

CANCER OF THE PANCREAS: AN INTEGRATIVE REVIEW ON TREATMENT

Alexandre Adler Viana Lima

Medical Student at Centro Universitário Cesumar – Unicesumar, Department of Medicine. Scholarship holder of the Institutional Scientific Initiation Scholarship Program (PIBIC/ICETI-UniCesumar). Maringá-PR
<https://orcid.org/0000-0002-8938-4930>

Marcelo Fonseca Corrêa

Medical Student at Centro Universitário Cesumar – Unicesumar, Department of Medicine. Maringá-PR
<https://orcid.org/0000-0002-3156-2335>

Arthur André Regovichi

Medical Student at Centro Universitário Cesumar – Unicesumar, Department of Medicine. Maringá-PR
<https://orcid.org/0000-0003-4628-016X>

André Vinícius Ferla

Medical Student at Centro Universitário Cesumar – Unicesumar. Maringá-PR
<https://orcid.org/0000-0002-8497-5520>

Karin Juliane Pelizzaro Rocha Brito

PhD in Functional and Molecular Biology; Advisor at Centro Universitário Cesumar – Unicesumar, Department of Medicine. Maringá-PR
<https://orcid.org/0000-0003-4499-314X>

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Abstract: Introduction: Pancreatic cancer is a pathology with high lethality and increasing incidence worldwide. In this sense, it is a condition characterized by being usually detected in advanced stages, thus contributing to low five-year survival rates for patients. On the other hand, treatment of pancreatic adenocarcinoma is evolving with the introduction of new surgical techniques and medical therapies. **Objective:** to outline, through an integrative review, the most up-to-date knowledge on current treatment data and innovative approaches related to pancreatic adenocarcinoma while identifying gaps that aim to stimulate further research on this malignancy. **Method:** Integrative literature review whose searches were carried out through the association of descriptors and keywords in the Pubmed database. **Result:** This review analyzed selected articles and published between the years 2015 - 2022 and identified knowledge deficits, especially regarding the development of effective techniques for the treatment of pancreatic cancer. **Conclusion:** Although there is a great effort to optimize diagnosis and treatment, currently, patients who develop pancreatic adenocarcinoma are still subjected to inefficient medical care processes. **Keywords:** Oncology; Pancreatic Neoplasm; Treatment.

INTRODUCTION

The most accepted hypothesis for the emergence of pancreatic neoplasia is based on the precedence of non-invasive lesions, among which pancreatic intraepithelial neoplasia (PANN) is the most common¹. This hypothesis is strengthened based on genetic and epigenetic evidence and the presence of these lesions adjacent to pancreatic carcinomas¹. Still, the factors that contribute to the development of the disease are unclear.

With the progression of time, pancreatic cancer has emerged as a notorious health problem worldwide. In this context, pancreatic neoplasia ranks seventh among the leading causes of cancer death among both sexes¹. In addition, in the last decade, there has been an increase in incidence and mortality rates, characterized with a predominance in males¹. Regarding the global scenario in the future, the Global Cancer Observatory of the International Agency for Research on Cancer projects that by 2040 there will be a 61.7% increase in the total number of pancreatic cancer cases worldwide³.

From this perspective, the high lethality of pancreatic cancer is mainly related to the ineffectiveness of early detection, which is directly related to the low specificity of the initial symptoms. In addition, the diagnosis must be made with the help of histopathological studies and imaging tests, however, the pancreas is an organ of difficult visualization which is associated with a large amount of connective tissue hyperplasia and inflammatory reactions are found around the lesions. tumors, thus making the biopsy method difficult¹.

Therefore, due to the great epidemiological relevance and low survival rates, the management of pancreatic cancer is an area of knowledge that is widely studied. Within this framework, from the first descriptions made of pancreatic cancer to the present day, there has been a great evolution in the aspect of the clinical and surgical treatment of this malignancy⁴. Therefore, this work has the objective of carrying out an updated review on the treatment of pancreatic cancer that is able to synthesize the most recent findings that can answer the following questions: What are the current therapeutic strategies and new approaches that are being developed for the pancreatic cancer?

