Most Successful Preventative Medical Interventions for Pancreatic Cancer

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Abstract

Pancreatic cancer remains one of the deadliest cancers in the world and has continued to increase in severity among people due to the increase in the aging population, rising rates of obesity, type 2 diabetes, and etc, resulting in low survival rates and significant impacts on the quality of lives (Klein, 2021). As a result, this cancer has led to the development of many different types of treatments in order to slow down or stop the rate of pancreatic cancer from spreading or becoming severe. Some of these treatments include surgical interventions (whipple procedure, total pancreatectomy, and distal pancreatectomy), immunotherapy, chemotherapy and radiation therapy, targeted therapy, and vaccines. This study aims to evaluate the most effective therapeutic strategies for enhancing patient outcomes by evaluating comprehensive analysis on clinical data, and investigating how these strategies affect the survival rates and overall patient well-being over 3 years after getting medical intervention. From this study, it can be concluded that distal pancreatectomy is preferable compared to other medical interventions due to its balance of lower complication rates, effective pain relief, and satisfactory survival outcomes, especially for tumors that are located in the tail of the pancreas. Comparatively, other treatments, while useful in specific contexts, present a higher risk and long term complications that can affect patients' quality of life.

Introduction

Pancreatic cancer is the third leading cause of cancer death in the United States with only 8.5% of pancreatic cancer patients being alive after five years after their diagnosis, and it is predicted in 2030 to become the second leading cause of cancer (University of Utah, 2019). Pancreatic cancer forms on the tissues of the pancreas, located between the stomach and the spine. This critical organ is tasked with making enzymes (juice) that breaks down food into nutrients, used for making sugar and hormones, which are important for controlling blood sugar levels and storing energy. If the pancreas fails to do its functions, several symptoms such as jaundice, yellowing of the skin and the white of the eye, light colored stools, dark urine, weight loss, fatigue, and upper or middle abdomen and back pain will result (National Cancer Institute, 2024). As a result, the introduction of preventative medical interventions was introduced. However, the reason for the lethalness of pancreatic cancer is due to three key factors: late diagnosis, Kinsey Cals, and the rapid spreadability of pancreatic cancers to other parts of the body. The earlier cancer is detected, the better the chance of surviving it, but since pancreatic cancer's symptoms do not show up until the late stages of the cancer, and there is currently no way to screen pancreatic cancer, which makes it difficult to prevent the spreading of it. Leading to the second reason, its ability to spread/metastasis. Pancreatic cancer has a tendency to spread throughout the body rapidly with 85% of patients who have this cancer unable to do surgery. Additionally, even when surgeons do try to remove the cancer, the pancreas, located by important blood vessels, makes surgery difficult as it is located in the "high-price real estate" known as Kinsey Cells. The pancreas is surrounded by several blood vessels and main parts of the guts (University of Utah, 2019). In light of these challenges, various therapies and medical interventions have been introduced to improve outcomes and enhance survival rates for patients diagnosed with pancreatic cancer. To address the challenges posed by pancreatic cancer, scientists and researchers have explored and implemented a range of innovative therapies and

medical interventions aiming to improve patient's quality of life and prognosis: surgery (whipple procedure, total pancreatectomy, distal pancreatectomy), radiation therapy, chemotherapy, chemoradiation therapy, targeted therapy, immunotherapy, and mRNA vaccines/vaccines. To provide a comprehensive overview of these therapies, it is essential to explore them in greater detail.

