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ORIGINAL ARTICLE

Prognostic indicators following curative pancreatoduodenectomy for pancreatic carcinoma: A retrospective multivariate analysis of a single centre experience

Athanasios Petrou[1-3], Zahir Soonawalla[3], Michael-Antony Silva[3], Antonio Manzelli[3], Demetrios Moris[4], Patric-Paul Tabet[2,5], Peter Friend[4]

[1]Department of Surgery, New Nicosia General Hospital, Nicosia, Cyprus; [2]St George's University of London Programme, University of Nicosia, Cyprus; [3]Centre of Hepaticopancreatobiliary and Transplant Surgery, Surgery and Diagnostics, Churchill Hospital, Headington, Oxford, UK; [4]Lerner Research Institute, Cleveland Clinic Foundation, Cleveland OH, USA; [5]St George's University of London Medical School, London, UK

Summary

Purpose: *Survival after curative resection of pancreatic, ampullary and lower common bile duct cancer remains very poor. The aim of this study was to assess important prognostic factors in patients with resectable pancreatic cancer.*

Methods: *From 2006 to 2010, 156 patients underwent pancreatoduodenectomy (PD) for malignancies of pancreatic, ampullary or lower common bile duct in our institution. Based on the inclusion criteria 101 patients were selected in our retrospective statistical analysis. Of these 101 cases of malignancies, 65.4% were located in the pancreatic head, 18.8% in the ampulla and 15.8% in the lower bile duct. 48.5% of patients underwent classical PD, and 51.5% pylorus-preserving pancreatoduodenectomy (PPPD). Clinical and pathological data were collected, Kaplan-Meier method and Cox proportional hazard models were used to evaluate prognostic factors.*

Results: *Multivariate analysis revealed that blood transfusion, vascular invasion, T4 vs T1 stage, and R0 resection margins were significant negative predictors of survival. Conversely, ampullary (vs pancreatic ductal) and adjuvant chemotherapy were significantly associated with longer survival. Lymph node ratio (LNR), in all its forms, was not found to have a significant effect on survival. For all patients, tumor grading (p=0.042), resection margins (p=0.004), T stage (p=0.001), perineural invasion (p=0.029), vascular invasion (p=0.007) and age >65 years (p=0.009) were factors that impacted survival.*

Conclusion: *Surgical resection margins, tumor grade, T stage, perineural invasion, vascular invasion, age >65 and adjuvant chemotherapy are the strongest predictors of survival after surgical resection of pancreatic, ampullary and lower common bile duct cancer. In this series, lymph node ratio did not impact survival.*

Key words: *lymph node ratio, multivariate analysis, pancreatic cancer, pancreatoduodenectomy, prognostic factors, Whipple procedure*

Introduction

Pancreatic cancer is the fifth leading cause of cancer death in the western world [1]. Surgical resection is the only chance of cure, however only 10-20% of patients with pancreatic cancer are candidates for surgical resection due to their late presentation [2]. Thus, most patients are treated palliatively to improve quality of life. When the disease is resectable, the survival benefit is controversial due to the high rates of local and systemic recurrence. Even in patients who have undergone resection, survival rates are poor ranging from 10-29%, with better survival rates reported

Correspondence to: Athanasios Petrou, MD, MSc (HPB), PhD. St George's University of London Programme, University of Nicosia, 93 Agiou Nikolaou Street, Engomi, 2408 Nicosia, Cyprus; Department of Su rgery, New Nicosia General Hospital, Limassol old road no. 215, Strovolos, 2029 Nicosia, Cyprus, Tel: +357 96636949, E-mail: thpetrou@gmail.com
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in large centres with a high volume of cases [3-5]. The 5-year overall survival for pancreatic cancers is less than 2% and has shown little improvement over several decades.

