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ORIGINAL ARTICLE

Recurrence Free Survival and Patterns of Recurrence in Pancreatic Ductal Adenocarcinoma: An Institutional Perspective

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ABSTRACT

Objective: To determine recurrence-free survival, patterns of loco-regional and systemic recurrence in patients with pancreatic adenocarcinoma.

Methods: We conducted a retrospective Study at the Department of Oncology in a tertiary care Hospital, Karachi Pakistan from January 2013 to December 2019. We studied the sample size of 67 adults of 18 to 70 years of age, diagnosed with adenocarcinoma of the pancreas and treated primarily with curative intent. All patients received complete treatment for the primary disease in our institution and data was extracted retrospectively from the hospital's medical record. Records were reviewed for recurrence of disease and patterns of loco regional and systemic recurrence. SPSS version 23 was used to analyze the data.

Results: Out of 67 patients with pancreatic adenocarcinoma, 65 patients (97%) had a complete clinical and radiological response on the follow up scans performed at three months after the completion of curative treatment. However 2 (3%) patients had disease recurrence/residual disease on first follow up scan. Subsequent follow ups showed cancer recurrence was observed in 60 (89.5%) patients, out of which 10 (14.9%) had loco regional while 7 (10.5 %) had systemic only recurrence. Most of the patients (n= 43; 64.1%) had systemic as well loco regional recurrences. The most frequent site of distant metastasis was the liver (66 %). The median recurrence free survival was 09 months (IQR= 8, 15).

Conclusion: This retrospective analysis highlights the patterns of recurrence after curative treatment of pancreatic ductal adenocarcinoma and indicates high recurrence rates which is expected for an aggressive disease like pancreatic carcinoma. By better understanding the patterns of recurrence, it can help in identifying subsets of patients with high risk of recurrence as well as in managing such patients more effectively.

Keywords: Pancreatic Adenocarcinoma, clinical outcomes, recurrence, metastasis, progression- free survival.

INTRODUCTION

Pancreatic cancer is a disease in which cancerous cells form in the tissues of the pancreas.[1] Globally, the incidence of all types of pancreatic cancer (85% of which are adenocarcinomas) ranges from 1 to 10 cases per 100,000 people, having a high prevalence for men in developed countries, and has shown stable relevance for the past 30 years relative to other common solid cancers. It is the fourth leading cause of death worldwide in men and women according to the recent cancer statistics, 2019[2].

According to the American Cancer Society, for all stages of pancreatic cancer combined, the one- year relative survival rate is 20%, and the five-year survival rate is 7%. These low survival rates are attributable to the fact that fewer than 20% of patients' cancers are confined to the pancreas at the time of diagnosis. Unfortunately, most patients are diagnosed with locally advanced or metastatic disease. Up to 15%-20% of patients are eligible for initial resection.[3] Reported five-year survival rates following pancreaticoduodenectomy for the node-negative and node-positive disease are 25%-30% and 10%, respectively.[2-4]

Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal disease characterized by a poor chemotherapeutic response. In particular, the effects of chemotherapy for PDAC are hampered by low vascularization, hypoxia, and diffusive transport limitations in the cancer microenvironment.[5]A study was done by Oettle et al in which patients with resected pancreatic cancer were treated with either gemcitabine in the adjuvant setting for six months in one group or to observe alone. The progression-free survival was 13.4 months in the treatment group compared with 6.7 months in the observation group.[6] Another study by Neoptolemos JP et al showed that adjuvant gemcitabine is the standard of care based on similar survival (43.1 months) and less toxicity than adjuvant 5-fluorouracil/folinic acid in patients with resected pancreatic cancer.[7] However, Neoptolemos JP et al found better survival and tumor response with gemcitabine and capecitabine than with gemcitabine alone for six months in resected pancreatic cancer with overall survival of 28.0 months' vs 25.5 months, respectively.[8] Another study by Thierry Conroy et al in patients with resected pancreatic cancer compared combination chemotherapy with fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) with gemcitabine monotherapy. The progression-free survival rate at 3 years was 39.7% in the modified-FOLFIRINOX group and 21.4% in the gemcitabine group and hence this is now the standard of care in patients with pancreatic cancer.[9] William Regine investigated fluorouracil-based chemo-radiation with either gemcitabine or fluorouracil and resulted in median survival and 5-year overall survival of 20.5 months and 22% with gemcitabine versus 17.1 months and 18 months with 5-FU.[10]