Surgical Interventions

Whipple Procedure

Surgical interventions on the pancreas is the removal of all or parts of the pancreas to treat cancer. One of the types of surgical procedures done is the whipple procedure, which is the removal of the head of the pancreas, gallbladder, part of the stomach, small intestine, and bile duct. This way, there is enough of the pancreas left to produce the digestive juices and insulin needed to support the body while removing the cancerous portions (National Cancer Institute, 2024). This procedure is usually used for tumors in the head of the pancreas, resulting in higher risk of complication but can be more curative as it preserves part of the pancreas. In a five year clinical, non-randomized interventional study, the scientists went through preoperative, operative, and postoperative procedures for 57 people, 19 females and 38 males who all had a mean age of 53 ± 5 years, symptoms containing 68.4% jaundice, 56.1% abdominal pain, and other symptoms such as vomiting, fever, and weightloss. The whipple procedure's mean operation time was 315 ± 38.3 minutes with a mean blood loss of 500 ± 130 mL. However, the incidence of postoperative complications was pancreatic fistula at 12.3%, hemorrhage at 10.5%, wound infection at 7% delayed gastric emptying at 5.3%, and enteric leak at 1.7%; overall, a total of 36.8% of patients experienced postoperative complications with the rest not having any issues. After a month, when the researchers went back to check the patients, patients who died, died of septic shock (8.78%), hemorrhage (5.3%), respiratory complications (ARDS) (1.7%), with a total of 15.8% of the patients in the study dying (Changazi, 2020). Based on this data, compared to previous data that studied the whipple procedure, the mortality of patients declined at 5%, resulting in 20-25% of patients being alive after 5 years of a whipple procedure, with overall mortality rates significantly high (Sheikh et al., 2023). The side effects of pancreatic fistula formation, which was the most frequent complication for the 12.3% of patients, are extremely life threatening as it can lead to infection, fluid loss, and sepsis, with 10.5% of the patients hemorrhaging as a result of shock, and gastric emptying leading to malnutrition, and dehydration. These severe side effects bring to question the safety and quality of life that patients would have after the procedure. Hence, while the whipple procedure demonstrated a decrease in mortality rates, concerns regarding the high incidence of postoperative complications remain significant; therefore it is important to compare this procedure with alternative surgical interventions.

Total Pancreatectomy

Total pancreatectomy is the removal of the whole pancreas, part of the stomach, small intestine, common bile duct, gallbladder, spleen, and nearby lymph nodes (National Cancer Institute, 2024), which is usually considered only when other options are not viable. In a retrospective

study, scientists conducted observations on 15 males and 32 females, all with a median age of 70 years who went to get total pancreatectomy, resulting in 19% and 2% mortality respectively. This study observed the after effects of total pancreatectomy 1, 2, and 3 years after the surgery with an average of 80%, 72%, and 65% survival, respectively. A total of 397 pancreatic resections were performed, with 47 of patients undergoing total pancreatectomy, 32 of which were females with a median age of 70 years old and having an operation time of 396 minutes and 800 mL of blood loss. Testing total pancreatectomy on the patients resulted in 65% of them being alive after three years, 95% of which had non-invasive intraductal papillary mucinous neoplasm, 34% for pancreatic adenocarcinoma, 49% with pancreatic adenocarcinoma from IPMN, and 0% of those with pancreatic adenocarcinoma de novo. Overall, total pancreatectomy had an average of 61% survival rate. However, this procedure resulted in surgical complications (36%), intra-abdominal abscess/sepsis (11%), biliary/GI fistula (9%), delayed gastric emptying (11%), wound infection (15%), reoperation (9%), medical complication (26%), gastric/colitis (2%), pulmonary (6%), cardiac (4%), thrombosis (2%), glycaemic event (4%), and renal insufficiency/urinary tract infection (6%) (National Library of Medicine, 2009). Hence, while total pancreatectomy had a lower rate in mortality compared to the whipple procedure, the post-operational symptoms and complications are still life-threatening, resulting in a need to consider a third surgical procedure: distal pancreatectomy.

Distal Pancreatectomy

Distal pancreatectomy removes the body and tail of the pancreas in addition to the spleen, only if the cancer spreads to it (National Cancer Institute, 2024). This procedure preserves the pancreas, maintaining most of the endocrine function, and tends to have a lower complication rate. In a retrospective analysis conducted on a cohort of 90 patients who underwent distal pancreatectomy for chronic pancreatitis over the past 20 years, with a mean postoperative follow up of 34 months, the pancreatic function was assessed preoperatively and postoperatively. Comparing the preoperative and postoperative data with each other, the patients had no significant difference in body weight post-surgery with a mean of 67.5 kg (pre-operation) vs 69.4 kg (post-operation), having a p-value= 0.06, or in albumin levels with a mean of 39.8 g/L (pre-operation) vs 37/6 g/L (post-operation) with a p-value = 0.14. These low p-values suggest that these results did not happen by coincidence and are rather accurate. While such was the case, complications occurred in 29 patients with 28% morbidity rate for spleen conserving procedures and 31% for splenectomies. The reoperation rate was 7% for bleeding and fistulas with an in-hospital mortality rate of 1% and exocrine function was abnormal in 61%, needing replacement therapy, and endocrine imbalance resulted in 52% of patients obtaining diabetes with a p-value of 0.025 and spleen conservation with a p-value of 0.04. On the brighter side, 57% of patients after receiving a distal pancreatectomy experienced little to no pain, compared to other diseases and were pain-free with only recurrent pain after 12 months. 53% of these patients were able to go back to work with no medical conditions (Hutchins et al., 2002). Overall, the distal pancreatectomy procedure performed well with low mortality and provided pain relief for around 60% of patients, but while it does not significantly affect the exocrine, it results in high risk of diabetes. However, the long-term survival rates suggest that 50-70% of patients were able to survive 5 years post-surgery.