There is a number of clinicopathological factors which are associated with prognosis following resection in pancreatic cancers. These factors include tumor grade, tumor stage, loco-regional invasion and the status of the surgical resection margin [6,7]. The presence of lymph node metastases is a predictor of prognosis with lymph node positive tumors having a significantly worse 1- and 5-year survival compared with patients with no nodal involvement [8-11]. In an attempt to improve survival, extended lymphadenectomy was often performed and initial results were positive [11,12]. However, subsequent randomized controlled trials (RCTs) on extended resections have contradicted these initial findings [13,14]. More recently the ratio of affected lymph nodes (positive vs negative) among the total number of lymph nodes examined (LNR), has been shown to be an important prognostic factor in pancreatic cancers [14-18]. Similar results have been reported in ampullary and lower common bile duct cancers [19]; however, to our knowledge only three series have been published for these subtypes of pancreatic cancer [20-22]. Using LNR as a categorical variable, previous studies have shown a cut-off point between 0.15 and 0.30 to have prognostic significance [17,18].

The aim of this study was to correlate clinical and pathological findings with survival in patients who underwent curative surgical resection for pancreatic cancer.

Methods

Between 2006 and 2010, comprehensive retrospective data were collected from 101 patients undergoing pancreatic head resection for lower common bile duct, ampullary and pancreatic ductal carcinoma.

All patients underwent tumor resection with curative intent and all surgical specimens had a confirmed pathologic diagnosis. Resected specimens were fixed in formalin and following dissection and sampling, tissue blocks were processed and embedded in paraffin. Peripancreatic lymph nodes were stained with hematoxylin and eosin prior to assessment. Specimens were assessed by experienced pathologists in all cases including documentation of total number of lymph nodes excised and the number of nodes containing metastatic tumor. Clinicopathological data assessment included age, tumor grade, tumor size, resection margins, lymph node involvement, lymphatic, perineural and vascular invasion and blood transfusion.

All patients were followed up at 6 monthly clinics to assess their clinical progress and any evidence of recurrence. Survival was confirmed through hospital and general practitioner records. No patients were lost to follow-up.

Statistics

Continuous variables were presented as median, interquartile range (IQR) and 95% confidence intervals (CI), while categorical ones were presented as absolute and relative frequencies (percentages). The LNR was calculated for all patients. A new categorical variable was then constructed, having 4 categories, according to LNR values (0, 0-0.199, 0.2-0.299, ≥0.3). Survival was estimated using the Kaplan-Meier method and the patients were censored at the date of death. Log-rank testing was used for the purposes of the univariate analysis. The combined effect of the explanatory variables on the probability of death was evaluated using multivariate semi-parametric Cox proportional hazard regression models, using stepwise method. All reported p values were based on two-sided tests and compared to a significance level of 0.05. Data were analyzed using STATA™ statistical software (Version 9.0, Stata Corporation, College Station, TX77845, USA).

Results

101 patients with the diagnosis of pancreatic, ampullary or lower common bile duct cancer underwent R0 or R1 resections. Patient demographics are shown in Tables 1 and 2.

The tabulated data and univariate and multivariate survival analysis are representative of all subtypes of pancreatic cancer (ductal, ampullary

Table 1. Patient demographics and pathological data for all subtypes of pancreatic cancer

Data	*Results*	
No. of patients	101	
Median survival (months) (95% CI)	17.9	(14.2-23.9)
Age (yrs) (median, IQR)	66	12
Tumor size (mm) (median, IQR)	30	14
No. of examined LN (median, range)	22	(6-51)
No. of examined LN (mean,mode)	23.2	12
No. of involved LN (median, range)	2	(0-17)
No. of involved LN (mean,mode)	3.4	0
LNR (median, IQR)	0.11	0.23
Transfusion (units) (median, IQR)	0	1
Follow-up time (months) (median, IQR)	10.2	12.2

CI: confidence interval, IQR: interquartile range, LN: lymph nodes, LNR: lymph node ratio

and lower common bile duct) (Tables 3 and 4). The statistical results for each individual subtype are discussed below.