Currently, all recommended adjuvant treatment options for patients with pancreatic cancer have their own limitations. Hence, the purpose of this study was to evaluate clinical outcomes in terms of recurrence-free survival and the patterns of loco regional and distant metastases in patients with adenocarcinoma of the pancreas treated at a tertiary care hospital of Karachi, Pakistan. To the best of our knowledge this study has not been performed in our population and it is clinically significant in designing future prospective studies/trials for subgroups of patients with early recurrence.

METHODS

We conducted a retrospective study conducted at the Department of Oncology, Aga Khan University Hospital, Karachi, Pakistan from January 2013 to December 2019. A sample size of 67 was estimated using the WHO sample size calculator by taking progression-free survival in patients with adenocarcinoma of the

pancreas of 39.7%[1], with 95% confidence interval, 5% level of significance, and 11.8% bound on an error on estimation. Data of 67 patients of age 18 to 70 years of either gender, diagnosed with adenocarcinoma of the pancreas and treated primarily with curative intent with either surgery only or surgery followed by adjuvant chemotherapy or chemo-radiation therapy were included. All patients received complete treatment for the primary disease in our institution. Data was extracted retrospectively from the hospital's medical record. Non-probability purposive sampling technique was applied for sample selection. Records of the patients with other malignancy diagnosed histologically in addition to the adenocarcinoma of the pancreas, metastatic disease, and patients treated for any other malignancy diagnosed histologically in the past were excluded. Patients were treated as per the primary physician's discretion. All records were assessed for a complete history and systemic examination followed by routine investigations to rule out confounders and bias in the study results. After selection of the patients who underwent full treatment in our institution, they were followed up for two years for recurrence by evaluating Computed tomography (CT) scan of Chest, Abdomen, and Pelvis with contrast or Positron emission tomography-computed tomography (PET CT) of whole body without contrast and CA 19-9. Recurrence-free survival was defined as the time from the end of curative treatment to the occurrence of first documented radiological or histopathological proven disease or death whichever comes first. Data was also extracted for the patterns of recurrence specifying loco regional or distant recurrence. Information regarding age, gender, dietary status, performance status, and co-morbid (hypertension, diabetes mellitus, ischemic heart disease, and cerebrovascular accidents) were also evaluated and all data was kept confidential.

Frequency and percentages were calculated for categorical variables like demographics, site of the tumor, primary treatment received, dose and type of chemo, interruptions in treatment, tumor size, nodal status, number of nodes, margins, and type of recurrence which can either be local or systemic The frequency of outcome variables was calculated and stratified by site of the tumor, tumor size, and nodal status, number of nodes, margins, and resection status by using the chi-square test/Fisher exact test. Recurrence-free survival was calculated using Kaplan-Meier estimator which was also stratified on the basis of the type of recurrences. A p-value of less than and equal to 0.05 was considered as statistically significant. Data were analyzed using SPSS version 23

RESULTS

Total 67 patients with adenocarcinoma of the pancreas were selected for the study. 43 (64.2%) of the patients were of 41-60 years and there were predominant males. Majority of the patients were smokers, and hypertension was the most common associated comorbid condition. 41 (61%) of the patients had the most common primary site of involvement as the head of pancreas. 40 (59.7%) of the patients had moderately differentiated i-e grade 2 (G2) of the tumor. 32 (46.3%) had tumor size as T2 and 30 (44.8%) had a nodal status of N1 while 35 (52.2%) had nodal status as No as per TNM staging of pancreatic ductal adenocarcinoma (8th ed., 2017). 60 (89%) patients had R0 resection. (Table 1)