Surgical Interventions Conclusion

Overall, based on the research studies conducted, the “best” surgical procedure for pancreatic cancer would be distal pancreatectomy. Distal pancreatectomy involved the removal of only the body and the tail of the pancreas, preserving much more of the endocrine function and allowing patients to maintain most of their metabolic functions. From the study, it can be seen that compared to the whipple and total pancreatectomy, distal pancreatectomy showed a significantly lower complication rate with 28-31% morbidity compared to the 36.8% morbidity observed in the whipple procedure and 36% in total pancreatectomy. There was a notable report that 57% of patients reported little to no pain following the procedure, indicating that distal pancreatectomy had a positive impact on the quality of life. In addition to the promising long-term survival rates with 50-70% of patients surviving 5 years post-surgery, it is better compared to other options. This however, does not discredit other procedures, this only suggests that distal pancreatectomy has the best results out of the three in terms of survival rates and overall quality of life after surgery. While the whipple procedure and total pancreatectomy had higher complication rates and morbidity, they have specific cases where these procedures can be better than distal pancreatectomy. The whipple procedure, for instance, can provide curative potential for patients that have localized diseases and alleviate symptoms such as obstructive jaundice, whereas total pancreatectomy can prevent the spread of cancer removing all pancreatic tissue, which is a significant approach for patients who are dealing with aggressive pancreatic tumors and offer significant pain relief for patients who are suffering from chronic pancreatic cancer pains. While the whipple procedure and total pancreatectomy have their drawbacks, such as the higher complication rates and negative impact on the patient’s quality of life due to the loss of pancreatic function, they still remain valuable surgical options under specific circumstances.

Immunotherapy

Another strategy that researchers have come up with targeting pancreatic cancer is immunotherapy. Immunotherapy involves using medication to activate one’s immune system that enables it to identify and eliminate cancer cells more effectively (American Cancer Society, 2024). From a retrospective analysis study of 407 clinical cases, patients had histological diagnosis, hospitalization between January 4th- December 31st 2012, adequate kidney and liver function, normal coagulation, and an expected survival of greater than 3 months. These researchers also had a control group who did not receive immunotherapy and compared their rate of survival and quality of life with each other. Researchers performed 407 clinical cases with 77 patients who received immunotherapy, 330 patients who received baseline treatment, and the rest who did not receive immunotherapy served as the control group. These patients were tested for 294 ± 207.5 days and compared using the Kaplan-Meier Method. When compared to the control group, the immunotherapy group had an overall survival at about 950 days, which was over 400 days greater compared with the control group. This data was measured to have a statistically significant p-value of 0.014. Additionally, 61% of patients developed a positive delayed-type hypersensitive response with 654% of patients having a greater improvement in their quality of life. While there was significant improvement, 28% of patients had fever, 25% had insomnia, 17% had anorexia, 12% had skin rash, and 31% had arthralgia. Therefore, it is evident that immunotherapy significantly enhances both the quality of life and survival rates of patients with pancreatic cancer.

Chemotherapy & Radiation & Chemoradiation Therapy

Additional treatment options for pancreatic cancer include chemotherapy, radiation, and chemoradiation therapy. Chemotherapy uses anti-cancer drugs to destroy cancer cells and are usually given intravenously (through the veins), orally, or as an injection whereas radiation uses high-energy rays, usually X-rays, to destroy cancer cells. This process can be external where the machine shoots radiation at the tumor or also internal where the radioactive source is placed in the body (Frysh, 2022). Furthermore, chemoradiation is a combination of both chemotherapy and radiation therapy (City of Hope, 2023).

Chemotherapy

In the context of chemotherapy for pancreatic cancer, studies have highlighted the importance of using specific drug regimens. The Radiation Therapy Oncology Group (RTOG) 9704 study found that 5-year overall survival rates were 22% for those receiving gemcitabine and 18% for those treated with 5-fluorouracil in combination with chemoradiotherapy, indicating that surgical intervention alone resulted in lower survival rates. The Charité Onkologie 001 (CONKO-001) trial further revealed that chemotherapy with gemcitabine improved the 5-year disease-free survival from 7% to 16.6%, emphasizing how adjuvant therapies reduce the recurrence likelihood. The Eastern Cooperative Oncology Group (ECOG) study also reported an improvement in the median survival from 9.2 months to 11.1 months for patients receiving only chemotherapy, indicating how chemotherapy extends patients' survival (Falco et al., 2023).