The univariate analysis shown in Table 3 and plotted in the graphs below indicates that in the total sample, tumor grade (p=0.042) (Figure 1), resection margins (p=0.004) (Figure 2), tumor stage (p<0.001) (Figure 3), perineural invasion (p=0.029) (Figure 4), vascular invasion (p=0.007) (Figure 5), LNR (0.2 as cut-off point) (Table 4) and age >65 years (p=0.009) (Figure 6) were characteristics that had an effect on the survival of all patients.

LNR, in all its other forms (0, >0-<0.2, >=0.2-<0.3, >0.3), (<0.2->=0.2), (<0.3->=0.3), was not found to have a significant effect on survival.

Multivariate analysis (Table 4) revealed that age >65 years, inpatient blood transfusion and vascular invasion were significant predictors of survival, increasing the hazard of death. In the same model, a marginally non-significant (p=0.056) effect of LNR≥0.2 (vs LNR<0.2) (hazard ratio/HR: 1.91) was also present.

In univariate analysis of pancreatic ductal cancer, tumor stage (p=0.007) and adjuvant chemotherapy (CHT) (p=0.028) were characteristics that had an effect on survival. LNR, in all its forms (0, >0-<0.2, >=0.2-<0.3, >0.3), (<0.2->=0.2), (<0.3->=0.3), was not found to have a significant effect on survival. Multivariate analysis revealed that T4 vs T1 stage was a significant predictor of survival, increasing the hazard of death (HR:27.26). On the contrary, female gender and adjuvant CHT were significantly associated with a decreased hazard of death (protective effect).

For ampullary cancer, univariate analysis revealed resection margins (p=0.004), tumor stage (p=0.001) and LNR (p=0.017) were characteristics that had an effect on the survival. However, as it is seen in the following graph, LNR effect should be evaluated with caution, given the low number of patients in the category >=0.2, <0.3 (N=1) (Figure 7) and the fact that when coded in the LNR group 1 (cut-off point: 0.2) and LNR group 2 (cut off point: 0.3), no significant results were produced. Multivariate analysis could not be applied.

The univariate analysis for lower common bile duct cancer showed resection margins (p<0.001) (Figure 2) and vascular invasion (p=0.004) were characteristics that had an effect on the survival. Multivariate analysis could not be applied.

Discussion

Pancreatic cancer is recognised as one of the most aggressive forms of cancer and surgery re-

Table 2. Demographic and clinical characteristics for all subtypes of pancreatic cancer

Characteristics	*Number*	*%*
Gender		
Men	61	60.40
Women	40	39.60
Resection type		
PD	49	48.51
PPPD	52	51.49
Cancer type		
Pancreatic ductal	66	65.35
Ampullary	19	18.81
Lower CBD	16	15.84
Tumor grading		
G1	9	8.91
G2	69	68.32
G3	23	22.77
Resection margins		
R0	50	49.50
R1	51	50.50
Tumor stage		
T1	5	4.95
T2	15	14.85
T3	78	77.23
T4	3	2.97
Lymphatic invasion		
0	30	29.70
1	71	70.30
Perineural invasion		
0	30	29.70
1	71	70.30
Vascular invasion		
0	46	45.54
1	55	54.46
Recurrence		
No	57	56.44
Yes	44	43.56
Adjuvant chemotherapy		
No	29	28.71
Yes	72	71.29
Transfusion		
No	67	66.34
Yes	34	33.66
LNR categories		
0,00	27	27.27
>0, <0.2	45	45.45
≥0.2, <0.3	10	10.10
≥0.3	17	17.17
Survival		
Survived	58	57.43
Deceased	43	42.57

LNR: lymph node ratio, PD: pancreatoduodenectomy, PPPD: pylorus-preserving pancreatoduodenectomy, CBD: common bile duct

Table 3. Univariate survival analysis according to several disease and therapeutic parameters

