoadjuvant therapy. Albeit there was no difference in resection rate between arms, neoadjuvant therapy had a significant survival benefit compared with immediate surgery.[78]

In conclusion, both FOLFIRINOX and GEM/nab-P could be suggested as induction therapy to patients with LAPC and in the neoadjuvant setting for RPC or BRPC cases. Chemoradiotherapy in the neoadjuvant setting seems to decrease the rate of local recurrence, improve R0 resection and, in some studies, is associated with a survival benefit.

Many trials are ongoing, that could improve our understanding about the best strategy to follow in the years to come.

CONCLUSION

Pancreatic duct adenocarcinoma has become a leading cause of cancer death worldwide, presently the fourth in Europe and in the United States. In Portugal, a significant increase of PDAC-associated deaths in the last two decades predicts its continuous rise, justifying the need to raise awareness of this disease.

Its only potentially curative treatment is *en-bloc* surgical resection with negative margins (R0), in combination with an adequate extent of lymphadenectomy, according to staging (represented in Fig. 1).

This is a systemic disease, with a high recurrence rate, even after curative resection, turning systemic therapy the mainstay of its management, largely based on adjuvant cytotoxic agents developed during the last few decades with improvement in OS.

In the continuous effort to achieve an R0 resection aiming for local radicality and oriented at the mesenteric and celiac vessels, surgery for PDAC has been changing and

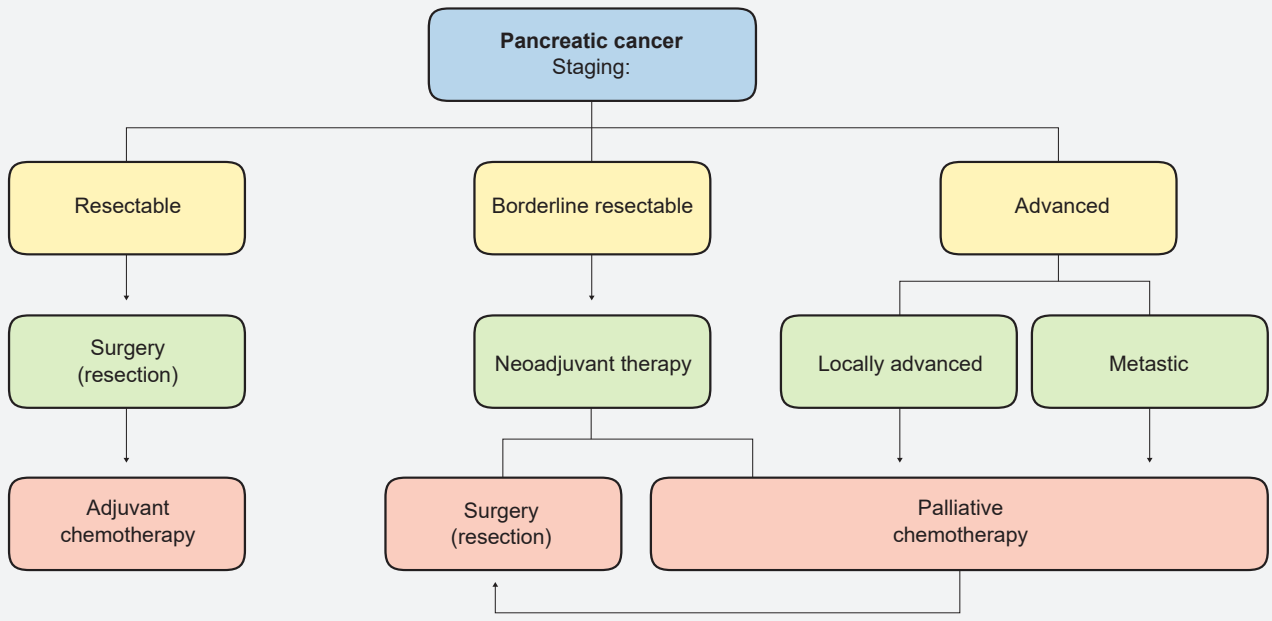

Figure 1 – Treatment algorithms for pancreatic cancer after staging

developing rapidly with specific technical approaches, including issues of efficacy and safety.

Neoadjuvant/induction strategies seem consensual, even though the best regimen is still not well established. Many trials that considered most different entities together, such as LAPC, BRPC and even RPC, showed significantly improved in OS in an intention to treat approach: there is an emerging emphasis in these strategies, to maximize R0 resections and early identification or failures.

There are several opportunities for progress through increased financial investment in fundamental research and the integration of data from diverse platforms of multi-omics (such as genome, proteome, transcriptome, epigenome, and microbiome combined analysis). The concept of using multi-omics as a valuable tool to subtype tumors and provide prognostic information is captivating, although its implementation in routine medical practice is still distant. Nevertheless, the use of these high-throughput technologies in the search for novel biomarkers and identification of therapeutic prospects holds tremendous potential. This approach can establish a framework wherein the data integration of multi-omics can yield valuable biomarkers with clinical usefulness. Moreover, understanding the influence of the stroma and its impact on tumor progression could represent a remarkable advancement in enhancing therapeutic efficacy. Investment should also prioritize the development of guidelines for early detection in high-risk groups, including those with genetic predisposition, individuals with family history of pancreatic cancer, smokers, alcohol consumers, patients with type 2 diabetes, patients with chronic pancreatitis, and individuals with obesity. Additionally, the implementation of national public health plans and raising awareness within the medical community and the public are crucial. These strategies have proven successful in other cancer types and are urgently needed to combat pancreatic cancer.

AUTHOR CONTRIBUTIONS

All authors contributed equally to this manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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