UNIVERSITY OF HELSINKI

https://helda.helsinki.fi

THE RESULTS OF PANCREATIC RESECTIONS AND LONG- TERM SURVIVAL FOR PANCREATIC DUCTAL ADENOCARCINOMA : A SINGLE-INSTITUTION EXPERIENCE

Seppänen, H.; Juuti, A.; Mustonen, H.; Haapamaki, C.; Nordling, S. ...

2017-03

SAGE Publications Inc.

http://hdl.handle.net/10138/311739

Seppänen, H, Juuti, A, Mustonen, H, Haapamaki, C, Nordling, S, Carpelan-Holmstrom, M, Sirén, J, Luettges, J, Haglund, C & Kiviluoto, T 2017, 'THE RESULTS OF PANCREATIC RESECTIONS AND LONG- TERM SURVIVAL FOR PANCREATIC DUCTAL ADENOCARCINOMA : A SINGLE-INSTITUTION EXPERIENCE', Scandinavian Journal of Surgery, vol. 106, no. 1, pp. 54-61. https://doi.org/10.1177/1457496916645963

Downloaded from Helda, University of Helsinki institutional repository. https://helda.helsinki.fi
This is an electronic reprint of the original article.
This reprint may differ from the original in pagination and typographic detail.
Please cite the original version.

The Results of Pancreatic Resections and Long-term Survival for Pancreatic Ductal Adenocarcinoma: A Single-Institution Experience

[1]Seppänen Hanna, [1]Juuti Anne, [1]Mustonen Harri, [1]Haapamäki Carola, [2]Nordling Stig, [1]Carpelan-Holmström Monika, [1]Sirén Jukka, [3]Luettges Jutta, [1]Haglund Caj, [1]Kiviluoto Tuula.

[1]Abdominal Center, [2]Department of Pathology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland. [3]Department of Pathology, Marienkrankenhaus, Hamburg, Germany.

Authors have no conflicts of interest to disclose.

Key words: pancreatic cancer, survival, pancreatic surgery

Word count: 2100

Corresponding author:

Hanna Seppänen, M.D., Ph.D.

Helsinki University Hospital

Department of Surgery,

PO Box 263,

00029 HUS, Finland

Tel. +358 50 427 0042

hanna.seppanen@hus.fi

ABSTRACT

Objectives: Since the early 1990's the low long-term survival rates following pancreatic surgery for pancreatic ductal adenocarcinoma (PDAC) challenged to improve the treatment. In this series we aim to show improved survival from PDAC during the era of centralized pancreatic surgery.

Methods: All pancreatic resections operated at Helsinki University Hospital and the survival of PDAC patients during 2000-13 were analysed. Post-operative complications such as fistulas, reoperations and mortality rates were recorded. Patient and tumour characteristics were compared with survival data.

Results: Of the 853 patients undergoing pancreatic surgery, there were 581 (68%) pancreaticoduodenectomies, 195 (21%) distal resections, 28 (3%) total pancreatectomies, and 49 (6%) other procedures. Mortality after pancreaticoduodenectomy was 2.1%. Clinically relevant B/C fistula rate was 7% after pancreaticoduodenectomy and 13% after distal resection. Re-operation rate was 5%. The 5- and 10-year survival rates for PDAC were 22 % and 14 %; for T1-2, N0 and R0 tumours, the corresponding survival rates were 49% and 31%. CA19-9 > 75 kU/l, CEA > 5 µg/l, N1, LNR >20%, R1 and lack of adjuvant therapy were independent risk factors for decreased survival.

Conclusion: After centralization of pancreatic surgery in Southern Finland, we have managed to enable PDAC patients survive markedly longer than in the early 1990's. Based on a 1.7-million population in our clinic, mortality rates are equal to those of other high-volume centres and long-term survival rates for PDAC have now risen to one of the highest reported.

INTRODUCTION

Pancreatic surgery has a high morbidity rate, and even very high-volume hospitals report high postoperative mortality. In hospital, 30-day or 60-day mortality in high volume centres for pancreatic-head resections varies between 0.9 and 8.1% (1-5). In a very high-volume centre in Heidelberg, Germany, with a case load more than 2000 pancreaticoduodenectomies, the in-hospital mortality rate was 3.9% (5). Overall morbidity after pancreaticoduodenectomy is even 59% and 27% of them being serious adverse events (6, 7). Post-operative pancreatic fistula is one of the most serious complications and may lead to death.

Overall long-term survival (> 5 years) of pancreatic ductal adenocarcinoma (PDAC), varies from 0 to 18 % (4, 8-10). In debate of the accuracy of histological diagnosis of PDAC one suggestion is that diagnosis of all long-time survivors needs re-evaluation by experienced pancreatic pathologists (8).

Only a few reports from high-volume centres have indicated longer survival for a certain very small proportion of PDAC patients (2, 4, 9). These cases contribute 5-6% of all patients operated on for PDAC (2, 4).