Parameters	*N*	*Median survival*	*95% CI*	*p (log rank)*
Gender				
Male	61	17.2	11.87, 21.6	0.191
Female	40	18.73	13.33, .	
Histology				
Pancreatic ductal	66	14.7	11.73, 19.1	0.061
Ampullary	19	.	12.33, .	
Lower CBD	16	19.77	11.87, .	
Resection type				
PD	49	17.2	11.87, 23.9	0.350
PPPD	52	19.77	12.2, .	
Tumor grading				
G1	9	.	11.87, .	0.042
G2	69	17.5	12.33, .	
G3	23	14.7	7.13, 23.9	
Resection margins				
R0	50	21.6	17.8, .	0.004
R1	51	13.33	7.5, 17.5	
Tumor stage				
T1	5	14.7	14.7, .	<0.001
T2	15	.	7.33, .	
T3	78	17.8	12.33, 23.9	
T4	3	6.47	1.93, .	
Lymphatic invasion				
0	30	.	12.2, .	0.078
1	71	17.5	12.33, 19.77	
Perineural invasion				
0	30	.	17.2, .	0.029
1	71	16.97	11.3, 21.6	
Vascular invasion				
0	46	.	17.8, .	0.007
1	55	13.33	7.5, 17.87	
Adjuvant chemotherapy				
No	29	17.2	6.53, .	0.117
Yes	72	19.1	14.23, .	
Transfusion(s)				
No	67	19.77	19.97, .	0.055
Yes	34	14.23	7.33, 19.1	
LNR				
0	27	.	11.87, .	0.165
>0, <0.2	45	18.73	14.23, .	
≥0.2, <0.3	10	6.9	3.9, .	
≥0.3	17	16.97	4.33, 23.9	
Tumor size (mm)				
≤20	23	.	14.7, .	0.055
>20 without lymph. invasion	21	17.2	7.23, .	
>20 with lymph. invasion	57	16.97	7.77, 19.77	
LNR group 1				
<0.2	72	18.73	14.43, .	0.033
>=0.2	27	11.3	6.3, 23.9	

Continued on next page

Parameters	*N*	*Median survival*	*95% CI*	*p (log rank)*
LNR group 2				
<0.3	82	17.87	14.23, .	0.165
>=0.3	17	16.97	4.33, 23.9	
Age (years)				
≤65	45	.	18.73, .	0.009
>65	56	14.23	11.3, 17.8	
No. of examined LNs in node-positive patients				
≤15	15	14.7	7.5, .	0.794
>15	56	17.8	12.33, 21.6	
No. of examined LNs in node-negative patients				
≤15	11	12.2	2.57, .	0.264
>15	19	.	14.43, .	
LNR group 1 in node-positive patients				
<0.2	47	17.87	13.33, 21.6	0.190
≥0.2	22	11.3	6.3, 23.9	
LNR group 2 in node-positive patients				
<0.3	55	17.8	11.73, 19.77	0.659
≥0.3	14	16.97	4.33, 23.9	

For abbreviations see footnote of Table 2

Table 4. Multivariate Cox regression survival analysis

Parameters	*Hazard ratio*	*95% Conf. interval*		*p value*
Age >65 vs ≤65 years	2.08	1.05	4.12	0.037
Inpatient blood transfusion	2.30	1.19	4.46	0.013
Vascular invasion	2.71	1.32	5.54	0.006
LNR ≥0.2 vs LNR <0.2	1.91	0.98	3.70	0.056

LNR: lymph node ratio

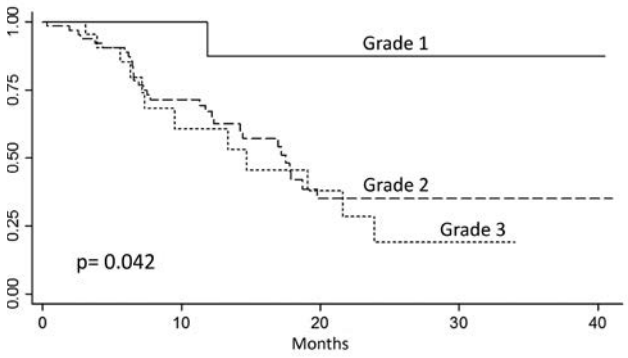

Figure 1. Kaplan-Meier cumulative survival related to tumor grade – univariate analysis.

