

Impact of Different Treatment Modalities on the Outcome of Pancreatic Cancer

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ABSTRACT

Objective: To analyze overall survival patterns of our pancreatic cancer patient population managed with a curative or palliative intent.

Study Design: Analytical study.

Place and Duration of Study: Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, from January 2000 till February 2015.

Methodology: A retrospective review of the data of all of our pancreatic cancer patients was performed, using the hospital information system. Patients with tumor other than adenocarcinoma or a histopathologic diagnosis not made at our hospital are excluded from the study, along with patients having an incomplete medical record for all included variables. The main outcome measure was overall survival in months from the date of diagnosis. All results were segregated and analyzed according to the intervention modality used, i.e. group A: surgery with curative intent, group B: Palliative chemotherapy, and group C: Supportive care. Results were controlled for the confounding variables including age, gender, significant comorbid conditions, stage of disease at initial presentation, tumor location, and histological grade.

Results: Among the 197 patients fulfilling the inclusion criteria, 21 (10.7%) were excluded as they were lost to follow-up. Overall Kaplan-Meier survival analysis gave a 56% one-year survival, 22% at 3- and 16% at 5-year. The subset analysis on Cox-regression survival plot showed inferior survival with advancing stage of the disease and a treatment less than definitive surgical resection and adjuvant chemotherapy. On Cox-proportional regression analysis, stage of the disease and treatment modality were only independent predictive factors for overall survival ($p < 0.01$).

Conclusion: Stage for stage, surgery with curative intent (group A) or palliative chemotherapy (group B) showed a trend towards improved survival as compared to supportive management (group C) alone. The results were more significant for surgical resection arm.

Key Words: *Pancreatic adenocarcinoma. Survival analysis. Pancreatic cancer. Overall survival. Curative surgery.*

INTRODUCTION

Pancreatic cancer is a malignancy associated with a higher initial stage at presentation and a poor prognosis in terms of overall survival.^{1,2} The expected survival for stage 3 disease is <15% at 2 years and <6% at 5 years.^{2,3} Surgery, chemotherapy and radiation are main treatment modalities to improve survival or relieve symptoms.^{4,5} To date, surgery remains the only possible curative treatment option with documented improvement in outcomes with the use of adjuvant and neo-adjuvant therapies, especially chemotherapy.^{6,7} Availability of published long-term survival data of pancreatic adenocarcinoma patients from Pakistan is limited.^{8,9}

The study centre being the country's largest oncology centre has been managing this particular disease for more than a decade in accordance with the international standards of care.⁵ This makes an evaluation of the local

pancreatic cancer patients' treatment and outcome imperative.

This study aimed at assessing the impact of different treatment modalities, i.e. surgical resection, palliative chemotherapy and supportive care on survival according to the initial tumor stage and treatment preferred.¹⁰

The objective of present study was to evaluate the overall survival patterns in the local pancreatic cancer patient population.

METHODOLOGY

After a formal approval by the Hospital Ethics Committee and Institutional Review Board, a retrospective collection of data of all of the pancreatic and peri-ampullary cancer patients was conducted via the Hospital Information System from January 2000 till February 2015. Patient demographic characteristics along with the other basic control variables, i.e. histopathologic tumor grade, tumor location, and initial stage, were recorded for each patient. Patients with tumor other than adenocarcinoma, and patients without a histopathologic diagnosis made at Shaukat Khanum Laboratory, were excluded from the study. The patients with cholangiocarcinoma or primary duodenal tumors

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and with an incomplete medical record for all the variables in the study and partial treatment (surgery/chemotherapy) at an outside hospital, were also excluded.