Of 67 patients, 18 (26.9%) patients underwent surgery only as a primary treatment. 12 (17.9%) patients had surgery followed by adjuvant chemo- radiation therapy and 37 (55.2%) received adjuvant chemotherapy. The most common type of chemotherapy regimen was gemcitabine (n = 18, 36.73%) followed by 5 FU + oxaliplatin +Irinotecan (FOLFIRINOX) in 11 (22.4%) patients. Among patients (n=12 i.e., 17.9%) who received radiation therapy, a total of 40- 50 Gy fractions of radiotherapy was delivered. Of all the patients who received adjuvant treatment, 9 (18.4%) patients had interruptions in the treatment plan due to poor tolerance and drug toxicities, with ≥ Grade 3 diarrhea being the most common cause in 4 (44.4%) patients that lead to hospitalization. However, these patients resumed treatment after stabilization of their clinical condition with drug-dose adjustments as per international guidelines. Out of 67 patients with pancreatic adenocarcinoma, 65 patients (97%) had a complete clinical and radiological response on the follow up scans performed at three months after the completion of curative treatment. However 2 (3%) patients had disease recurrence/residual disease on first follow up scan. (Fig. 1).

Table 1: Baseline characteristics of study variables

Characteristics	n (%)	Characteristics	n (%)
Age groups		Tumor size	
18-40	7 (10.4)	To	1 (1.6)
41-60	43 (64.2)	T1	10 (14.8)
60-70	17 (25.4)	T2	31 (46.3)
		T3	24 (35.7)
		T4	1 (1.6)
Gender		Nodal Status	
Male	41 (61.2)	No	35 (52.2)
Female	26 (38.8)	N1	30 (44.8)
		N2	2 (2.9)
Addictions		Number of nodes	
No	42 (62.7)	<3	26 (38.8)
Smoking	20 (29.9)	3-6	6 (9.0)
Alcohol intake	2 (2.9)		
Betel nut intake	2 (2.9)		
Gutka intake	1 (1.6)		
Comorbid		Grade of tumor	
No	14 (20.9)	G1	16 (23.9)
DM	20 (29.9)	G2	40 (59.8)
HTN	26 (38.8)	G3	9 (13.4)
IHD	7 (10.4)	GX	2 (2.9)
Site of tumor		Resection status	
Body	21 (31.3)	Ro	60 (89.5)
Head	41 (61.1)	R1	07 (10.4)
Tail	3 (4.5)		
Body and Head	2 (2.9)		

Fig 1: Response rate after completion of curative treatment (n=67)

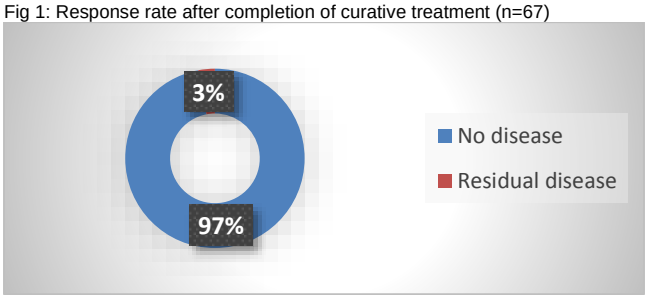


Table 2: Comparison of treatment outcomes after definitive treatment with the tumor characteristics

