

Pancreatic Cancer, Recurrence and Re-resections

Birgir Gudjonsson

Department of Medical Clinics, Reykjavik, Iceland

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***Corresponding author:** Birgir Gudjonsson, Department of Medical Clinics, Reykjavik, Grandaveg 47, 107 Reykjavík, Álfheimum 74, Iceland

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Abstract

Resections for pancreatic carcinoma have been carried out since 1935 Whipple reported his first. They have been done on the assumption that only this therapy would achieve 5-year survival.

Cattel reported in 1957 a patient having lived 9 years after only bypass. Glenn and Thorbjarnarson expressed doubts in 1964 and said that cure was unlikely because of adjacent vascularity and spread of tumour cells.

Crile in 1970 claimed that there was more advantage of a bypass rather than resection. His only survivor was not resected. Lea and Stalhgren in 1987 and Neil in 2005 reported the cost of resections which with inflation would now be close to quarter of million USD.

More authorities acknowledge lack of success and attention has been focused on recurrence and therapeutic options including re-resection. The enormous cost of this is obvious. Resections should be abandoned and emphasis placed on biologic research and palliation.

Keywords: Pancreatic cancer; Recurrence and re-resections

Introduction

The incidence of pancreatic cancer has been increasing in western societies. In the USA it represents 3% of new cancer cases annually but is the third most common cause of cancer death and is projected to become the second leading cause of cancer-related deaths by the year 2030 and a major health burden [1-4].

The first successful resection for pancreatic adenocarcinoma was performed by Whipple in 1935 [5] but had earlier been attempted by Codivilla in 1898 [6] and by Kausch in 1912 [7].

Resections have since been carried out regularly over the last 88 years on the assumption that resections are the only possible curative therapy. However, opinions have differed as to the results achieved [8].

Reservation, Non-resected Survivors

The first doubts regarding the effect of resection for this disease were expressed by Glenn and Thorbjarnarson of Cornell in 1964 [9]. They reported on 236 patients with 30 resections over a thirty-year period. They pointed out the difficult location with adjacent major vessels and noted that “the profuse and variable lymphatic and venous drainage of

the pancreas invites early and widespread dissemination of the tumour cells.”

Their only 5-year survivor was resected but subsequently died following recurrence. They concluded that the same result might have been achieved by means of palliative procedures and saw resection, as such, offering symptomatic relief but neither prolonging life to an appreciable degree nor providing more than doubtful prospects of cure.

Non-Resected Survivors

The existence of non-resected 5-year survivors has been disputed, but Cattell at Lahey Clinic reported in 1957 a survivor who lived 9 years after bypass procedures only [10]. Gallitano reported in 1968 on the experience at MD Anderson from 1944 to 1965 and had doubts about the effect of resections [11]. Their only 5-year survivor was non-resected.

Crile from Cleveland Clinic “shocked the profession” by criticizing resections strongly in 1970 and claiming greater advantages of bypass operations over radical pancreatoduodenectomy in the treatment of pancreatic cancer.

His only survivor was non-resected [12]. Crile criticized the high mortality rate and survival calculations that were sometimes based only on those who survived the operation.

In addition to the above, in an earlier review of mine 41 reports of non-resected survivors were found from 31 institutions in 12 countries [8].

In my study and review at Yale, ending in 1972, I could find reports of approximately 15000 patients with 124 five-year survivors in the literature, but 8 of these survivors were not resected [13]. In a repeat study at Yale covering the years 1972-1982, approximately 37000 patients were found reported in the literature with approximately 4100 resections. Only 156 five-year survivors were found reported, but 12 of these had not undergone resection [14].

The 5-year survival percentage for both these studies would be 0.5%. In both of my ten-year studies at Yale there was only one non-resected survivor in each.

I concluded in my papers that resections had minimal impact on 5-year survival.

Occasional survival in the “90% unresectable group” after symptomatic and palliative therapy is a fact and should be kept in mind in assessing overall therapeutic results [14].