The main outcome measure was overall survival in months from the date of diagnosis. The date of diagnosis was taken as the date of initial diagnostic investigation with the documentation of primary tumor (CT scan/abdominal USG / Endoscopic ultrasound / ERCP). The minimum length of follow-up was kept as one year from the date of diagnosis for inclusion into study; and hence, data of the patients after February 2015 was not included. All included patients are followed-up and their health status is verified by checking our hospital record or for patients with missing data by confirmation from patient or their family over the telephone, for such patients date of telephonic contact (1st May 2016) was taken as the last date of follow-up. The patients with missing data and inability to contact via phone were labeled as lost to follow-up. The comorbidity status for each patient was graded according to Charlson comorbidity scoring system. All the included patients got an initial multi-phasic contrast enhanced CT scan of the abdomen, pelvis and an endoscopic ultrasound (EUS) of pancreas as part of their staging workup along with an EUS guided FNAC. Tumors are staged according to their initial higher radiological or EUS stage. All staging was done in accordance with the American Joint Committee on Cancer (AJCC) TNM Staging of Pancreatic Cancer 2010.

All results were segregated and analyzed according to the intervention modality used, i.e. group A = surgery with curative-intent arm, group B = palliative chemo, and group C = supportive care. Patients in Group A surgery with curative intent arm underwent pancreatoduodenectomy with lymph node dissection for completely resectable peri-ampullary and pancreatic head tumors or distal pancreatectomy with splenectomy for pancreatic body and tail tumors. The final decision was made preoperatively and if the disease was found grossly irresectable, incomplete resections were not performed at our institute. M1 disease for adenocarcinoma pancreas/peri-ampullary as per protocol was never attempted for resection after an initial staging laparoscopy. A combination of gemcitabine and capecitabine was used as adjuvant chemotherapy for stage II and above tumors. Either gemcitabine or 5-fluorouracil-based chemotherapy with palliative intent was given to patients in Group B. Supportive/palliative treatment arm (Group C) included patients managed for jaundice with biliary stents and or palliative biliary bypass operations, pain control and a palliation of gastroduodenal obstruction with stent placement or gastric bypass. The results were controlled for confounding variables including stage of disease at initial presentation, histological tumor grade (well

differentiated, moderately and poorly differentiated) and tumor location (peri-ampullary / head of pancreas / body and tail of pancreas) along with the patient age, gender and any significant comorbid conditions (Table I).

Table I: Clinical and demographic parameters.

Parameters	Findings No. (%)
Age	Median=57 years Range 21-86 IQR: 49-67
Gender	
Male	124 (62.9%)
Female	73 (37.1%)
Comorbidity Index*	
0	107 (54.3%)
1-2	80 (40.6%)
>3	10 (5.1%)
Tumor grade	
Well	32 (16.2%)
Moderately	66 (33.5%)
Poorly	27 (13.7%)
Not specified	72 (36.5%)
Tumor Location	
Ampulla/periampullary	81 (41.1%)
Pancreas head	82 (41.6%)
Body and tail	34 (17.3%)
Tumor stage**	
Stage 1A,1B,2A	32 (16.2%)
Stage 2B	39 (19.8%)
Stage 3	75 (38.1%)
Stage 4	51 (25.9%)
Treatment modality	
Curative resection	49 (24.9%)
Palliative chemotherapy	63 (32.0%)
Supportive/Palliative care	85 (43.1%)

* Charlson co-morbidity scoring system; ** (AJCC) TNM Staging of pancreatic cancer 2010.¹⁰

All analyses were done with IBM SPSS Statistical Software version 19.0. for determining frequencies and proportions. Kaplan-Meier analysis was done for investigation of overall survival. Cox-proportional hazards model was used for identification of risk factors. Continuous variables (age) for this purpose were dichotomized according to their median value. Cox-regression survival plots were constructed for identified individual risk factors. A p-value of less than < 0.05 was taken as a level of significance for all analyses.

RESULTS

Out of 197 included patients, 21 (10.7%) were labeled as lost to follow-up due to an inability to establish contact; and hence, were excluded from final analysis of survival outcome. Forty-four (25%) patients were managed with curative intent surgery, 53 (30.1%) with chemotherapy and 79 (44.9%) with palliative/supportive management only. The overall Kaplan-Meier survival curve analysis is shown in Figure 1, with a 56% one-year survival, 22% 3-year and 16% 5-year survival for the study cohort on a median follow-up of 1.2 years. On