Former high postoperative mortality and complication rates and very low long-term survival rates for PDAC after pancreatic surgery have led to demand for improved treatment for this devastating disease. Internationally, centres for pancreatic surgery have been established with a multidisciplinary treatment. By this approach diagnostic accuracy of PDAC, postoperative mortality, and long-term survival for PDAC patients could be improved

remarkably (11-14). In southern Finland all pancreatic resections were centralized to Helsinki University Hospital, having 1.7 million population basis from the year 2000.

Aim

The aim of this study was to evaluate the outcome of patients undergoing pancreatic surgery in general as well as the possible survival benefits of PDAC patients in our hospital during centralization.

PATIENTS AND METHODS

From Helsinki University Hospital database we identified all patients undergoing pancreatic surgery other than necrosectomy between January 2000 and September 2013. Survival data came from patient records and from Finnish population registry on September 2014. Cause of death (COD) from pancreatic cancer or unrelated cause were analyzed. Information on age, gender, American Society of Anesthesiologists Physical Status Classification (ASA), tumour histology, grade, Union for International Cancer Control (UICC) TNM-stage, lymph-node status, margin-resection status (R, considered R0 when the clear resection margin is > 1 mm), type of resection, complications, adjuvant therapy, and tumour-marker levels came from patient records. Postoperative pancreatic fistula rates were analysed according to the international study group of post-operative pancreatic fistula (ISGPF) criteria (15).

Our pancreaticoduodenectomy operation technique was developed during the 1990's to become a standardised procedure by the year 2000. In malignant disease, operations started with laparoscopy to exclude peritoneal metastases. When none were detected, a transverse laparotomy followed. Pancreatic resection was according to the non-touch en-block principal

including distal gastrectomy. Resection included right-sided omentectomy, excision of the right cranial peritoneal leaf of the transverse colon exposing the caval vein and renal veins. Excision of the lymph nodes of the hepaticoduodenal ligament, around the right side of the caeliac axis, and excision of the aorto-caval notch caudally to the inferior arterial mesenterial axis, as well as along the anterior and right lateral side around the origin of the superior mesenteric artery were performed. If the tumour infiltrated the superior mesenteric or portal vein a resection was performed. Pancreatico-jejunal anastomosis was routinely performed end-to-side with a double-layer duct-to-mucosa suture line. All the patients were referred to adjuvant therapy. Neo-adjuvant therapy was administered when the tumour was radiologically borderline resectable (16).

All histological specimens were re-evaluated and the diagnosis for PDAC was made by two experienced pancreatic pathologists. All slides from 2000-2006 were re-evaluated by both our local pancreatic pathologist (S.N.) and a German pancreatic pathologist (J.L.). Centralisation of surgery in time led to centralization of pathology, as well, and specimens from 2007 and later were re-evaluated locally (S.N.). Pancreatic malignancies other than PDAC were excluded from survival analysis.

This study complies with the declaration of Helsinki and was approved by the Surgical Ethics Committee of Helsinki University Hospital, and the National Supervisory Authority of Welfare and Health.

Statistics

Life tables were calculated according to the Kaplan-Meier survival analysis, and the log rank test served for comparisons. Pancreatic cancer-specific overall survival was calculated from

date of operation to death. Cox proportional hazards regression served for multivariate analysis. The Cox model assumption of constant hazard ratios over time was tested by including the time dependent covariate separately for each testable variable, when the assumption was valid. Variables included in the analyses were T-classification, N-classification, disease-free margin R0, lymph-node ratio below 20%, adjuvant treatment, grade, and perivascular invasion, CA19-9 < 75 kU/l, CEA < 5.0 µg/l. Backward conditional stepping removed insignificant variables at $p<0.1$. Results are age- and sex-adjusted. All statistical analyses were performed with SPSS (v21, IBM, New York). Statistical significance was $p < 0.05$.

RESULTS

From January 2000 to September 2013, 853 patients underwent pancreatic surgery, (Table 1). Of the 853, 581 (68%) patients underwent pancreaticoduodenectomy, 195 (21%) distal pancreatic resection, 28 (3%) total pancreatectomy and 49 (6%) other pancreatic procedures such as middle pancreatic resection, enucleation, or uncinate resection.

Post-operative outcome

Out of 853, 13 (1.5%) patients died post-operatively. The in-hospital mortality after pancreaticoduodenectomy was 2.1 % (Table 2.) Clinically relevant grade B or C fistulas occurred in 7 % after pancreaticoduodenectomy and in 13 % after distal resection (Table 2). There were 44 (5%) patients who were re-operated.