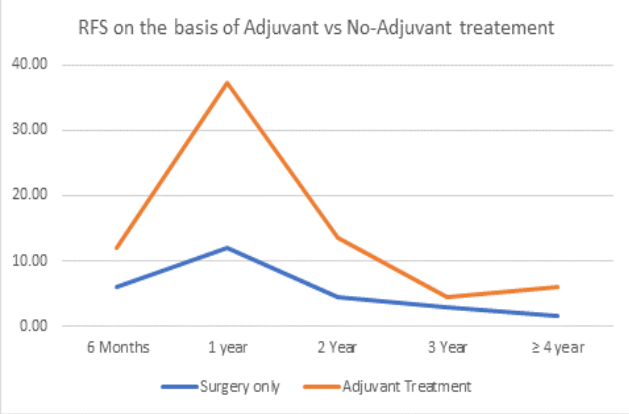
Characteristics	Treatment outcomes		p- value
	Complete Response n (%)	Residual/Recurrence disease n (%)	
Site of tumor			
Body	18 (26.8)	2 (2.9)	
Head	41 (61.1)	0 (0.0)	0.999
Tail	3 (4.6)	0 (0.0)	
Body and Head	2 (2.9)	0 (0.0)	
Grade of tumor			
G1	16 (24.0)	0 (0.0)	
G2	38 (56.8)	2 (2.9)	0.999
G3	9 (13.4)	0 (0.0)	
GX	2 (2.9)	0 (0.0)	
Tumor size			
To	1 (2.9)	0 (0.0)	
T1	10 (14.9)	0 (0.0)	0.267
T2	31 (46.3)	0 (0.0)	
T3	22 (32.8)	2 (2.9)	
T4	1 (2.9)	0 (0.0)	
Nodal Status			
No	35 (52.2)	0 (0.0)	0.267
N1	38 (56.8)	2 (2.9)	
N2	2 (2.9)	0 (0.0)	
Resection status			
Ro	58 (86.5)	2 (2.9)	0.999
R1	7 (10.4)	0 (0.0)	

Subsequent follow ups showed cancer recurrence was observed in 60 (89.5%) patients, out of which 10 (14.9%) had loco regional while 7 (10.5 %) had systemic only recurrence. Most of the patients (n= 43; 64.1%) had systemic as well loco regional recurrences. The most frequent site of distant metastasis was the liver (66 %). The median recurrence free survival was 09 months (IQR= 8, 15).

The relationship between treatment outcomes and tumor characteristics is displayed in table 2. Statistically, no significant relationship was found between treatment outcomes and site, grade, size, nodal status, and resection status of tumor (p>0.05).

Out of 67 patients who received any adjuvant treatment (n=49 i.e., 73.13 %), the median recurrence free survival was significantly prolong compared to those who did not receive any adjuvant treatment (n=18 i.e., 26.86) as shown in Fig 3.

Fig 2: Recurrence free survival comparison on the basis of adjuvant treatment.



DISCUSSION

Pancreatic adenocarcinoma is an aggressive condition with poor outcomes. The recurrence rates are still high even after curatively planned therapy, with local recurrence occurring in 35% to 86% of primary pancreatic tumor cases, with over 90% of patients relapsing within 5 years. [11] Resection techniques such as wider lymph node dissection and extended surgical resection are ineffective in terms of reducing recurrent cases or extending progression-free survival.[12] As a result, tumor recurrence occurs in the majority of patients, and treatment options are restricted.[13]

In this study, we looked at the treatment results in terms of recurrence- free survival and the patterns of loco regional and distant metastases in patients with pancreatic adenocarcinoma treated at a tertiary care hospital in Karachi, Pakistan. In our study, 97% of the patient had a complete response after curative treatment as evaluated by the follow up scans, three months after the completion of their treatment. The majority of them were treated with gemcitabine in our study, however, with recent advancement in identifying multi-agent chemotherapeutic regimen and significant outcomes of the clinical trials results by using such drug regimens, the treatment paradigm has changed significantly over the time with modified FOLFIRINOX as well as the combination of gemcitabine and capecitabine are now considered the preferred treatment options in adjuvant settings in patients with pancreatic adenocarcinoma [8-9].

Van den Broeck A et al. conducted a similar retrospective analysis of 145 patients with pancreatic cancer, the progression-free survival was estimated as 9.8 (7.5-12.4) months after curative resection.[14] Another research by Chaobin et al. looked at the timing and patterns of recurrence or metastasis following curative resection and showed that 44 out of 302 patients had recurrence within a year following resection. Further, they estimated patients who experienced recurrences, the median progression-free survival was 7.0 months (95 percent CI 6.2– 8.4).[15] According to the literature, progression-free survival of more than one year does not imply full cure, and these patients must have close follow-up visits.[11,15] Various time intervals or recurrence patterns would both contribute to different survival rates, therefore, it is important to assess the factors associated with progression-free survival in such patients to explore the different biological aspects of pancreatic ductal adenocarcinoma.[16]

