

## Pancreatic Cancer Are Resections Justified?

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### **ABSTRACT**

Resections for pancreatic cancer have been carried out for 86 years. Doubts about the efficacy were first expressed in 1964. Resections are costly and recent reports have failed to show success. It is suggested that resections should be abandoned, but biologic research and palliation emphasized.

### **KEYWORDS**

Pancreatic cancer; Resections; Survival

### **INCIDENCE**

The incidence of pancreatic cancer has been increasing in western societies and is considered to become the second leading cause of cancer-related deaths by the year 2030 and a major burden [1,2]. The incidence is estimated to be 64430 in the USA in 2021 and increase to 88,000 for both sexes in 2030 [3]. Incidence differs between ethnic groups for many cited between 10-15/100,000 but has been reported up to 20/100,000 in certain ethnic groups [1].

Resection for pancreatic adenocarcinoma was first attempted by Codivilla A in 1898 [4] and then by Kausch W in 1912 [5] but was first successfully performed by Whipple A in 1935 [6].

Resections have since been carried out systematically over the last 86 years, but opinions have differed as to the results [7].

### **RESERVATION, NON-RESECTED**

#### **SURVIVORS**

The first doubts about the effect of a resection for this disease was expressed by Glenn F and Thorbjarnarson B from Cornell in 1964 [8]. They reported on 236 patients over 30-years period with 30 resections. They pointed out difficult location with adjacent major vessels and “the profuse and variable lymphatic and venous drainage of the pancreas invites early and widespread dissemination of the tumor cells”. Their only 5-years survivor was resected but then died of recurrence. They concluded that same result might have been achieved by palliative procedures and saw resection as such, offering symptomatic relief but not prolonging life to an appreciable degree and doubted cure.

#### **NON-RESECTED SURVIVORS**

Cattell RB at Lahey Clinic 1957 reported a survivor who lived 9 years and had only bypass procedures [9]. Gallitano A reported in 1968, on MD Anderson’s experience from,

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1944 to 1965 and had doubts about the effect of resections [10]. Their only 5-years survivor was non-resected.

Crile G from Cleveland Clinic criticized resection strongly in 1970, his only survivor was also non-resected [11]. Crile G criticized the high mortality rate and the survival calculations. In my two ten-year studies at Yale there was only one non-resected survivor in each [12,13].

The presence of non-resected survivors has been disputed, but in addition to above in a previous review 41 reports were found from 31 institutions in 12 countries [14]. Occasional survival in the “90% unresectable group” after palliative therapy is a fact and should be kept in mind in assessing overall therapeutic results.

### **RESECTION RATE**

The resection rate can only be assessed accurately if the total number of the original group is known or TN. In a previous study by this author the resection rate was 10.8% [12]. In earlier large US studies, the rate was, respectively, 8.4% and 12% [15,16]. In two European national studies the rate was from 8%-12% over the last 5 years [17,18]. In a recent study of the English National Cancer Registration by Exerchakou A the resection rate was 8.9% and five-years survival of those not resected 2.1% [19].

It is therefore practical to assume that the resection rate is in general approx. 10% in order to estimate the TN when it is not reported and thus estimate 5-years survival of that respective group.

### **SURVIVAL CALCULATIONS**

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

Overall survival success must be based on the total number of patients TN diagnosed with pancreatic cancer and the

number of survivors, and not only on a small subgroup of resected patients.

Initially most reports detailed the course of all patients, i.e. TN diagnosed at a particular institution, the number of resections and bypasses and simply the number of survivors.

In the late 1980's papers started reporting survival as actuarial percentages based on the resections only or subgroups thereof, usually calculated with the Kaplan-Meier method, with or without the actual number of survivors being reported [20]. It has been shown how censoring in this method increases the outcome [21,22]. 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” [23].

In a frequently quoted paper, 11 survivors out of 201 resections are claimed as a 22% survival rate using the Kaplan-Meier method [24]. The initial cohort must have been close to 2000 [24] and the overall survival of that group 0.5%.

In previous paper 424 reports with survival calculations by actuarial methods the number of survivors is known in 48.3% [22]. The actuarial and actual percentage figures can therefore be compared, showing that the actuarial percentage can be up to 10 times higher but is on the average 2.75 higher than the actual percentage. This figure has therefore been used to estimate the number of survivors and the survival percentage in the studies where only the actuarial percentage has been reported.

Of the studies published in the last 5 years of the present study, 156 of 161 or 97% report only the number of resections and the percentage usually by actuary methods [7].

In a recent report the original TN of patients studied was revealed in only 90 or 14.5% of the papers with survivors,

and in these the actual number of survivors was reported in only 66 papers [7]. Detailed information on the original TN studied, the number of resections and the actual number of survivors has therefore only been reported in 66 or 10.6% of all papers on pancreatic cancer. In the remaining 89.4% some form of estimate or calculation must be used to assess survival percentage.