Histological diagnosis was PDAC for 309 patients. After excluding those cases with a diagnosis not congruent, 306 patients remained for final analysis (Table 3). Of the PDAC patients, 52 (17%) received neoadjuvant therapy, consisting of either gemcitabine, gemcitabine combined with cisplatin, oxaliplatin, or radiation therapy. There were 151 (53%, information was available on 285 patients) patients who received adjuvant therapy, mainly gemcitabine or its combination with cisplatin, kabesitabine, or radiation therapy. There were 23 (8%) patients who turned out to have metastasis at imaging after surgery before they had received adjuvant therapy (occult metastasis during surgery), and these patients received palliative therapy.

Long-term outcome

The overall one-, three-, five- and ten-year survival rates for the 306 patients radically operated for PDAC were 74%, 36%, 22% and 14% (Table 4). In univariate analysis longer survival was significantly associated with CA19-9 < 75 kU/l (p=0.001), CEA < 5.0 µg/l (p=0.001), smaller tumor (T1-2) (p<0.001), lack of the lymph node metastasis (p=0.001) or LNR < 20% (p=0.001), higher histological differentiation grade (p=0.004), lack of perivascular invasion (p=0.001), and adjuvant therapy (p=0.016) (Table 5, Fig 1.). Lack of perineural invasion was associated with a tendency for better survival (p=0.055) (Table 5). Neither age, gender, ASA class, nor neoadjuvant therapy was significantly associated with survival.

When the R0N0 and tumour stage T1-2 patients (n=49, 16%) were analysed separately, their survival rates for five and ten years were 49% and 31% (median survival 46 vs. 23 months, p<0.001) (Table 3). More than half of the N1 patients (111, 57 %) received adjuvant therapy and benefitted significantly from it (median survival 25 vs. 13 months, p=0.021).

In multivariate analysis, patients who received post-operative adjuvant treatment had a significantly decreased hazard ratio, while patients with N1 status or patients with R1 had significantly poorer, increased hazard ratios than did patients with N0-status, radical operation (R0), and who had received no adjuvant treatment. Patients with CA19-9 > 75 kU/l, CEA > 5.0 µg/l, LNR > 20 % also had significantly increased hazard ratios (Table 6). Multivariate analyses were adjusted for age and sex.

DISCUSSION

Since the beginning of the year 2000 the population basis of our hospital has increased to 1.7 million. Larger hospital volume and improved surgical treatment may explain our very low post-operative in-hospital mortality rate nowadays of 2.1% after pancreaticoduodenectomy, which is at the same level as reported from very-high-volume international pancreatic centres. For example, Johns Hopkins Hospital in the U.S.A. has reported 1-2% postoperative mortality rates among almost 1500 pancreaticoduodenectomies, and Heidelberg in Germany, an in-hospital mortality of 3.9% after more than 2000 pancreatic resections (2, 5). In one Japanese pancreatic surgery database with 8575 pancreaticoduodenectomies the in-hospital mortality was 2.8% (17).

In our hospital a clinically relevant ISGPF grade B or C fistula occurred in 7% of the patients who had undergone pancreaticoduodenectomy. Johns Hopkins Hospital reported a 5% fistula rate after pancreaticoduodenectomy (2). The variation has been high (5-16%) in different centres (5, 17). After distal resections fistula rates vary even more (0-40%) (5, 18). In our hospital the grade B or C fistula rate after distal resection was 13%. Several attempts have been made to reduce the number of fistulas by different surgical techniques and with

somatostatine analogues. A Cochrane analysis recommended octreotide for high-risk patients only (19). Prophylactic pasireotide has decreased the number of clinically significant fistulas to half in a recent randomized single centre study (20). Pasireotide has been in prophylactic use in our centre since that publication, but after the current study period.

In our series, the overall 5-year survival of PDAC was 22% and in a subgroup of patients with T1-2, N0, and R0 tumours (49 patients, 16% of all) the 5-year survival was a very high 49% and even the 10-year survival 31%. In 2006, at Johns Hopkins Hospital, the overall 5-year survival for pancreatic head cancer was 18%. When the tumour was < 3 cm, and well or moderately differentiated, radically operated (R0), and lymph nodes were free of cancer, 5-year survival improved to 43% (2). Patients with these features numbered 56 (4.8%) of 1175 pancreaticoduodenectomies for pancreatic head cancer (2). In Heidelberg, the survival, among 1071, of almost similar group of 62 patients (5.8%) (tumour grading Tis-T2), the 5-year survival was 54% (4). In our series, Tis was considered high-grade dysplasia, and these patients were not included in PDAC survival analysis. One explanation for our notably good survival results may be that an increasing number of patients are operated on an earlier stage of the disease. In our series, tumour stage was T1-2 in 96 (32%) of the patients or the lymph nodes were free of metastasis in 105 (35 %) patients compared to other centres with a 76-78 % N1 prevalence (2, 4). Several other favourable tumour characteristics such as CA19-9 < 75 kU/l, CEA < 5.0 μg/l, higher cancer-differentiation grade, and lack of perivascular invasion favoured longer survival in both univariate and multivariate analysis, as could be expected. Our results stress the need for earlier diagnosis of PDAC.