Radiation

When examining radiation therapy, neoadjuvant treatment strategies have shown promise. From the National Cancer Database, it revealed that the neoadjuvant systemic treatment yielded a median survival for 26 months compared to the 21 months for undergoing immediate surgery. In the Preoperative Chemoradiotherapy versus Immediate Surgery for Resectable and Borderline Resectable Pancreatic Cancer (PREOPANC-1) trial, which focused on borderline resectable pancreatic cancer, there was a median survival of 14.3 months while the immediate surgery group had a median survival of 15.7 months. From this study, local recurrence rates were clearly lower in patients who received radiation with the Locally Advanced Pancreatic Cancer 07 (LAP07) trial indicating that patients who underwent radiotherapy after four cycles of gemcitabine experienced a median survival of 15.2 months, slightly lower than the 16.5 months for chemotherapy alone, though chemotherapy had a reduction in lower recurrence rates (Falco et al., 2023).

Chemoradiation Therapy

Chemoradiation therapy, a combination of chemotherapy and radiation, has also been a focus of research. According to the study, the median overall survival reported for chemoradiotherapy was 23 months, while the median survival for post-operative chemotherapy alone was 22 months. This suggests that combining the two medical therapies may have some benefits. The greater R0 resection rate with neoadjuvant chemoradiotherapy, at 91.2%, is much higher than the rate of 79.2% observed with chemotherapy alone, further demonstrating the effectiveness

and suggesting better long-term outcomes. This is further corroborated by the PREOPANC-1 trial, which showed R0 resection rates of 70% in the neoadjuvant group and 40% in the group undergoing immediate surgery. Despite these advantages of chemoradiation therapy, toxicity remains a concern, as the Francophone Federation of Digestive Oncology (FFCD) and Selective Chemoradiation in Advanced Localized Pancreatic Cancer (SCALOP) trials found that 75% of patients could not complete the planned radiation due to the effects, resulting in poorer treatment outcomes compared to receiving gemcitabine alone (Falco et al., 2023).

Chemotherapy, Radiation, & Chemoradiation Therapy Conclusion

Based on the results of the study in 2023 done by Michal Falco, Bartlomiej Masojć, and Tadeusz Sulikowski, chemoradiation therapy stands out as the most effective approach for treating pancreatic cancer, especially where the tumor is borderline resectable or unresectable. The combination treatment of chemotherapy and radiation was able to enhance the overall treatment efficacy. The research states that chemoradiation therapy has higher R0 resection rates (91.2% compared to 79.2% for chemotherapy alone), which is crucial for long-term survival. Additionally, the median overall survival for patients undergoing chemoradiation has been reported at 23 months, higher comparatively to radiation and chemotherapy alone. While there are side-effects such as toxicity, the advantages provided by chemoradiation therapy outweighs it and improves the chances of disease-free survival, reducing locoregional recurrence rates, making it the best option out of the three when it comes to managing pancreatic cancer.

Targeted Therapy

Targeted therapy avoids healthy tissues but pinpoints and kills cancers through prescription of drugs (American Cancer Society, n.d.). In the clinical trials studied, one approach was the use of poly(ADP-ribose) polymerase (PARP) inhibitors like olaparib, which shows promise for patients with breast cancer gene 1 and 2 (BRCA1/2) mutations. In the Phase II clinical trial, olaparib achieved a tumor response of 50% with 25% of patients experiencing stable disease for at least eight weeks, leaning towards a median of 9.8 months. Studies involving ataxia telangiectasia mutated (ATM) inhibitors are exploring their potential benefits in combination with therapies such as olaparib, although more research is needed. Tyrosine kinase (Wee1) inhibitors such as adavosertib (AZD1775) have improved the overall survival rates to 22 months compared to 11.9 to 13.6 months for gemcitabine and radiation. Conversely, checkpoint kinase 1 and 2 (CHK1/2) inhibitors have shown limited efficacy with only partial responses and potential cardiotoxicity, raising concerns regarding their use (Leroux & Konstantinidou, 2021). Overall, the targeted therapies represent a significant advancement in the treatment of pancreatic cancer, though their efficacy and aftereffects vary, highlighting the need for ongoing research to optimize treatment strategies.