METHODOLOGY

The bibliographic survey of the present study was carried out using the PubMed database. In this sense, the determinant in the selection of articles for this review were studies that aimed to evaluate aspects of the treatment of pancreatic cancer. For this, the following criteria were adopted for the initial selection: (I) articles in English, Spanish and/or Portuguese; (II) title of the article that portrayed the theme; (III) integrative reviews; (IV) systematic reviews; (V) clinical studies; (VI) multicenter studies; (VII) articles published and indexed in the aforementioned database in the period between 2015 and 2022. Subsequently, the articles were tabulated and the selection was carried out jointly and discussed among all researchers based on the evaluation, first, of the title according to the following criteria: (I) exclusion of articles that do not contain the terms in the title: “*Pancreatic cancer*”, “*Pancreatic adenocarcinoma*”, “*Pancreatic tumor*”, “*Pancreatic ductal adenocarcinoma*” e “*Pancreatic neoplasms*” and (II) article titles that restrict the study to a specific population group. After this step, the screening was performed based on the reading of the abstracts and, ultimately, the complete reading of the remaining articles was carried out, being chosen which presented relevant content for this review.

The selection of information from the articles was carried out in pairs of researchers simultaneously (A.A.V.L and M.F.C) and (A.A.R and A.V.F), independently and blindly, later verified by a third researcher/ advisor (K.J.P.R.B), in order to avoid divergences. Therefore, the analyzes and the syntheses of the data extracted from the articles were carried out in a descriptive way, making it possible to observe, describe and classify the data in order to gather the knowledge produced on the topic explored in the review.

RESULTS AND DISCUSSION

Surgical resection is the treatment that offers a potential cure for patients with pancreatic cancer and, when associated with adjuvant treatment, it demonstrates better results related to the survival rate⁵. However, only 15-20% are able to perform tumor resection and are associated with a very low 5-year survival rate after the surgical procedure around 10-20% with an average of 24 months⁶. In addition, neoadjuvant therapies and innovative techniques of immunotherapies have shown promising results, however, more studies are needed to prove their effectiveness^{5,6}.

PREOPERATIVE EVALUATION

Preoperative preparation is critical to optimizing patient care⁷. Such assessment includes analyzing the relationship of the tumor to the vessels adjacent to it, such as the portal vein (PV), superior mesenteric vein (SMV), superior mesenteric artery (SMA), celiac axis (CA), hepatic artery (HA), along with the presence of metastases (most commonly liver, peritoneum, lungs). In addition, the evaluation of tumor operability also takes into account the risk-benefit of pancreatic resection for the patient. Thus, the physical and mental state of the patient must be considered before the surgical process, due to the stress that this process imposes on the individual. In addition, age is not an excluding factor for surgery, however, it is important to note that with increasing age, there is an increase in comorbidity⁸.

CRITERIA FOR SURGICAL RESECTION

Depending on the location of the tumor, surgical options for resection of pancreatic cancer include pancreatoduodenectomy, distal or total pancreatectomy⁵. Therefore, for

a pancreas tumor to be classified as resectable, it is necessary the absence of distant metastases and distortion of the SMV or PV, tumor contact less than 180° in vessels adjacent to the organ and the presence of clear fat planes around the CA, HA and SMA^{8,9}. In addition, a new concept introduced in pancreatic surgery addresses borderline resectable pancreatic cancer, which includes tumors involving the mesenteric-portal or arterial axis associated with the absence of distant metastasis, thus constituting an intermediate stage between resectable disease and technically unresectable.⁸

Another point to be considered regarding tumor resectability is the presence of pancreatic head tumors that can affect the lining of the gastroduodenal artery and AH which, to be considered resectable, cannot involve more than 50% of the circumference of the SMA wall. and affect CA. On the other hand, in cases of borderline tumors in the body and tail, contact with the CA is allowed, but only if the involvement of this is less than 50%⁸.

SURGICAL PROCEDURES

The surgical procedure for pancreatic cancer located in the head, uncinate region, or both is pancreatoduodenectomy, also called the Whipple procedure. Such surgery involves two steps including gastroenterostomy, ligation of the common bile duct and cholecystogastrostomy followed by resection of the duodenum and partial excision of the pancreatic head⁴. Therefore, perioperative mortality after pancreatic resection is derived from complications and almost half of all patients undergoing Whipple's operation develop one or more complications⁸. In this context, one of the main processes that drive the mortality of patients with pancreatic cancer undergoing the surgical process is the formation of pancreatic fistulas⁸. At another

junction, patients with tumors located in the body and tail eligible for surgery undergo a distal pancreatectomy and splenectomy.¹⁰

Predictors of better outcomes after the surgical procedure include tumor size, absence of lymph node metastases, negative resection margins, well-differentiated tumors, and intraoperative blood loss.¹⁰

Currently, with the improvement in mortality and morbidity of pancreatic surgery over time, the focus of research has focused on performing interventions with minimally invasive techniques⁷. In this sense, laparoscopic pancreatoduodenectomy is related to lower blood loss, length of stay and general postoperative complications compared to the open technique⁷.