Resection Rate

The resection rate can only be assessed accurately if the cohort of the original group is known. In the cohort of a previous study by this author the resection rate was 10.8% [13]. In two earlier large US studies the rates were 8.4% and 12%, respectively [15,16]. In two European national studies the rates ranged from 8%-12% [17,18]. In a recent study of the English National Cancer Registration the resection rate was 8.9% [19].

In a paper based on CDC information the disease was localized in 9.5% of cases [20]. In a recent Dutch report the resection rate was 8%-15% based on different groups, but with various exclusions [21].

It is therefore practical to assume that the resection rate is, in general, approximately 10% when estimating the original cohort where only the number of resected patients is reported and thereby estimate the 5-year survival of that respective group.

Survival Calculations

The survival percentage depends not only on the number of survivors but not less on the denominator from which the number is calculated.

Overall survival success must be based on the cohort of the total number of patients diagnosed with pancreatic cancer and the number of known survivors, and not only on a small subgroup of resected patients.

Initially, most reports from specific institutions detailed the course of the total number of patients diagnosed, frequently with emphasis on the number of resections and the number of survivors.

In the late 1980's papers started reporting mainly the number of resections and survival as actuarial percentages based on the resections only, or subgroups thereof, usually calculated using the Kaplan-Meier method, with or without the actual number of survivors being reported [22]. It has been shown how censoring in this manner enhances the outcome [23,24]. Sir Austin Bradford Hill pointed out in his

book in 1937 that when a “large number of patients is lost sight of the outcome might be erroneously high” [25].

In a frequently quoted paper, 11 survivors out of 201 resected patients are said to represent a 22% survival rate using the Kaplan-Meier method. The initial cohort must have been close to 2000 and the overall survival rate of that group therefore only 0.5% [26].

In a previous paper of mine 424 reports with survival calculations by actuarial methods and the number of survivors is known in 205 reports. The actuarial and actual percentage figures can therefore be compared, and they show that the actuarial percentage is on average 2.75 times higher than the actual percentage but has been reported up to 10 times higher [24].

These figures have therefore been used to estimate the number of survivors and the survival percentage in studies where only the number of resections and the actuarial percentage has been reported.

Papers on the surgical aspects of pancreatic cancer differ as to the patient groups and the method of reporting. This author had earlier found approximately 1470 papers which deal with resections and reveal some survival information, but of these, only 760 papers report 5-year survivors. Special attention has been paid to the statistical method used in each case [24].

If the survival percentage of the 760 studies with survivors is assessed assuming a 10 percent resection rate and adjustment using the Kaplan-Meier correction, the average survival percentage is 0.9%. Taking into account that a similar number of studies are without any survivors the survival percent for the overall cohort of pancreas cancer patients cannot be higher than 0.5%.

Repetitions

Repetition of reporting the same survivors in different papers was first pointed out in 1978, [13] and further details given in 1995 [14]. Repetition occurs mainly when the patient population and survivors from a certain year are reported several times from the same institution. Repetition has occurred up to 6-8 times in Germany, Italy and Japan, and up to 20 times in the US [14].

Repetition also occurs when papers include survivors from many different institutions in a specific country, or even when a study includes patients from many countries. Thus, 92 of the 760 studies with 5-year survivors are from many institutions in a specific country, or 14.8%, and 10 of these from many countries or 1.6%.

There is no scientific method to assess the number of repetitions accurately, but each reported 5-year survivors, and therefore the respective resection and the TN, seem to be reported 3-5 times.

Economics

Lea and Stahlgren from Denver reported in 1987 that the cost of a resection was \$61,000, while a bypass cost \$35,000. They asked whether a resection at this cost was appropriate. Their only 5-year survivor was non-resected [27].

O’Neill and colleagues at Memorial Sloan Kettering studied the total direct medical cost of treatment in the US of pancreatic cancer patients 66 years and older who were diagnosed from 2000-2007 [28].