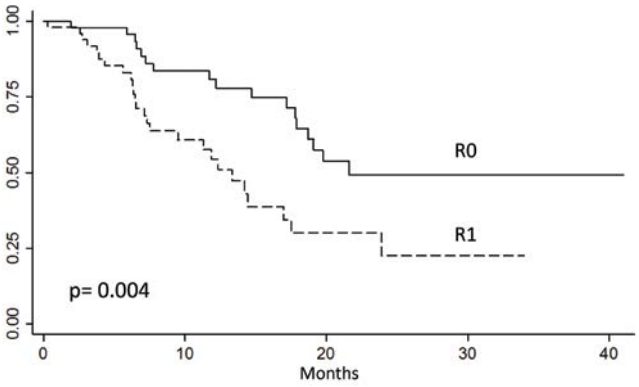

Figure 2. Kaplan-Meier cumulative survival related to resection margins – univariate analysis.

mains the only curative option. Even in patients who are surgical candidates, the 5-year overall survival (OS) remains dismal [3-5]. Several large studies have reported a number of prognostic factors which positively influence surgical outcome and include absence of lymph node involvement, small tumor size, R0 resection and well-differentiated tumor [7,23,24].

The present study has dealt with the outcome of a single centre analysis of the survival in 101 patients after surgical resection for pancreatic cancer during a 5-year period between 2006 and

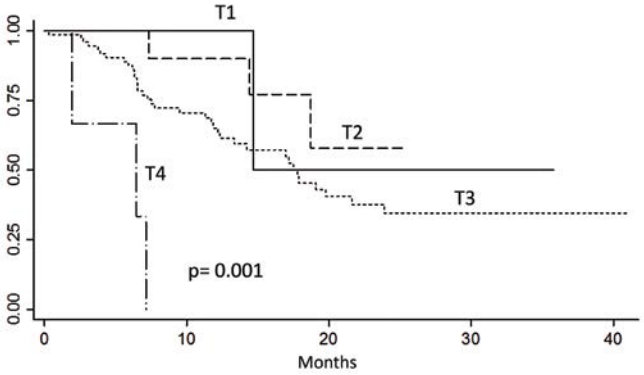

Figure 3. Kaplan-Meier cumulative survival related to tumor stage – univariate analysis.

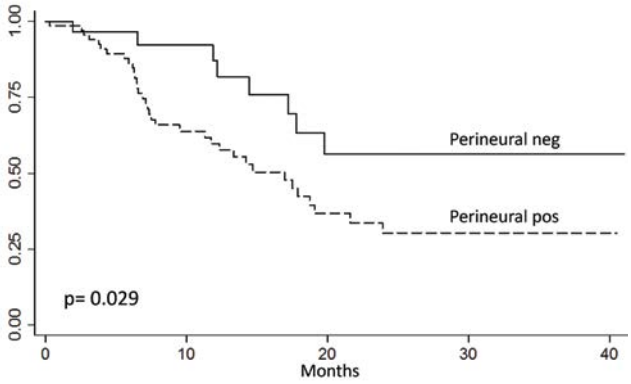

Figure 4. Kaplan-Meier cumulative survival related to perineural invasion – univariate analysis.