Isolated recurrences were rare in our analysis, with 64.1% having loco regional as well as systemic recurrences. The liver and lung were the most common sites of metastatic recurrence found in our analysis. Recent studies have discovered a similar pattern of recurrences among pancreatic adenocarcinoma patients. [16-18] Regardless of the recurrence site, cytotoxic chemotherapy can control most recurrences. However, this may be sufficient for patients with evidence of loco regional disease. Organ-specific therapies may be appropriate for patients with the single-site disease. Trans arterial chemoembolization (TACE), radiofrequency ablation, radiation for local recurrence, and SIR-Spheres for the liver-only disease are examples of such treatments.[18-21] Surgical resection of single-site metastasis has also been reported recently with inconsistent reports of survival benefit with mixed results.[22- 24] Because there is a lack of high-quality data to inform these treatment decisions, further research in the form of randomized control trials is needed to determine the efficacy of this loco regional treatment options.[19, 20]

In the past few years, with the efforts for identifying molecular targets with the help of next generation sequencing (NGS), a large number of attractive therapeutic targets has been approved in pancreatic ductal adenocarcinoma. However, none of them have been approved so far in the adjuvant setting in patients with pancreatic carcinoma. Clinical trials are required to understand the molecular mechanics and the use of therapeutic targets in the adjuvant settings to improve the recurrence free survival as well as the quality of life among patients having such aggressive disease.

Further, our research had limitations because of a small sample size. Moreover, our study did not evaluate the quality of life, which should be the focus of future studies. Longitudinal studies are required to conclusively ascertain the findings of our study.

CONCLUSION

This retrospective analysis highlights the patterns of recurrence after curative treatment of pancreatic ductal adenocarcinoma and indicates high recurrence rates which is expected for an aggressive disease like pancreatic carcinoma. By better understanding the patterns of recurrence, it can help in identifying subsets of patients with high risk of recurrence as well as in managing such patients more effectively.

REFERENCES

1. Vareedayah AA, Alkaade S, Taylor JR. Pancreatic Adenocarcinoma. Mo Med. 2018;115(3):230-5.
2. Rawla P, Sunkara T, Gaduputi V. Epidemiology of Pancreatic Cancer: Global Trends, Etiology and Risk Factors. World J Oncol. 2019;10(1):10-27.
3. Gillen S, Schuster T, Meyer Zum Büschenfelde C, Friess H, Kleeff J. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta- analysis of response and resection percentages. PLoS Med. 2010;7(4):e1000267.
4. Saif MW. Controversies in the adjuvant treatment of pancreatic adenocarcinoma. Jop. 2007;8(5):545-52.
5. Sarantis P, Koustas E, Papadimitropoulou A, Papavassiliou AG, Karamouzis MV. Pancreatic ductal adenocarcinoma: Treatment hurdles, tumor microenvironment and immunotherapy. World J Gastrointest Oncol. 2020;12(2):173-81.
6. Oettle H, Neuhaus P, Hochhaus A, Hartmann JT, Gellert K, Ridwelski K, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. Jama. 2013;310(14):1473-81.
7. Neoptolemos JP, Moore MJ, Cox TF, Valle JW, Palmer DH, McDonald AC, et al. Effect of adjuvant chemotherapy with fluorouracil