The role of extended lymphadenectomy has been under debate. In gastric cancer, the increased survival after D2 lymph node dissection encouraged us to change the surgical technique towards the same principle also in PDAC (21, 22). In some studies extended lymhadenectomy has led to an increased number of R0 resections associated with better survival. Whether extended lymphadenectomy improves overall survival remains beyond the scope of our study. Thus far, five prospective randomized studies show no survival benefit after extended lymphadenectomy. Conversely, one meta-analysis showed a decrease in two- and three-year survival after extended lymphadenectomy (4, 23-28).

Covering the years 1990-96 a former Finnish study showed that only one patient with PDAC survived clearly longer than five years in Finland (8). There was a high number of misdiagnosis among the long-term survivors that were falsely listed in the tumour registry. Our current data are the results of the era of centralisation of pancreatic surgery. Also pathology has been centralized and with the increase of cases an increase of experience in that field was gained. In high-volume centres high diagnostic experience is achieved and therefore limited outside reference evaluation is needed. This was confirmed by two independent pathologists confirming the diagnosis of PDAC between 2000-2006 (S.N. and J.L.). In addition the classification of pancreatic tumours (WHO) has been unified and is in general use also due to the increasing amount of pancreatic resection specimen.

In the Carpelan-Holmström's study (2005) no patients (data from 1990-96) received oncological adjuvant treatment, although now it has become routine after pancreatic cancer surgery (8). In the 21th century, prospective randomized ESPAC 1-3 and CONCO-001 trials have shown that patients receiving adjuvant chemotherapy survive significantly longer (29,

30). Our retrospective series showed a similar result in favour of adjuvant therapy. Neoadjuvant therapy has in some series improved surgical results, raising the number of R0 resections. Further randomized controlled studies are necessary (31, 32).

CONCLUSIONS

Pancreatic surgery is safe in high-volume centres. Our centre's low hospital mortality for pancreaticoduodenectomy (2.1%) is similar to that reported from other high volume centres. Our long-term survival for PDAC is now one of the highest reported. Early detection and multidisciplinary treatment of PDAC is essential for better survival. During the era of centralisation of pancreatic (cancer) surgery more patients have lived markedly longer than did those operated on in the early 1990's.

ACKNOWLEDGEMENTS

Mary and Georg C. Ehrnrooth foundation, Sigrid Juselius Foundation and Helsinki University Hospital Research Funds are acknowledged for supporting the study. None of the foundations have been involved in the study design. Authors have no conflicts of interest to disclose.

FIGURE LEGEND

Fig. 1. The association of **A.** preoperative CA19-9 < 75 kU/l (p=0.001), **B.** preoperative CEA < 5.0 µg/l (p=0.001), **C.** tumor stage T1-2 (p<0.001), **D.** N-stage (p<0.001), **E.** LNR < 20 % (p<0.001), **F.** the disease free margins (R0) (p<0.001), **G.** the lymph node status and resection margin (p<0.001), **H.** small tumor stage (T1-2), no lymph node metastasis (N0) and clear resection margins (R0) (p<0.001), **I.** the histological differentiation grade (p=0.004), **J.** perivascular invasion (p=0.001) and **K.** adjuvant therapy compared to observation alone (p=0.016) on survival after the pancreatic resection in PDAC patients.

REFERENCES

1 Alexakis N, Sutton R, Raraty M, et al. Major resection for chronic pancreatitis in patients with vascular involvement is associated with increased postoperative mortality. Br J Surg 2004; 91: 1410–27.

2 Winter JM, Cameron JL, Campbell KA, et al. 1423 pancreaticoduodenectomies for pancreatic cancer: A single-institution experience. J Gastrointest Surg. 2006; 10: 1199-210.

3 Carroll JE, Smith JK, Simons JP, et al. Redefining mortality after pancreatic cancer resection. J GastrointestSurg. 2010; 14: 1701-8.

4 Hartwig W, Hackert T, Hinz U, et al. Pancreatic cancer surgery in the new millennium: better prediction ofoutcome. Ann Surg. 2011; 254: 311-9.

5 Hackert T, Hinz U, Hartwig O, et al. Evolution of Pancreatico-Duodenectomy: Experience of 2055 Consecutive Resections [abstract]. Pancreas 2013; 42 (suppl): 1325

6 DeOliveira ML, Winter JM, Schafer M, et al. Assessment of complications after pancreatic surgery: A novel grading system applied to 633 patients undergoing pancreaticoduodenectomy. Ann Surg. 2006; 244: 931-7.

7 Greenblatt DY, Kelly KJ, Rajamanickam V, et al. Preoperative factors predict perioperative morbidity and mortality after pancreaticoduodenectomy. Ann Surg Oncol. 2011; 18: 2126-35.