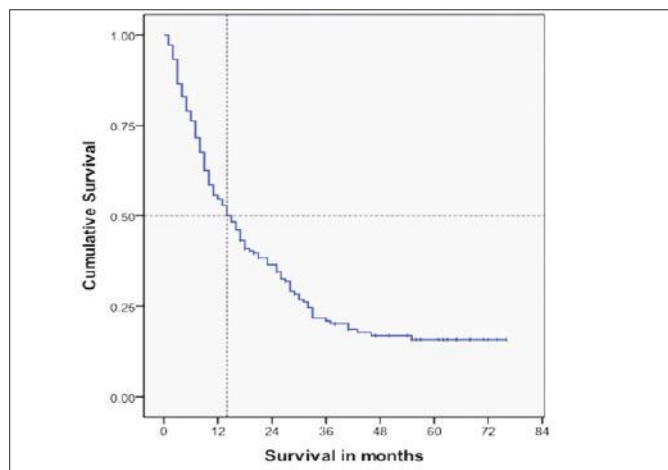


Figure 1: Kaplan-Meier estimates for overall survival.

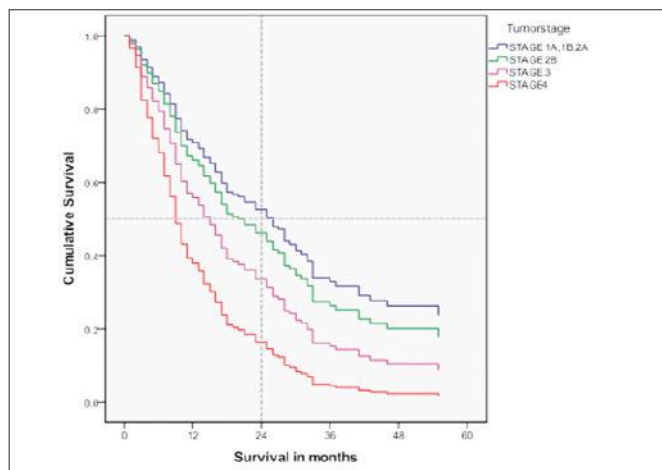


Figure 2A: Cox-regression survival plots: tumor stage.

Table II: Cox-proportional hazards model fitted to data for time to death in patients who died.

	Adjusted Hazard ratio	95% Confidence Interval
Age > 55 years compared to > 55 years	0.74	0.51-1.07
Females compared to males	1.17	0.81-1.69
Tumor grade (compare to poorly differentiated)		
Not specified	1.21	0.67-2.17
Well differentiated	0.91	0.47-1.75
Moderately differentiated	1.33	0.72-2.43
Tumor location (ampullary/periampullary)		
Head of pancreas	0.99	0.64-1.55
Pancreas body and tail	1.35	0.74-2.46
Tumorstage* (compare to stage 1A to 2A)		
Stage 2B	1.19	0.61-2.35
Stage 3	1.69	0.90-3.17
Stage 4**	2.80	1.43-5.49
Treatment** (compare to palliative management)		
Curative resection**	0.28	0.15-0.54
Chemotherapy**	0.59	0.39-0.87
Charlson score		
Score 1-2	1.060	0.72-1.57
Score >3	1.222	0.57-2.63

* Significant at $p < 0.05$; ** Significant at $p < 0.01$.

Cox-proportional regression analysis, the stage of the disease and treatment modality used were the only identified independent predictive factors for overall survival ($p < 0.01$). Tumor grade, location, patient age, and presence of comorbid conditions had no significant impact on overall survival (Table II).

The subset analysis on Cox-regression survival plots showed a worse survival with advancing stage of the disease and a treatment less than definitive surgical resection (Figure 2). Kaplan-Meier survival analysis gave comparable results with a median survival of 33 and 28 months for stage 1 - 2A and stage 2B, respectively which was significantly better than stage 3 and 4 with a