The total direct cost for resectable cases was \$134,700, and for unresectable locoregional cases \$65,300. Medical care experienced an average inflation rate of 4.69% per year according to U.S. Bureau of Labor Statistics. Even assuming a lower inflation rate these figures would today be close to quarter of a million USD.

Resections

After the Whipple operation, resections were carried out with enthusiasm all over the world, but most frequently at tertiary referral centres repeatedly stating that resections are the only possible curative therapy, that is to say for a 5-year survival. The papers certainly reported gradually lower operative mortality rate but, alas, few survivors.

In 1996 Conlon et al. reported 12 five-year survivors from the Memorial Sloan Kettering Cancer Center [29] Five of these patients died shortly after by reason of recurrence after the 5 years had passed, confirming abysmal prognosis. They concluded that five-year survival could not be equated with cure and that pancreatectomy should be considered the best palliative procedure.

In the last decades reports from major centres with pessimistic views have appeared [30-44].

These include the following:

- “Extremely poor clinical outcome” [31].
- “Prognosis not improving.” [32].
- “No improvement in long-term survival” [33].
- “Pancreatic cancer is considered a systemic disease.” [35].
- “Most patients with pancreatic cancer have microscopic locally advanced disease that cannot be cured by surgery alone” [36].
- “Long-term survival among patients with pancreatic adenocarcinoma is extremely rare” [37].

It has thus been acknowledged by renowned authorities that resections have had a minimal effect on longevity in pancreatic cancer.

Recurrence

Attention has recently been focused on the early rate of recurrence and various therapeutic options have been discussed, even re-resections [45-56].

Considering the above, and considering the misleading survival information with repetitions and actuarial survival calculations, I must again conclude that resections have had a minimal impact on survival, if any, and that same results might have been obtained by means of simpler palliative measures as Glenn and Thorbjarnarson suggested in 1964 [8].

Conclusion

Pancreatic cancer is both a costly and devastating disease and has usually already metastasized at the time of diagnosis and treatment.

Considering the documented cost of resection and inflation, subsequent re-resection might therefore be at a cost of half a million dollars for the patient in question. It must be obvious that this is not appropriate, neither from a medical nor a financial perspective.

As van Heerden quotes Esselstyn “It is the basic biological aggressiveness of the tumour rather than the lack of effort on the part of the surgeon which ultimately determines the outcome.” [57-59].

I conclude that resections are not justified and should be abandoned, and that the emphasis should be on biological research and palliation.

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References

1. Boyle P, Hsieh C-C, Maisonneuve P, Vecchia CL, Macfarlane GJ, Walker AM, et al. Epidemiology of pancreas cancer. *Int J Pancreatol.* 1989;5(4):327-46.
2. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisan LM. Projecting cancer incidence and deaths to 2030: The unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Research.* 2014;74(11):2913-21.
3. Siegel RL, Miller KD, Sandeep W, Ahmedin J. Cancer statistics, 2023. *CA Cancer J Clin.* 2023;73(1):17-48.
4. Abboud Y, Saaman JS, Oh J, Jiang Yi, Randhawa N, Lew D, et al. Increasing pancreatic cancer incidence in young women in the United States: A population-based. A time-trend analysis. *Gastroenterology.* 2023;164(6):978-89.e6.
5. Whipple AO, Parsons WB, Mullins CR. Treatment of carcinoma of the ampulla of Vater. *Ann Surg.* 1935;102(4):763-76.
6. Howard JM, Hess W. History of the pancreas. *Mysteries of a hidden organ.* New York: Kluwer Academic/Plenum Publishers; 2002, p. 471-6.
7. Kausch W. Das Carcinom der Papilla duodeni und seine radikale Entfernung. *Beitr Klin Chir.* 1912; 78:439.
8. Gudjonsson B. Pancreatic cancer: 80 years of surgery-Percentage and repetitions. *HPB Surg.* 2016;2016:6839687.
9. Glenn F, Thorbjarnarson B. Carcinoma of the pancreas. *Ann Surg.* 1964;159(6):945-57.
10. Cattell RB, Young WC. Long survival of carcinoma of the pancreas. *Lahey Clin Bull.* 1957;10(5):131-4.
11. Gallitano A, Fransen H, Martin RG. Carcinoma of the pancreas. Results of treatment. *Cancer.* 1968; 22(5):939-44.