8 Carpelan-Holmström M, Nordling S, Pukkala E, et al. Does anyone survive pancreatic ductal adenocarcinoma? A nation wide study re-evaluating the data of the Finnish Cancer Registry. Gut. 2005; 54: 385-7.

9 Cameron JL, Riall TS, Coleman J, Belcher KA. One thousand consecutive pancreaticoduodenectomies. AnnSurg. 2006; 244: 10-5.

10 Ferrone CR, Brennan MF, Gonen M, et al. Pancreatic adenocarcinoma: the actual 5-year survivors. J Gastrointest Surg. 2008; 12: 701-6.

11 Nordback L, Parviainen M, Räty S, et al. Resection of the head ofthe pancreas in Finland: effects of hospital and surgeon on short-term andlong-term results. Scand J Gastroenterol. 2002; 37: 1454-60.

12 Hines OJ, Reber HA. Pancreatic surgery. Curr Opin Gastroenterol. 2006; 22: 520-6.

13 Gooiker GA, van Gijn W, Wouters MW, et al. Signalling Committee Cancer of the Dutch Cancer Society. Systematic review and meta-analysis of the volume-outcome relationship in pancreatic surgery. Br J Surg. 2011; 98: 485-94.

14 de Wilde RF, Besselink MG, van der Tweel I, et al. Dutch Pancreatic Cancer Group.Impact of nationwide centralization of pancreaticoduodenectomy on hospitalmortality. Br J Surg. 2012; 99: 404-10.

15 Bassi C, Dervenis C, Butturini G, et al. International Study Group on Pancreatic Fistula Definition. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery. 2005; 138: 8-13.

16 Callery MP, Chang KJ, Fishman EK, et al. Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. Ann Surg Oncol. 2009; 16: 1727-33.

17 Kimura W, Miyata H, Gotoh M, et al. A Pancreaticoduodenectomy Risk Model Derived From 8575 Cases From a National Single-Race Population (Japanese) Using a Web-Based Data Entry System: The 30-Day and In-hospital Mortality Rates for Pancreaticoduodenectomy. Ann Surg. 2014; 259: 773-80.

18 Hackert T, Werner J, Büchler MW. Postoperative pancreatic fistula. Surgeon. 2011; 9: 211-7.

19 Gurusamy KS, Koti R, Fusai G, Davidson BR. Somatostatin analogues for pancreatic surgery. Cochrane Database Syst Rev 2010;2:CD008370.

20 Allen PJ, Gönen M, Brennan MF, et al. Pasireotide for postoperative pancreatic fistula. N Engl J Med. 2014; 370: 2014-22.

21 Sasako M, McCulloch P, Kinoshita T, Maruyama K. New method to evaluate the therapeutic value of lymph node dissection for gastric cancer. Br J Surg. 1995; 82: 346-51.

22 Wu CW, Hsiung CA, Lo SS, et al. Nodaldissection for patients with gastric cancer: a randomised controlled trial. Lancet Oncol. 2006; 7: 309-15.

23 Yeo CJ, Cameron JL, Lillemoe KD, et al. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma, part 2: randomized controlled trial evaluating survival, morbidity, and mortality. Ann Surg. 2002; 236: 355-66

24 Sergeant G, Melloul E, Lesurtel M, et al. Extended Lymphadenectomy in Patients With Pancreatic Cancer Is Debatable. World J Surg. 2013; 37: 1782-8.

25 Jang JY, Kang MJ, Heo JS et al. A prospective randomized controlled study comparing outcomes of standard resection and extended resection, including dissection of the nerve plexus and various lymph nodes, in patients with pancreatic head cancer. Ann Surg. 2014; 259: 656-64.

26 Pedrazzoli S, DiCarlo V, Dionigi R, et al. Lymphadenectomy Study Group: Standard versus extended lymphadenectomy associated with pancreatoduodenectomy in the surgical treatment of adenocarcinoma of the head of the pancreas: a multicenter, prospective, randomized study. Ann Surg 1998; 228**:** 508–17.

27 Farnell MB, Pearson RK, Sarr MG, et al. A prospective randomized trial comparing standard pancreatoduodenectomy with pancreatoduodenectomy with extended lymphadenectomy in resectable pancreatic head adenocarcinoma. Surgery 2005; 138**:** 618–28.

28 Nimura Y, Nagino M, Takao S, et al. Standard versus extended lymphadenectomy in radical pancreatoduodenectomy for ductal adenocarcinoma of the head of the pancreas: long-term results of a Japanese multicenter randomized controlled trial. J Hepatobiliary Pancreat Sci 2012; 19: 230–41.

29 Neoptolemos JP, Stocken DD, Tudur Smith C, et al. Adjuvant 5-fluorouracil and folinic acid vs observation for pancreatic cancer: composite data from the ESPAC-1 and -3(v1) trials. Br J Cancer. 2009; 100: 246-50.