INTRAOPERATIVE IMAGING EXAMS

Intraoperative ultrasound is currently the only imaging technique that the surgeon uses to delineate pancreatic adenocarcinoma and its surrounding structures during the surgical resection process¹¹. In this sense, such an exam is capable of providing high-resolution real-time images and, consequently, helps in the detection of lesions during the procedure, and can be used to determine tumor resectability, surgical planning, differentiation of cystic and non-cystic lesions, and identification of metastases.¹¹

Furthermore, recently, intraoperative imaging technologies using fluorescence with near-infrared (NIR) wavelengths have progressed significantly¹¹. In this sense, the advantages that this type of technique can offer include the ability to obtain images in real time with a NIR fluorescence camera system without interfering with the physician's workflow and, consequently, providing tumor resection with a greater preservation of normal structures and in a shorter time, thus reducing the period of anesthesia and its associated risks¹¹.

Finally, photoacoustic imaging (PAI) is a new technique with relevant potential. In this context, PAI is based on the photoacoustic effect in which a laser beam is used to stimulate the thermoplastic expansion of tissues, which, in turn, generates pressure waves which can be detected by the transducer and converted into images¹¹. From this perspective, the combination of light and sound that this method provides generates a considerable advantage over other imaging modalities such as CT, PET or ultrasound¹¹.

ADJUVANT TREATMENT

Neoadjuvant therapy corresponds to a treatment used for borderline and locally advanced lesions that consists of the combination of chemotherapy and radiotherapy⁷. The benefits of such a procedure include decreasing the likelihood of metastatic disease and tumor shrinkage to optimize surgical resection, as well as being associated with a greater survival advantage even in early-stage pancreatic adenocarcinoma^{10,12}. However, some evidence has not demonstrated benefits associated with this procedure in the management of pancreatic cancer and, in addition, has suggested that it may be harmful to treatment and therefore is not a recommended treatment in all oncology guidelines¹³. At this juncture, the mFOLFIRINOX (modified FOLFIRINOX) chemotherapy regimen is the current adjuvant standard in treatment-eligible patients¹³.

NEOADJUVANT TREATMENT

Neoadjuvant treatment is used for borderline and locally advanced lesions and consists of the combination of chemotherapy and chemoradiation⁷. Therefore, the preferred method applied in patients with good functional status is the administration of 5-Fluoracil, irinotecan and

oxaliplatin (FOLFIRINOX) associated with radiotherapy.⁷

PALLIATIVE TREATMENT

Palliative care aims to improve the quality of life of patients and their families, preventing and alleviating physical, mental, social and spiritual problems. Therefore, the main objective of this treatment is pain relief, nutrition and jaundice⁸.

Pain relief for pancreatic cancer requires a multimodal approach. Thus, according to the WHO analgesic scale, treatment with non-opioid drugs such as paracetamol or NSAIDs must be initiated⁸. If there is ineffective pain control, analgesic treatment with a weak opioid and subsequently a strong opioid is performed⁸.

For neuropathic pain, amitriptyline, sodium valproate, or gabapentin can be used⁸. In addition, a celiac plexus block can also be performed in cases of severe and intractable pain, either intraoperatively or guided by CT/endoscopic ultrasound⁸. In selected patients with severe local low back pain refractory to analgesia, palliative radiation may be considered to improve pain¹⁴.

Regarding malnutrition, pancreatic enzyme replacement can be performed, in addition to using nutritious drinks to promote patient weight stability, as this is associated with prolonged survival and better quality of life for patients with unresectable pancreatic cancer.⁸

Finally, for the treatment of obstructive jaundice in patients with unresectable pancreatic cancer, the use of self-expanding endoscopic metal stents is preferred over plastic stents and the surgical biliary bypass procedure, since it is associated with a lower incidence of cholangitis^{8,14}. In addition, in situations where there is no possibility of using endoscopic stents, percutaneous biliary drainage is a viable alternative option¹⁴.

IMMUNOTHERAPY

Immunotherapy corresponds to a procedure based on passive or active therapy. From this perspective, active immunotherapy has as the principle of action the stimulation of the recognition and elimination of tumor cells through a previously promoted immune response. This is done through a vaccine which can be administered as whole cells, proteins, peptides, DNA and RNA, which may result in antigen-specific T cell responses that promote tumor regression. On the other hand, passive immunotherapy consists of the exogenous administration of immunomodulators, such as mAbs (monoclonal antibodies), checkpoint inhibitors or cytokines⁸. Therefore, within this scope of research, there are great expectations for new treatments for pancreatic neoplasia,

however, the therapeutic role of this type of therapy still remains uncertain.⁶

CONCLUSION

In this review, the description of relevant information regarding current knowledge and possible advances associated with therapy involving pancreatic cancer was performed. In this sense, during the study, a wide area of scientific research was detected that are being carried out in order to improve the treatment of pancreatic neoplasia, aiming to increase the quality of life and survival of patients. However, it is noticeable that there are great challenges to be overcome and that there is still a long way to go in order to reach the stage of significant efficiency in the management of this disease.