12. Crile G. The advantages of bypass operations over radical pancreatoduodenectomy in the treatment of pancreatic cancer. *Surg Gyn Obst.* 1970;130(6):1049-53.
13. Gudjonsson B, Livstone EM, Spiro HM. Cancer of the pancreas: Diagnostic accuracy and survival statistics. *Cancer.* 1978;42(5):2494-6.
14. Gudjonsson B. Cancer of the pancreas. 50 years of surgery. *Cancer.* 1987;60(9):2284-303.
15. Wade TP, Virgo KS, Johnson FE. Distal pancreatectomy for cancer: Results in U.S. Department of Veterans Affairs Hospitals, 1987-1991. *Pancreas.* 1995;11(4):341-4.
16. Edge SB, Schmiege RE, Wilhelm MC. Pancreas cancer resection outcome in American University Centers in 1989-1990. *Cancer.* 1993;71(11):3502-8.
17. Nienhuijs SW, van den Akker, de Vries E, de Hingh IH, Visser O, Lemmens VE. Nationwide improvement of only short-term survival after resection for pancreatic cancer in the Netherlands. *Pancreas.* 2012;41(7):1063-6.
18. Bjerregaard JK, Mortensen MB, Schönemann KR, Pfeiffer P. Characteristics, therapy, and outcome in an unselected and prospectively registered cohort of pancreatic cancer patients. *Eur J Cancer.* 2013; 49(1):98-105.
19. Exarchakou A, Papacleovoulou G, Rous B, Magadi W, Rachet B, Neoptolemos JP, et al. Pancreatic cancer incidence and survival and the role of specialist centres in resection rates and survival in England 2000-2014: A population-based study. *Pancreatology.* 2020;20(3):454-61.
20. Niksié M, Minicozzi P, Weir HK, Zimmerman H, Sxhymura MJ, Rees JR, et al. Pancreatic cancer survival trends in the US from 2001 to 2014: a CONCORD-study. *Cancer Comm.* 2023;43(1):87-99.
21. Daamen LA, Groot VP, Besselink MG, Bosscha K, Busch OR, Cirkel GA, et al. Detection, treatment, and survival of pancreatic cancer recurrence in the Netherlands: A nationwide analysis. *Ann Surg.* 2022;275(4):769-75.
22. Kaplan EL, Meier P. Nonparametric estimation from incomplete observation. *J Am Stat Assoc.* 1958; 53(282):457-81.
23. Gudjonsson B. Survival statistics gone awry. *Pancreatic cancer, a case in point. J Clin Gastroenterol.* 2002;35(2):180-4.
24. Gudjonsson B. Pancreatic cancer: survival, errors and evidence. *Eur J Gastroenterol Hepatol.* 2009;21(12):1379-82.
25. Bradford HA. Principles of medical statistics. London: The Lancet limited; 1971, p. 235.
26. Yeo CJ, Cameron JL, Lillemoe KD, Sitzman JV, Hruban RH, Goodman SN, et al. Pancreaticoduodenectomy for cancer of the head of the pancreas. 201 patients. *Ann Surg.* 1995; 221(6):721-31; discussion 731-3.
27. Lea MS, Stahlgren LH. Is resection appropriate for adenocarcinoma of the pancreas? A cost-benefit analysis. *Am J Surg.* 1987;154(6):651-4.
28. O'Neill CB, Atoria CL, O'Reilly EM, LaFemina J, Henman MC, Elkin EB. Costs and trends in pancreatic cancer treatment. *Cancer.* 2012;118(20):5132-9.
29. Conlon KC, Klimstra DS, Brennan MF. Long-term survival after curative resection for pancreatic ductal adenocarcinoma. Clinicopathological analysis of 5-year survivors. *Ann Surg.* 1996;223(3):273-9.
30. He J, Ahuja N, Makary M, Cameron JL, Eckhauser FE, Choti MA, et al. 2564 resected periampullary adenocarcinoma at a single institution: trends over three decades. *HPB.* 2014;16(1):83-90.
31. Yeo TP. Demographics, epidemiology, and inheritance of pancreatic ductal adenocarcinoma. *Semin Oncol.* 2015;42(1):8-18.
32. Lavu H, Yeo CJ. Pancreatic ductal adenocarcinoma treatment. The past, present and future. *Semin Oncol.* 2015;42(1):4-7.
33. Rishi A, Goggins M, Wood LD, Hruban RH. Pathological and Molecular Evaluation of Pancreatic Neoplasms. *Semin in Oncol.* 2015;42(1):28-39.