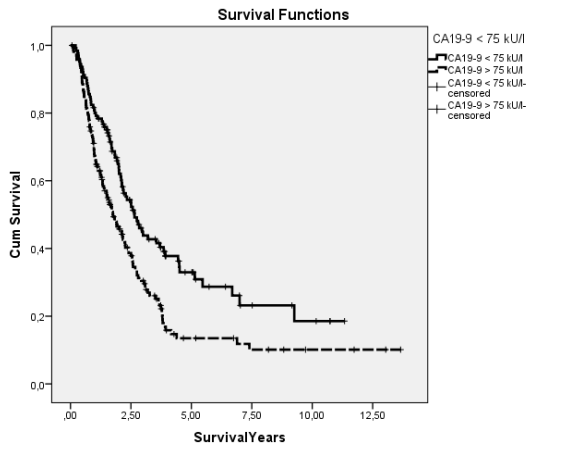
30 Oettle H, Neuhaus P, Hochhaus A, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. JAMA. 2013; 310: 1473-81.

31 Katz MH, Wang H, Balachandran A, et al. Effect of neoadjuvant chemoradiation and surgical technique on recurrence of localized pancreatic cancer. J Gastrointest Surg. 2012; 16: 68-78.

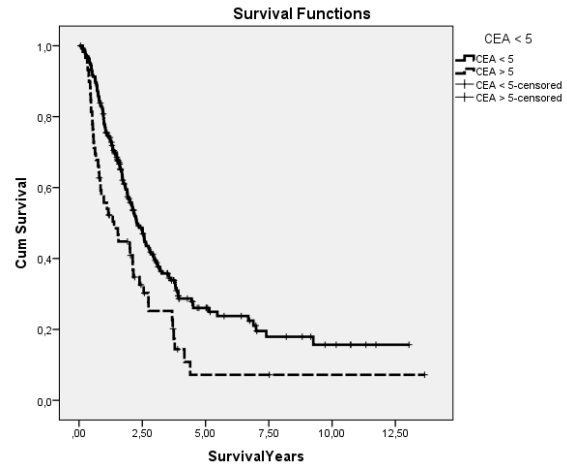
32 Hartwig W, Werner J, Jäger D, et al. Improvement of surgical results for pancreatic cancer. Lancet Oncol. 2013; 14: e476-85.

Fig. 1. The association of **A.** preoperative CA19-9 < 75 kU/l (p=0.001), **B.** preoperative CEA < 5.0 µg/l (p=0.001), **C.** tumor stage T1-2 (p<0.001), **D.** N-stage (p<0.001), **E.** LNR < 20 % (p<0.001), **F.** the disease free margins (R0) (p<0.001), **G.** the lymph node status and resection margin (p<0.001), **H.** small tumor stage (T1-2), no lymph node metastasis (N0) and clear resection margins (R0) (p<0.001), **I.** the histological differentiation grade (p=0.004), **J.** perivascular invasion (p=0.001) and **K.** adjuvant therapy compared to observation alone (p=0.016) on survival after the pancreatic resection in PDAC patients.

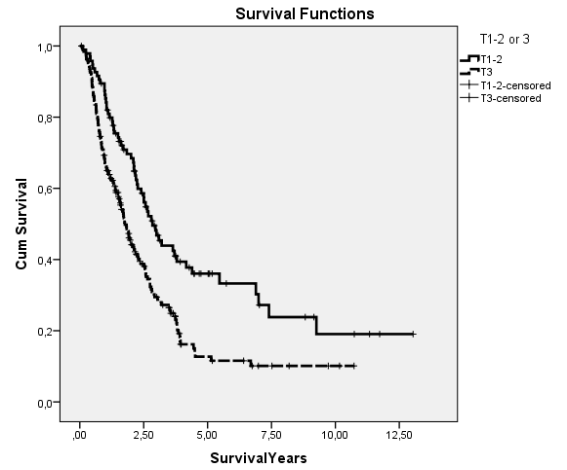
A.



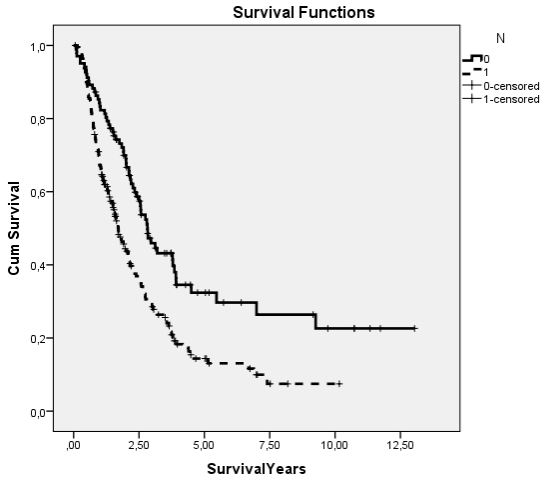
B.


