Pancreatic resection in very elderly patients: A critical analysis of existing evidence

Cosimo Sperti, Lucia Moletta, Gioia Pozza

Cosimo Sperti, Lucia Moletta, Gioia Pozza, Department of Surgery, Oncology and Gastroenterology, 3rd Surgical Clinic, University of Padua, 35128 Padua, Italy

Author contributions: Sperti C and Moletta L conceived the article and drafted the manuscript; Pozza G reviewed the Literature; all authors read and approved the final manuscript.

Conflict-of-interest statement: All the Authors have no conflicts of interests to declare.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Correspondence to: Cosimo Sperti, MD, Department of Surgery, Oncology and Gastroenterology, 3rd Surgical Clinic, University of Padua, via Giustiniani 2, 35128 Padova, Italy. experti@libero.it
Telephone: +39-049-8218845
Fax: +39-049-8218821

Received: August 9, 2016
Peer-review started: August 10, 2016
First decision: September 12, 2016
Revised: September 19, 2016
Accepted: November 16, 2016
Article in press: November 17, 2016
Published online: January 15, 2017

Abstract
The aging of the population results in a rise of number of elderly patients (aged 80 years and older) with pancreatic or periampullary cancer, and more pancreatectomies could eventually be performed in such complex patients. However, early and long-term results after pancreatic resection in octogenarians are still controversial, and may trouble the surgeon when approaching this type of population. Evaluation of reported experiences shows that for almost all Authors, pancreatectomy can be performed safely in elderly population, although overall morbidity and mortality rates were 34.9% and 13.2% respectively, with a mean length of hospital stay of 18 d. These features appear higher in older patients compared to the younger counterpart. Less than 50% of patients underwent adjuvant therapy after operation. Long-term survival is reported not significantly different in aged 80 years and older patients, with a median overall survival time of 17.6 mo. The quality of life after pancreatic resection is only sporadically evaluated but, when considered, it highlights the need of health facility service after operation for these “frail” patients. Prospective studies on the quality of life of pancreatectomized octogenarians are welcome. Proper selection of patients, geriatric assessment with multidisciplinary approach, centralization of pancreatic surgery in high-volume centres and rehabilitation programs after surgery appear to be crucial points in order to improve surgical treatments of pancreatic tumors in very elderly patients.

Key words: Elderly; Octogenarian; Pancreatectomy; Pancreatic neoplasms; Survival

© The Author(s) 2017. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Although not statistically significant, pancreatic resection in very older patients carried a greater risk of complications, mortality and nursing facility after discharge than in younger patients. Thus, pancreatectomy in 80 years and older patients, should be performed after careful consideration of potential benefit, surgical risk, and patient's preferences.
Sperti C, Moletta L, Pozza G. Pancreatic resection in very elderly patients: A critical analysis of existing evidence. World J Gastrointest Oncol 2017; 9(1): 30-36 Available from: URL: http://www.wjgnet.com/1948-5204/full/v9/i1/30.htm DOI: http://dx.doi.org/10.4251/wjgo.v9.i1.30

INTRODUCTION
The number of elderly in Western countries is rapidly increasing and it constitutes the fastest-growing age group of the population[1]. In the United States, the proportion of people 65 years of age or older will reach 18.2% by 2025[2], and the oldest elderly (individuals 85 years old or older) will account for 5% of the overall population[3]. The number of octogenarian patients referred to surgeons is going to gradually increase as well. This is particularly true for gastrointestinal cancers, which are characterized by the greatest incidence in the elderly, pancreatic cancer included. In past years, the high mortality and morbidity rates associated with pancreatic resections made this kind of surgery a rare indication for elderly people, considering also the limited survival time associated with pancreatic cancer. Recent data have clearly shown that pancreatic surgery is safe and feasible in high-volume centres, with reported mortality rates less than 2% and acceptable morbidity rates[4,5]. As postoperative outcome after pancreatic resections improved, many authors began to report pancreatectomies also in elderly patients. However, there are limited data on outcomes in octogenarian patients after pancreatic surgery. So, some crucial points may arise when treating very elderly patients with pancreatic tumors: (1) Is pancreatic resection safe and feasible in octogenarians? (2) Is surgical risk justified by long-term outcome after resection of malignancy? (3) Is quality of life preserved after major pancreatic resection?

The aim of this study was to analyse the existing literature and the available data on early postoperative outcomes and long-term results after pancreatic resection in patients 80 years and older.

EVIDENCE ACQUISITION
The published Literature was systematically searched using PubMed and free text search engines up to December 2015. The following search terms were used: Pancreaticoduodenectomy, pancreatectomy, duodenal neoplasm/surgery, pancreatic neoplasm/surgery, pancreatic neoplasm/surgery, 80 years of age and over, elderly and octogenarian. The “related articles” function was used to broaden the search and all abstracts, studies, and citations retrieved were reviewed. The preliminary literature search showed 113 studies matching the initial criteria. After screening, 16 studies evaluating octogenarians patients and their outcome after pancreatic resections were selected[2,3,6-19]. Information about 3793 aged 80-years or older patients who underwent pancreatic resections, were collected (Table 1). There were 13 single institution’s series, 2 nation or regional inpatient samples, and 1 multicentric report. In the population selected, there were 1710 male patients (45.1%) and the mean age was 82.2 years. Information about preoperative comorbidities were available for 489 patients. The most frequent reported comorbidities were cardiovascular disease (53.8%, n = 263 patients), in particular hypertension was reported for 168 patients, and coronary disease for 95 patients. Other frequent major comorbidities were diabetes mellitus (n = 94, 19.2%), pulmonary disease (n = 30, 6.1%) and chronic renal failure (n = 10, 2.0%). Elderly patients are often reported to have two or more concomitant major comorbidities. Finlayson et al[9] and Khan et al[11] reported a percentage of respectively 67.6% and 51% patients with 2 or more concomitant diseases. Six studies[3,11,14-16,18] reported data on the American Society of Anesthesiologists (ASA) score, with ASA grades 3 or 4 more frequently observed (60.3% of patients) (Table 2).