34. Loehrer AP, Chang DC, Hutter MM, Song Z, Lillemoe KD, Warshaw AL, et al. Health insurance expansion and treatment of pancreatic cancer: Does increased access lead to improved care? *J Am Coll Surg.* 2015;221(6):1015-22.
35. Li Daneng, O'Reilly EM. Adjuvant and neoadjuvant systemic therapy for pancreas adenocarcinoma. *Semin Oncol.* 2015;42(1):134-43.
36. Foley K, Kim V, Jaffee E, Zheng L. Current progress in immunotherapy for pancreatic cancer. *Cancer Lett.* 2016;381(1):244-51.
37. Bednar F, Zenati MS, Steve J, Winters S, Ocuin LM, Bahary N, et al. Analysis of predictors of resections and survival in locally advanced stage III pancreatic cancer: Does the nature of chemotherapy regimen influence the outcomes? *Ann Surg Oncol.* 2017;1406(5):1406-13.
38. Kang MJ, Jang J-Y, Kim SW. Surgical resection of pancreatic head cancer: What is the optimal extent of surgery? *Cancer Lett.* 2016;382(2):259-65.
39. Zijlstra M, Nienke B, Hingh IHJT, van de Wouw AJ, Goey SH, Jacobs EMG, et al. Does long-term survival exist in pancreatic adenocarcinoma? *Acta Oncol.* 2016;55(3):259-64.
40. Luberic K, Drowns D, Sadowitz B, Ross S, Rosemurgy A. Has survival improved following resection for pancreatic adenocarcinoma. *Am J Surg.* 2017;214(2):341-6.
41. Ahola R, Siiki A, Vasama K, Vornamen M, Sand J, Laukkanen J. Effect of centralization on long-term survival after resection of pancreatic ductal adenocarcinoma. *Br J Surg.* 2017;104(11):1532-8.
42. Van Roessel S, Kasumova GG, Tabatabaie O, Chau Ng SC, van Rijssen LB, Vewrheij J, et al. Pathological margin clearance and survival pancreaticoduodenectomy in a US and European center. *Ann Surg Oncol.* 2018;25(6):1760-7.
43. Van der Geest LGM, Van Eijck CHJ, Koerkamp, BG, Lemmens VEPP, Busch OR, Vissers PAJ, et al. Trends in treatment and survival of patients with non-resected nonmetastatic pancreatic cancer: A population-based study. *Cancer Med.* 2018;7(10):4943-51.
44. Schneider M, Strobel O, Hackert T, Büchler MW. Pancreatic resection for cancer-the Heidelberg technique. *Langenbecks Arch Surg.* 2019;404(8):1017-22.
45. Hue J, Bingmer K, Sugumar K, Ocuin LM, Rothermel LD, Winter JM, et al. Mortality and survival among octogenarians with localized pancreatic head cancer: a National cancer database analysis. *J Gastrointest Surg.* 2021;25(10):2582-92.
46. Kpoussou AR, Gbessi DG, Gnagnon FHR, Ba Boukari MM, Vignon RK, et al. Cancers of the pancreas at the National Hospital and University Center of Cotonou: epidemiological, diagnostic, therapeutic and prognostic features. *Pan Afr Med J.* 2021;39:18.
47. Zhao Y, Wang C. Clinicopathological features, recurrence patterns, and prognosis of pancreatic adenocarcinoma with normal serum CA19-9. A consecutive series of 154 cases from a single institution. *Gastrointest Surg.* 2020;24(4):855-65.
48. Tsuchiya N, Matsuyama R, Murakami T, Yabushita Y, Sawada Y, Kumamoto T, et al. Risk factors associated with early recurrence of borderline resectable ductal adenocarcinoma after neoadjuvant chemotherapy and curative resection. *Anticancer Research.* 2019;39(8):4431-40.
49. Nappo T, Donisi G, Capretti G, Ridolfi C, Pagnanelli M, Nebbia M, et al. Early recurrence after upfront surgery for pancreatic ductal adenocarcinoma. *Curr Oncol.* 2023;30(4):3708-20.
50. Jethwa KR, Neibart SS, Truty MJ, Jabbour SK, Hallemeier CL. Patterns of recurrence after primary local therapy for pancreatic ductal adenocarcinoma- A critical review of rationale and target delineation for (neo) adjuvant radiation therapy. *Pract Radiat Oncol.* 2022;12(6):e463-73.
51. Kim JR, Hongbeom K, Wooil K, Jang J-Y, Kim S-W. Pattern of local recurrence after curative resection in pancreatic ductal adenocarcinoma according to the