plus folinic acid or gemcitabine vs observation on survival in patients with resected periampullary adenocarcinoma: the ESPAC-3 periampullary cancer randomized trial. Jama. 2012;308(2):147-56.
8. Neoptolemos JP, Palmer DH, Ghaneh P, Psarelli EE, Valle JW, Halloran CM, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. The Lancet. 2017;389(10073):1011-24.
9. Conroy T, Hammel P, Hebbar M, Ben Abdelghani M, Wei AC, Raoul JL, et al. FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer. N Engl J Med. 2018;379(25):2395-406.
10. Regine WF, Winter KA, Abrams R, Safran H, Hoffman JP, Konski A, et al. Fluorouracil-based chemoradiation with either gemcitabine or fluorouracil chemotherapy after resection of pancreatic adenocarcinoma: 5-year analysis of the U.S. Intergroup/RTOG 9704 phase III trial. Ann Surg Oncol. 2011;18(5):1319-26.
11. Lambert A, Schwarz L, Borbath I, Henry A, Van Laethem JL, Malka D, et al. An update on treatment options for pancreatic adenocarcinoma. Ther Adv Med Oncol. 2019;11:1758835919875568.
12. Sugawara T, Ban D, Nishino J, Watanabe S, Maekawa A, Ishikawa Y, et al. Prediction of early recurrence of pancreatic ductal adenocarcinoma after resection. PLoSOne. 2021;16(4):e0249885.
13. Moletta L, Serafini S, Valmasoni M, Pierobon ES, Ponzoni A, Sperti C. Surgery for Recurrent Pancreatic Cancer: Is It Effective? Cancers (Basel). 2019;11(7).
14. Van den Broeck A, Sergeant G, Ectors N, Van Steenbergen W, Aerts R, Topal B. Patterns of recurrence after curative resection of pancreatic ductal adenocarcinoma. Eur J Surg Oncol. 2009;35(6):600-4.
15. He C, Huang X, Zhang Y, Cai Z, Lin X, Li S. A Quantitative Clinicopathological Signature for Predicting Recurrence Risk of Pancreatic Ductal Adenocarcinoma After Radical Resection. Front Oncol. 2019;9:1197.
16. Wolfgang CL, Herman JM, Laheru DA, Klein AP, Erdek MA, Fishman EK, et al. Recent progress in pancreatic cancer. CA Cancer J Clin. 2013;63(5):318-48.
17. Herman JM, Swartz MJ, Hsu CC, Winter J, Pawlik TM, Sugar E, et al. Analysis of fluorouracil-based adjuvant chemotherapy and radiation after pancreaticoduodenectomy for ductal adenocarcinoma of the pancreas: results of a large, prospectively collected database at the Johns Hopkins Hospital. J Clin Oncol. 2008;26(21):3503-10.
18. Groot VP, Rezaee N, Wu W, Cameron JL, Fishman EK, Hruban RH, et al. Patterns, Timing, and Predictors of Recurrence Following Pancreatectomy for Pancreatic Ductal Adenocarcinoma. Ann Surg. 2018;267(5):936-45.
19. Gibbs P, Do C, Lipton L, Cade DN, Tapner MJ, Price D, et al. Phase II trial of selective internal radiation therapy and systemic chemotherapy for liver-predominant metastases from pancreatic adenocarcinoma. BMC Cancer. 2015;15(1):802.
20. Filippini DM, Grassi E, Palloni A, Carloni R, Casadei R, Ricci C, et al. Searching for novel multimodal treatments in oligometastatic pancreatic cancer. BMC Cancer. 2020;20(1):271.
21. Lu F, Poruk KE, Weiss MJ. Surgery for oligometastasis of pancreatic cancer. Chin J Cancer Res. 2015;27(4):358-67.
22. Jones RP, Psarelli EE, Jackson R, Ghaneh P, Halloran CM, Palmer DH, et al. Patterns of Recurrence After Resection of Pancreatic Ductal Adenocarcinoma: A Secondary Analysis of the ESPAC-4 RandomizedAdjuvant Chemotherapy Trial. JAMA Surg. 2019;154(11):1038-48.
23. Schorn S, Demir IE, Samm N, Scheufele F, Calavrezos L, Sargut M, et al. Meta- analysis of the impact of neoadjuvant therapy on patterns of recurrence in pancreatic ductal adenocarcinoma. BJS Open. 2018;2(2):52-61.
24. Hishinuma S, Ogata Y, Tomikawa M, Ozawa I, Hirabayashi K, Igarashi S. Patterns of recurrence after curative resection of pancreatic cancer, based on autopsy findings. J Gastrointest Surg. 2006;10(4):511-8.