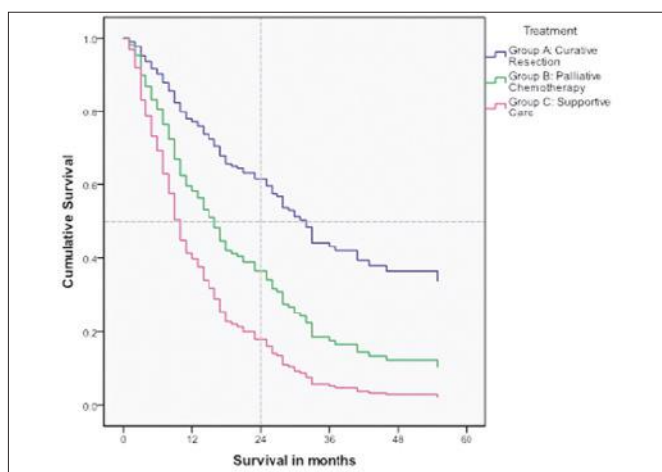


Figure 2B: Cox-regression survival plots: treatment received.

respective median survival of 14 and 6 months only. Treatment modality on Kaplan-Meier analysis had a significant survival impact with a 55 months median survival for Group A patients treated with curative intent and 17 months for group B palliative chemotherapy arm. The median survival for supportive care patients (group C) without any active intervention was only 8.

DISCUSSION

The last ten years data of pancreatic adenocarcinoma managed at the study centre showed an overall median survival of 14 months for all patients treated with curative or palliative intent. However, survival was significantly better for an earlier stage disease and for patients treated with a curative resection with or without adjuvant chemotherapy. Moreover, survival was also better for patients treated with palliative chemotherapy alone without surgery as compared to supportive management independent of the stage of disease.

Pancreatic cancer is the fourth most common cause of cancer related death in the United States and worldwide;

it is the eighth and ninth leading cause of cancer deaths in men and women, respectively.^{11,12} Despite advances in the diagnosis and treatment, the 5-year overall survival rate internationally remains bleak (up to 5%), partly because the majority of patients present with an advanced disease.^{13,14} This can possibly be a reason why no survival data from Pakistan, including the study centre, has been reported so far, with pancreatic cancer management being taken as a lost cause.^{9,15}

Variable median survival of 17-27 and in some series upto 50 months has been reported in literature for pancreatic cancer treated with curative resection;^{16,17} in contrast, this series showed a longer survival (median survival = 55 months) for patients managed with surgical resection with and without adjuvant treatment. Although overall median survival in the presently selected patient population for all stages combined was only 14 months, it certainly was better for early stage 1 and 2 tumors having a 2 years survival of 50%; while less than 40 percent for palliative chemotherapy (group B) and less than 20 % for supportive management only (group C). These results were depicted on Cox-regression plot, independent of tumor stage and other co-variables distribution in each treatment arm.

Overall median survival of 7-10 months, has been demonstrated by multiple studies for palliative chemotherapy compared with 2-4 months in patients with advanced pancreatic cancer managed with supportive care only.^{14,18} Here again, the survival figures are higher for the selected patient population, i.e. 17 months for palliative chemotherapy group and 8 months for the group managed with supportive care only.

The percentage distribution of total number of early stage 1 and 2 cases (86.4%) was higher in surgery arm as compared to 20% each for palliative chemotherapy and supportive arm. Moreover, stage 3 and stage 4 distributions were also found to be similar for these two arms. Stage 3 patients constituted 45.3% and 43% of Group B and Group C; while stage 4 comprised 34% and 36.7% for the two arms, respectively.

Limitations of the study in addition to its retrospective design are the dependence of health status verification from family on phone, which has a potential for substantial recall bias. However, this was the only available option due to a good percentage of included patients from neighboring country Afghanistan and a lack of availability and access to their birth and death records system. Also, in comparison with a number of other large series, patients managed with surgical resection of primary tumor with or without adjuvant chemotherapy were treated as a single group.¹⁹

CONCLUSION

These results showed a stage-for-stage trend towards improved survival for patients managed with a curative

surgical intervention when compared to palliative chemotherapy. However, patients treated with supportive management alone had inferior prognosis when compared to palliative chemotherapy group. Also stage of the disease and curative treatment option are found to be independent factors for having an impact on overall survival.

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ERRATUM

In the issue of July 2017, at the page No: 459 & 460 it was published erroneously as 459-560 instead of 459-460, due to oversight.

The error is regretted.