Papers on the surgical aspects of pancreatic cancer differ as to the patient groups and the method of reporting. This author has found approx. 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 [7].

Assessing the survival percentage of the 760 studies with survivors assuming 10 percent resection rate and adjusting with Kaplan-Meier correction the average survival percentage is 0.9% [7]. Realizing that similar number of studies are without any survivor 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 times - 8 times each in Germany, Italy and Japan, and up to 20 times in the US [7].

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-years survivors are from many institutions in a specific country or 14.8%, and 10 of these from many countries or 1.6% [7].

Examination of reports from a single institution which together cover a specific study period and state the number of survivors, and then adding up the number of survivors from all reported studies from that institution, reveals that the total number reported is 10 times higher [7].

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

Repetitions occur also in the “no-survivor” group of reports, but not as frequently.

### **ECONOMICS**

Lea MS and Stahlgren LH asked in 1987 whether a resection at a cost of \$61,000 was appropriate, given that a bypass cost USD 35,000, where their only survivor was found [26].

O’Neill CB 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 [26]. The total direct cost for resectable disease was \$134,700, and for unresectable locoregional disease \$65,300 for a difference of \$69,400. Medical care experienced an average inflation rate of 4.69% per year according to U.S. Bureau of Labor Statistics.

Assuming a minimum 2.5% inflation rate over 14 years, the cost in 2021 could be \$189,000 for a resection and for unresectable (or bypasses) \$92,000 for a difference of \$97,000.

Assuming 10% resection rate one might expect approximately 6500 resections in the US this year for a cost of at least \$1,235,000,000 or 630,000,000 more than for palliative procedure.

## **RESECTIONS**

After Whipple operation, resections were carried out with enthusiasm all over the world but most frequently from volume institutions repeatedly stating that resections are the only possible curative therapy. The papers certainly reported gradually lower operative mortality rate but alas few survivors.

In two earlier papers I concluded that resections have had minimal impact on survival [7,13].

KC. Conlon et al. reported 12 survivors from Memorial Sloan Kettering Cancer Center in 1996 [27]. Five patients died shortly of recurrence after 5 years. They concluded that five-years survival cannot be equated with cure, but that pancreatectomy should be considered best palliative procedure.

In the last decades or so more reports with pessimistic views have appeared.

## **FEW EXCPERTS FROM PAPERS**

1. (2012) J He “Safe resections have increased, overall long-term outcomes have not improved significantly” [28].
2. (2015) TP Yeo “Continuing poor long-term survival” [29].
3. (2015) H Lavu “After all, the 5-year survival rate for patients with PDA has been fairly stagnant over the last three decades” [30].
4. (2015) A Rishi “Extremely poor clinical outcome” [31].
5. (2015) A Loehrer “Prognosis not improving” [32].
6. (2015) D Li “No improvement in long term survival” [33].
7. (2016) K Foley “Pancreatic cancer remains a difficult to treat with very few treatment regiments showing substantial improvements in survival” [34].

8. (2016) F Bednar “Pancreatic cancer is considered a systemic disease” [35].
9. (2016) MJ Kang “As most patients with pancreatic cancer have microscopic locally advanced disease that cannot be cured by surgery alone” [36].
10. (2016) M Zijlstra “Long-term survival among patients with pancreatic adenocarcinoma is extremely rare” [37].
11. (2017) SWL de Geus “Recurrence after surgery range from from 46%-89%” [38].
12. (2017) K Luberic “These patients lived more years ..... but without 5-year survival” [39].
13. (2017) KJ Roberts “Globally, outcomes among patients with pancreatic cancer have not improved over past 40 years” [40].
14. (2017) R Ahola “Pancreatic ductal adenocarcinoma (PDAC) has a poor overall prognosis even after radical surgery” [41].
15. (2018) S van Roessel “Failed to demonstrate survival benefit” [42].
16. (2018) LGM van der Geest “Overall survival of pancreatic cancer poor” [43].
17. (2019) M Schneider “High recurrence rate” [44].
18. (2019) N Tsuchiya “Early recurrence” [45].
19. (2019) Y Zhao “Death rate almost equal to rate of incidence” [46].
20. (2020) S van Roessel “Extremely poor 5-year rate” [47].
21. (2021) JJ Hue “Has historically poor outcomes” [48].
22. (2021) AR Kpossou “Survival zero at five years” [49].
23. (2021) EJ Olecki “Systemic disease” [50].

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

As van Heerden JA quotes Esselstyn “It is the basic biological aggressiveness of the tumor rather than the lack of effort on the part of the surgeon which ultimately determines the outcome” [51].

## **CONCLUSION**

Pancreatic cancer is thus both a costly and devastating disease and has usually metastasized at the time of

diagnosis and treatment. Emphasis should be on biologic research and palliation.

I conclude that resections are not justified and should be abandoned.

## **COMPETING INTERESTS**

The author declares that there are no financial or competing interests.

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