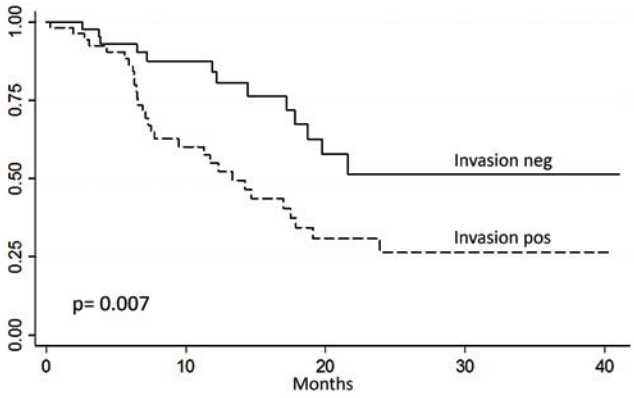

Figure 5. Kaplan-Meier cumulative survival related to vascular invasion – univariate analysis.

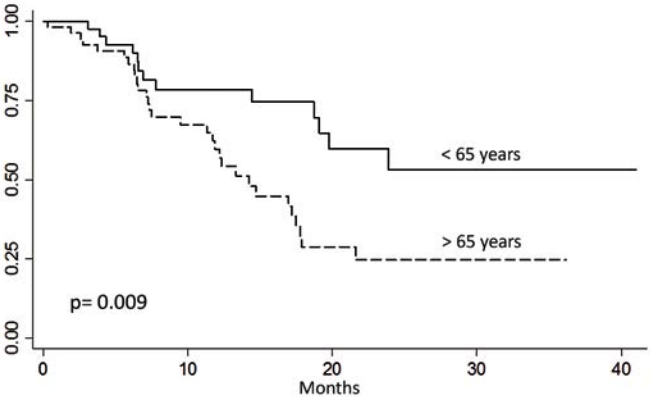

Figure 6. Kaplan-Meier cumulative survival related to age – univariate analysis.

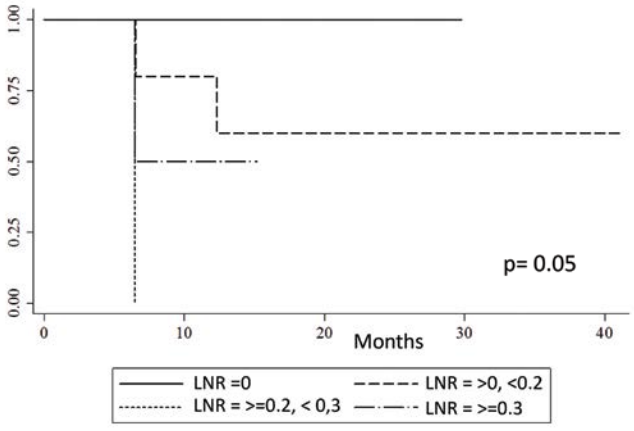

Figure 7. Kaplan-Meier cumulative survival in ampullary cancer related to lymph node ratio – univariate analysis.

2010. In multivariate analysis of the total sample, this study revealed that blood transfusion, vascular invasion and T4 vs T1 stage were significant predictors of survival, increasing the hazard of death. On the contrary, ampullary (vs pancreatic ductal) and adjuvant CHT were significantly associated with a decreased hazard of death. In univariate analysis, tumor grade, resection margins, tumor stage, perineural and vascular invasion and age >65 years were factors that had an effect on the survival of all patients.

The presence of nodal disease has been demonstrated to be an important prognostic factor in pancreatic cancer. Recent studies have suggested that LNR and number of involved lymph nodes, rather than simply positive or negative nodal status, are more potent prognostic factors [15-18,25]. In our study, LNR was not seen to be an important prognostic factor in univariate and multivariate analysis. However, Murakami et al. mention the prognostic significance of LNR may be altered depending on the total number of examined lymph nodes [25]. The largest studies in the area examined between 7 to 17 lymph nodes. In a smaller series by Massucco et al. the medi-

an number of examined lymph nodes was 28 and they did not show prognostic significance of LNR on multivariate analysis, only on univariate analysis [26]. In our study the median number of assessed nodes was 22. It is unclear why the prognostic significance of LNR was not demonstrated in our series. There are a couple of factors which may be important here. Occult tumor cells may be found in seemingly tumor-free nodes and may be overlooked in conventional histopathology [27]. In addition, the use of multiple pathologists to cross-examine the specimens was not implemented in our study.