Vaccines

Researchers are developing mRNA vaccines as a tool against pancreatic cancer. As a result of mRNA vaccines currently being in preclinical and early clinical trials, specific outcomes are still being investigated. In order for these vaccines to halt pancreatic cancer growth, identifying tumor-specific antigens are important. The development of effective vaccines must be

exclusively associated with tumor cells, play a role in tumor progression, avoid immune tolerance, and stimulate antitumor immunity. In the 2022 study conducted by Xing Huang, Gang Zhang, Tian-Yu Tang, Xiang Gao, and Ting-Bo Liang, the two main types of antigens studied was tumor-associated antigens (TAAs) which were present in both normal and tumor cells but tolerized by the immune system and tumor-specific antigens (TSAs) that exhibit strong immunogenicity and diverse epitopes, making them ideal candidates for personalized vaccines. Pancreatic cancer is characterized by a complex immunosuppressive microenvironment that hinders T cell infiltration. mRNA vaccines have the potential to significantly activate immune responses, leading to reduction in tumor burden that can prevent the rapid spreading of pancreatic cancer. Evidence suggests that the mRNA vaccines can elicit sustained immune responses while offering long-term protection against tumor recurrence. While this is the case, mRNA vaccines are still emerging in preclinical and early clinical studies indicating promising improvements in overall survival and T cell response. There are still more clinical trials that are essential to confront the efficacy of mRNA vaccines and their ability to enhance patient survival outcomes. Ongoing research is critical to elucidating the full potential of mRNA vaccines in improving outcomes for pancreatic cancer patients (Huang et al., 2022).

Conclusion

Based on the studies and analysis of surgical interventions, immunotherapy, chemotherapy, radiation, chemoradiation therapy, targeted therapies, and vaccines, the treatment for pancreatic cancer that is the most successful is currently distal pancreatectomy. This assessment is grounded by several factors including patient outcomes, complication rates, and overall quality of life.

Distal pancreatectomy is the removal of the body and the tail of the pancreas while preserving a significant portion of the pancreatic tissue, which helps maintain the patient's endocrine function reducing the likelihood of other diseases such as diabetes and metabolic disorders post-surgery. In terms of survival rates, 50-70% of patients survived 5 years post-surgery, which is a strong indicator of the procedure's effectiveness compared to the alternative procedures. Additionally, it has lower complication rates. Compared to the Whipple procedure (36.8%) and total pancreatectomy (36%), it had a complication rate of 28-31%, contributing to a better quality of life for the patients. Additionally, a significant 57% of patients reported experiencing little to no pain following the procedure, suggesting that distal pancreatectomy positively impacts the quality of life. In contrast, patients undergoing whipple and total pancreatectomy experience higher rates of complications. This leads to a discussion of other treatments and their limitations highlighting the need for a more comprehensive approach.

Looking at the current treatment options available, it is essential to recognize their potential shortcomings, starting with the whipple procedure. While the whipple procedure has curative potential for localized tumors, the higher complication rates of 36.8% creates concerns for patients as they may face serious side effects including pancreatic fistula, hemorrhage, and delayed gastric emptying, which can lead to severe health complications and impact recovery. Despite the mortality rate improvement, the potential life-threatening complications makes this option less favorable for patients. Additionally, total pancreatectomy, the removal of the entire pancreas along with adjacent structures, results in higher likelihood of endocrine dysfunction,

leading to diabetes and other health complications. Although there was a lower mortality rate, the overall survival rates after three years are lower than distal pancreatectomy, which averages at a survival rate of about 61%. This high complication rate (36%) raises concerns about long-term patient outcomes. Regarding immunotherapy, chemotherapy, radiation, and chemoradiation, while these therapies show promise of improving overall survival and quality of life, there are often varying degrees of toxicity and side effects. For instance, chemotherapy has been proven to improve survival rates, but can also lead to severe adverse reactions. Targeted therapies and mRNA vaccines are still in clinical trials and are not yet standard treatments, thus making it difficult to evaluate their effectiveness compared to established surgical interventions.

To conclude, distal pancreatectomy stands out as the most successful surgical and medical option for treating pancreatic cancer, when applicable, due to the lower complication rates, higher long-term survival rates, and positive impact on the quality of life. While the whipple procedure and total pancreatectomy have their specific application, the associated risks and complications make them less favorable. Therapies such as immunotherapy, chemotherapy, and targeted therapies also have risks and complications such as toxicity that adds complication to the patients' quality of life, thus making them less favorable in comparison to distal pancreatectomy. Other innovative ideas such as mRNA vaccines and targeted therapies show potential but they still require further investigations and are not currently considered in primary treatment options compared to established surgical techniques.

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