REFERENCES

1. MIHALJEVIC AL, MICHALSKI CW, FRIESS H, KLEEFF J. Molecular mechanism of pancreatic cancer — understanding proliferation, invasion, and metastasis. *Langenbecks Arch Surg.* 2010; 395(4):295-308.
2. GLOBOCAN. Pâncreas. GLOBOCAN; 2020 [citado 9 maio 2020]. Disponível em: <https://gco.iarc.fr/today/home>.
3. Gupta N, Yelamanchi R. Pancreatic adenocarcinoma: A review of recent paradigms and advances in epidemiology, clinical diagnosis and management. *World J Gastroenterol.* 2021;27(23):3158-3181. doi: 10.3748/wjg.v27.i23.3158.
4. Torphy RJ, Fujiwara Y, Schulick RD. Pancreatic cancer treatment: better, but a long way to go. *Surg Today.* 2020 Oct;50(10):1117-1125. doi: 10.1007/s00595-020-02028-0. Epub 2020 May 30. PMID: 32474642; PMCID: PMC7837389.
5. McGuigan A, Kelly P, Turkington RC, Jones C, Coleman HG, McCain RS. Pancreatic cancer: A review of clinical diagnosis, epidemiology, treatment and outcomes. *World J Gastroenterol.* 2018;24(43):4846-4861. doi: 10.3748/wjg.v24.i43.4846
6. Amin S, Baine M, Meza J, Alam M, Lin C. The impact of immunotherapy on the survival of pancreatic adenocarcinoma patients who received definitive surgery of the pancreatic tumor: a retrospective analysis of the National Cancer Database. *Radiat Oncol.* 2020;15(1):139. doi: 10.1186/s13014-020-01569-5.
7. Gupta N, Yelamanchi R. Pancreatic adenocarcinoma: A review of recent paradigms and advances in epidemiology, clinical diagnosis and management. *World J Gastroenterol.* 2021;27(23):3158-3181. doi: 10.3748/wjg.v27.i23.3158.
8. Ansari D, Tingstedt B, Andersson B, Holmquist F, Stureson C, Williamsson C, Sasor A, Borg D, Bauden M, Andersson R. Pancreatic cancer: yesterday, today and tomorrow. *Future Oncol.* 2016 Aug;12(16):1929-46. doi: 10.2217/fon-2016-0010. Epub 2016 Jun 1. PMID: 27246628.
9. Kaufmann B, Hartmann D, D'Haese JG, Stupakov P, Radenkovic D, Gloor B, Friess H. Neoadjuvant Treatment for Borderline Resectable Pancreatic Ductal Adenocarcinoma. *Dig Surg.* 2019;36(6):455-461. doi: 10.1159/000493466. Epub 2018 Nov 8. PMID: 30408790.
10. Vareedayah AA, Alkaade S, Taylor JR. Pancreatic Adenocarcinoma. *Mo Med.* 2018 May-Jun;115(3):230-235. Erratum in: *Mo Med.* 2018 Nov-Dec;115(6):517. PMID: 30228728; PMCID: PMC6140147.

11. Tummers WS, Willmann JK, Bonsing BA, Vahrmeijer AL, Gambhir SS, Swijnenburg RJ. Advances in Diagnostic and Intraoperative Molecular Imaging of Pancreatic Cancer. *Pancreas*. 2018 Jul;47(6):675-689. doi: 10.1097/MPA.0000000000001075. PMID: 29894417; PMCID: PMC6003672.
12. Wang, D., Liu, C., Zhou, Y. et al. Effect of neoadjuvant radiotherapy on survival of non-metastatic pancreatic ductal adenocarcinoma: a SEER database analysis. *Radiat Oncol* 15, 107 (2020). <https://doi.org/10.1186/s13014-020-01561-z>
13. Mas L, Schwarz L, Bachet JB. Adjuvant chemotherapy in pancreatic cancer: state of the art and future perspectives. *Curr Opin Oncol*. 2020 Jul;32(4):356-363. doi: 10.1097/CCO.0000000000000639. PMID: 32541325.
14. Brunner M, Wu Z, Krautz C, Pilarsky C, Grützmann R, Weber GF. current clinical strategies of pancreatic cancer treatment and open molecular questions. *Int J Mol Sci*. 2019;20(18):4543. doi: 10.3390/ijms20184543