Survival Functions
CEA < 5
CEA < 5
CEA > 5
CEA < 5-censored
CEA > 5-censored
Cum Survival
1,0
0,8
0,6
0,4
0,2
0,0
,00
2,50
5,00
7,50
10,00
12,50
SurvivalYears

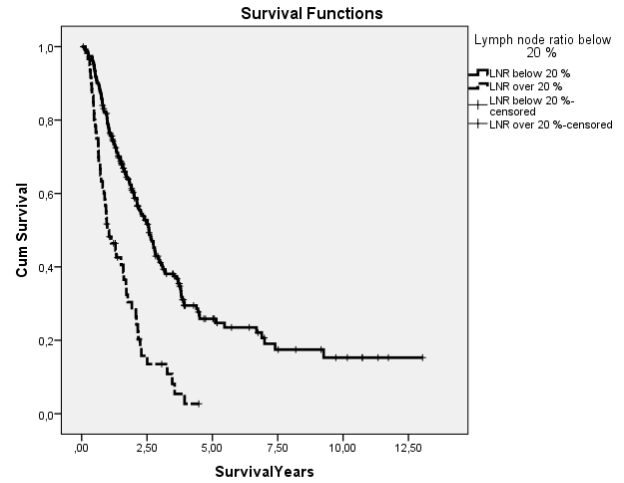
C.


Survival Functions
T1-2 or 3
T1-2
T3
T1-2-censored
T3-censored
Cum Survival
1,0
0,8
0,6
0,4
0,2
0,0
,00
2,50
5,00
7,50
10,00
12,50
SurvivalYears

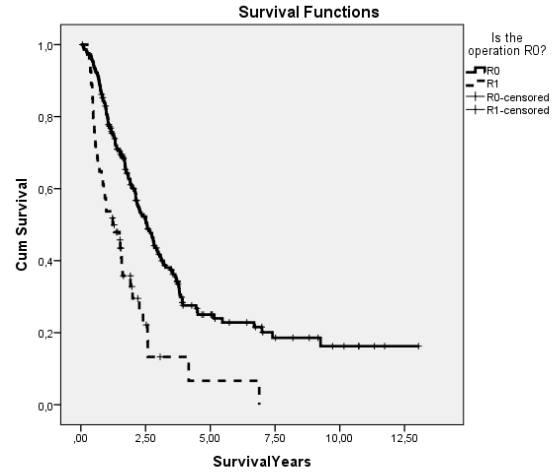
D.


Survival Functions
N
0
1
0-censored
1-censored
Cum Survival
1,0
0,8
0,6
0,4
0,2
0,0
,00
2,50
5,00
7,50
10,00
12,50
SurvivalYears

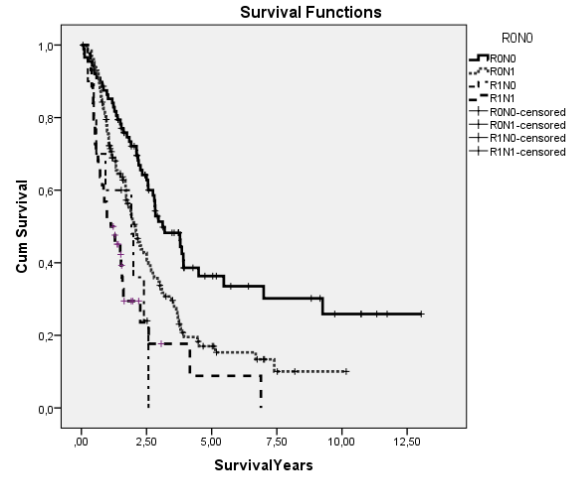
E.


Survival Functions
Lymph node ratio below 20 %
LNR below 20 %
LNR over 20 %
LNR below 20 %-censored
LNR over 20 %-censored
Cum Survival
1,0
0,8
0,6
0,4
0,2
0,0
,00
2,50
5,00
7,50
10,00
12,50
SurvivalYears

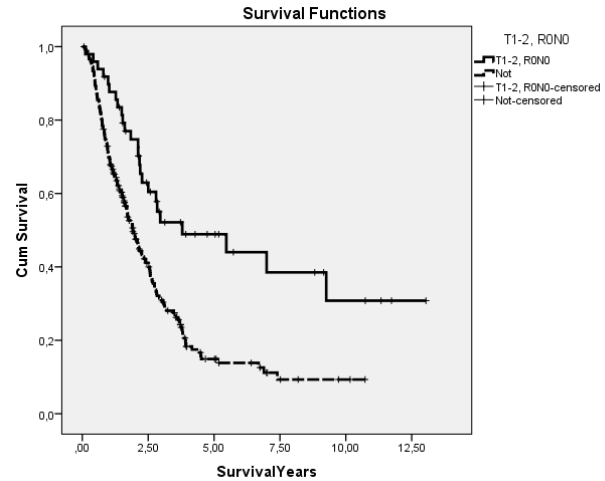
F.