- initial location of the tumor. *J Hepatobiliary Pancreat Sci.* 2021;28(1):105-14.
52. Narayanan S, AlMasri S, Zenati M, Nassour I, Chopra A, Rieser C, et al. Predictors of early recurrence following neoadjuvant chemotherapy and surgical resection for localized pancreatic adenocarcinoma. *J Surg Oncol.* 2021;124(3):308-16.
53. Zambirinis DP, Midya A, Chacraborty J, Coue JF, Zheng J, McIntyre CA, et al. Recurrence after resection of pancreatic cancer: Can radiomics predict patients at greatest risk of liver metastases? *Ann Surg Oncol.* 2022;29(8):4962-74.
54. Ono S, Adachi T, Ohtsuka T, Kimura R, Nishihara K, Watanabe Y, et al. Predictive factors for early recurrence after pancreaticoduodenectomy in patients with resectable pancreatic head cancer: +A multicenter retrospective study. *Surgery.* 2022;172(6):1782-90.
55. Nienhüser H, Büchler MW, Schneider M. Resection of recurrent pancreatic cancer: Who can benefit? *Visc Med.* 2022;38(1):42-8.
56. Sato H, Yoshida R, Yasul K, Umeda Y, Yoshida K, Fuji T, et al. Feasibility of local therapy for recurrent pancreatic cancer. *Pancreatology.* 2022;22(6):774-81.
57. Daamen LA, Groot VP, Besselink MG, Bosscha K, Busch OR, Cirkel GA, et al. Detection, treatment, and survival of pancreatic cancer recurrence in the Netherlands: A nationwide analysis. *Ann Surg.* 2022;275(4):769-75.
58. Seelen LWF, Floortje van OA, Brada LJH, Groot VP, Daamen LA, Walma MS, et al. Early recurrence after resection of locally advanced cancer following induction therapy: An international multicenter study. *Ann Surg.* 2023;278(1):118-26.
59. Van Heerden JA. Pancreatic resection for carcinoma of the pancreas: Whipple versus total pancreatectomy - An institutional perspective. *World J Surg.* 1984;8(6):880-8.

Author's Contact Information:

Birgir Gudjonsson, Department of Medical Clinics, Reykjavik, Grandaveg 47, 107 Reykjavík, Álfheimum 74, Iceland, Tel: +354 5682005; E-mail: bghav[.]simnet[.]is