A number of reports has demonstrated the requirement for intraoperative blood transfusion as a predictor of long-term survival [28]. We also revealed blood transfusion as an adverse prognostic factor on multivariate analysis (p=0.026). However, it is unclear whether with the improvements in surgical technique in pancreatectomies it is only in the complicated cases that transfusion is required. In this instance, patients requiring transfusion may have been associated with perioperative complications which in fact influence survival rather than the transfusion itself [29].

In a large randomized trial, the European Study Group for Pancreatic Cancer (ESPAC) reported the benefits of postoperative chemotherapy using combined 5-fluorouracil and leucovorin; 5-year survival rate was 21% in patients who received chemotherapy compared to 8% in those who did not [30]. More recently, the CONKO-001 trial reported that adjuvant chemotherapy using gemcitabine produced a significant improvement in disease-free survival with borderline significance in overall survival [31]. In our series 71% of the patients received postoperative chemotherapy and this had a significant impact on survival in multivariate analysis (p=0.010). A standard regime was not used but the majority received a 5-fluorouracil–based chemotherapy. Although our survival results are comparable to other series, the overall benefit from postoperative chemotherapy remains poor [32]. Further analysis on post-resection therapy is required.

Neoadjuvant (preoperative) therapy is the treatment of choice for locally invasive and unresectable pancreatic cancer in an attempt to downstage the tumor and bridge the gap to allow radical or palliative surgical management [33]. In our series, R1 resection status (p=0.004) and vascular invasion (p=0.006) were adverse prognostic factors on univariate and multivariate analysis. In a systematic review of 111 studies, Gillen et al. assessed the evidence for the use of neoadjuvant therapy in patients with resectable and unresectable pancreatic cancer [34]. After neoadjuvant treatment, 33.2% of the patients initially staged unresectable underwent a successful surgical resection and the survival rates were comparable to patients with initially resectable tumors. Survival rates were also improved from 10.2 to 20.5 months in patients who received neoadjuvant therapy relative to no intervention.

Interestingly there were no differences in survival between patients with resectable disease who received neoadjuvant therapy and resection vs resection and adjuvant (postoperative) therapy [34].

A limitation of the study was the loss of several patients before a satisfactory follow-up time was completed. However, we believe that the main findings are not influenced.

In a soon to be published mini-series from our centre we demonstrated the potential benefits of neoadjuvant therapy. With a histological diagnosis of locally advanced pancreatic adenocarcinoma involving the superior mesenteric artery (SMA) and superior mesenteric vein (SMV), we present a patient in a phase II trial study involving serine/threonine kinase (Akt) inhibition by nelfinavir and chemoradiation with gemcitabine and cisplatin. After completion of the trial the patient underwent restaging and was subsequently submitted to a SMA and SMV vascular reconstruction pylorus-preserving pancreaticoduodenectomy (PPPD). The histopathology report demonstrated no evidence of malignancy and was compatible with a TNM staging of pT0, N0, Mx, L0, V0, and R0. The future use of neoadjuvant chemoradiation may also be considered to improve the quality of surgical resection in patients considered ideal for early surgery and in turn may play a role in improving long term survival in this patient group.

Conclusion

Early detection is the key to improve long term survival of patients with pancreatic cancer, as complete resection offers the only potential cure. Patients with T1 tumors, who have a successful R0 resection, avoid peri-operative blood transfusion and receive post operative chemotherapy, demonstrate the best outcomes from surgery. Further advancements in both pre and post operative therapy remains the key with potential promising results from ongoing clinical trials.

Conflict of interests

The authors declare no confict of interests.

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