Survival Functions
Is the operation R0?
R0
R1
R0-censored
R1-censored
Cum Survival
1,0
0,8
0,6
0,4
0,2
0,0
,00
2,50
5,00
7,50
10,00
12,50
SurvivalYears

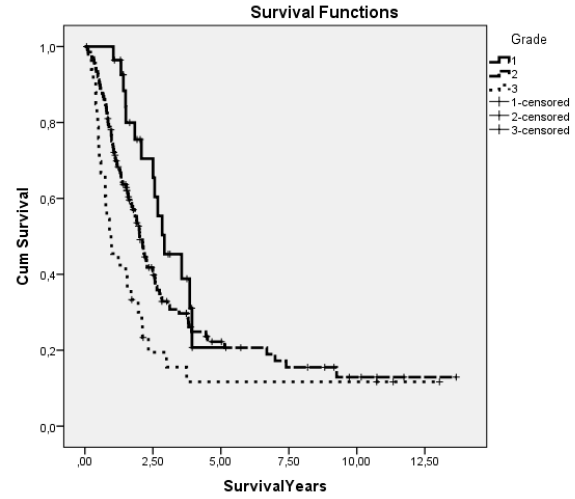
G.


Survival Functions
R0N0
R0N0
R0N1
R1N0
R1N1
R0N0-censored
R0N1-censored
R1N0-censored
R1N1-censored
Cum Survival
1,0
0,8
0,6
0,4
0,2
0,0
,00
2,50
5,00
7,50
10,00
12,50
SurvivalYears

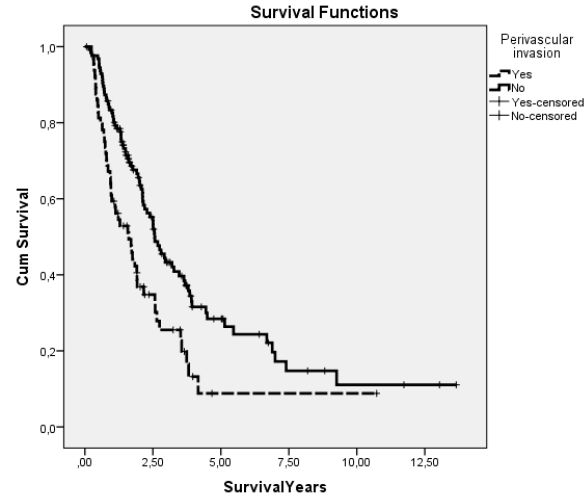
H.


Survival Functions
T1-2, R0N0
T1-2, R0N0
Not
T1-2, R0N0-censored
Not-censored
Cum Survival
1,0
0,8
0,6
0,4
0,2
0,0
,00
2,50
5,00
7,50
10,00
12,50
SurvivalYears

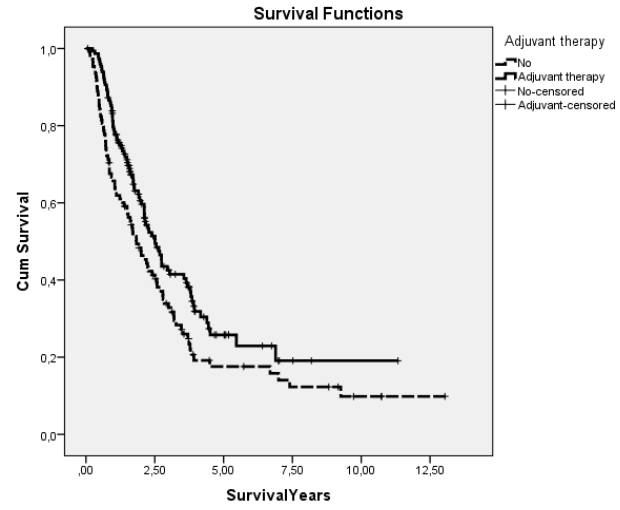
I.


Survival Functions
Grade
1
2
3
1-censored
2-censored
3-censored
Cum Survival
1,0
0,8
0,6
0,4
0,2
0,0
,00
2,50
5,00
7,50
10,00
12,50
SurvivalYears

J.


Survival Functions
Perivascular invasion
Yes
No
Yes-censored
No-censored
Cum Survival
1,0
0,8
0,6
0,4
0,2
0,0
,00
2,50
5,00
7,50
10,00
12,50
SurvivalYears

K.


Survival Functions
Adjuvant therapy
No
Adjuvant therapy
No-censored
Adjuvant-censored
Cum Survival
1,0
0,8
0,6
0,4
0,2
0,0
,00
2,50
5,00
7,50
10,00
12,50
SurvivalYears