Surgery
Thirteen studies[2,3,6-7,10-16,18,19] reported the type of pancreatic neoplasm treated (n = 626 patients). In particular, four reports evaluated only outcome after resections for pancreatic adenocarcinoma, whereas other two authors considered also patients with other primary malignancies. Finally, the remaining 7 studies addressed also resections for benign pancreatic conditions. Malignant indications for surgery accounted for 89.8% of cases (n = 562), with pancreatic adenocarcinoma being the most frequent primary
tumor (74.6% of malignant cases, n = 419), followed by peripancreatic carcinoma (11.6%, n = 65) and cholangiocarcinoma (6.6%, n = 37). Other malignant tumor types reported were neuroendocrine tumors, intraductal papillary mucinous neoplasms (IPMNs) with invasive carcinoma, and pancreatic secondary tumors. Among benign neoplasms (n = 64, 10.2%), the most frequent indications were benign or borderline IPMNs (n = 25, 39.1%), cystic neoplasms (n = 20, 30.8%) and neuroendocrine tumors (n = 3, 4.7%). A vascular resection was as low as 23.4%. Finally, Hardacre et al reported 13 out of 26 resected patients who received adjuvant treatment (50%) who received adjuvant treatment. Six out of 13 patients completed the planned adjuvant chemotherapy, which was discontinued in the other patients because of poor general conditions, chemotherapy-related adverse-events or postoperative recurrence. Beltrame et al reported 30% of resected patients who received adjuvant treatment, while in the study by Turrini et al the patients’ rate receiving postsurgical treatment was as low as 23.4%. Finally, Hardacre et al excluded, because only severe complications were reported.

Table 2 Type of surgical resections and American Society of Anesthesiologists score

| Ref.        | Type of surgical procedure | Vascular resections | ASA SCORE |
|-------------|----------------------------|---------------------|-----------|
| PD          | DP                         | TP                  | % (n)     | 1-2 | 3-4 |
| Chen et al[8] | 16 0 NR NR NR NR |                     |           |     |     |
| Makary et al[9] | 197 0 10 2.4 (5) NR NR |                     |           |     |     |
| Finlayson et al[10] | NR NR NR NR NR |                     |           |     |     |
| Riall et al[11] | 155 46 48 2.4 (5) NR NR |                     |           |     |     |
| Hardacre et al[12] | 26 5 1 12.5 (4) 8 24 |                     |           |     |     |
| Tani et al[13] | 25 0 0 4 (1) NR NR |                     |           |     |     |
| Lee et al[14] | 74 0 0 14.9 (11) NR NR |                     |           |     |     |
| Khan et al[15] | 18 10 4 6.25 (2) 7 46 |                     |           |     |     |
| Stauffer et al[16] | 20 5 0 NR NR NR |                     |           |     |     |
| Hatzaras et al[17] | 53 0 0 NR NR NR |                     |           |     |     |
| Melis et al[18] | 25 0 0 4 (1) 7 17 |                     |           |     |     |
| Oguro et al[19] | 22 0 0 23 (5) 21 1 |                     |           |     |     |
| Turrini et al[20] | 56 8 0 11 (7) 37 23 |                     |           |     |     |
| Belyaev et al[21] | 27 3 8 NR NR NR |                     |           |     |     |
| Beltrame et al[22] | 21 2 0 8.7 (2) 5 18 |                     |           |     |     |
| Kinoshita et al[23] | 16 9 1 39 (10) NR NR |                     |           |     |     |
| Total        | 751 90 24 85 129 |                     |           |     |     |

PD: Pancreatoduodenectomy; DP: Distal pancreatectomy; TP: Total pancreatectomy; NR: Not reported; ASA: American Society of Anesthesiologists.

EARLY OUTCOME

Overall morbidity and mortality rates were 34.9% and 13.2% respectively, with a mean length of hospital stay of 18 d (Table 3). Detailed information on specific type of postsurgical complications were available for 569 patients. Most frequent complications were pancreatic fistula (12.1%, n = 69), delayed gastric emptying (10.9%, n = 62) and cardiopulmonary complications (9.3%, n = 53). Reoperations rate was 7.5% (Table 4). Four studies[2,8,9,11] focused on hospital discharge and the need for skilled nurse facilities after surgical resection. Finlayson et al[8], Riall et al[9] and Khan et al[11] observed a percentage of respectively 63.3%, 61.8% and 79% of resected patients who were discharged directly home, with or without home health care support. The other patients were discharged to health care facilities (nursing home, skilled care or other intermediate care facilities)

ADJUVANT THERAPY

Only few studies reported data on adjuvant therapy after pancreatic resections for cancer (Table 5). Kinoshita et al[19,20] reported 13 out of 26 resected patients (50%) who received adjuvant treatment. Six out of 13 patients completed the planned adjuvant chemotherapy, which was discontinued in the other patients because of poor general conditions, chemotherapy-related adverse-events or postoperative recurrence. Beltrame et al[20] reported 30% of resected patients who received adjuvant treatment, while in the study by Turrini et al[19] the patients’ rate receiving postsurgical treatment was as low as 23.4%. Finally, Hardacre et al[19] reported 10/25 patients resected for adenocarcinoma who were administered adjuvant chemotherapy. Specific survival outcome for patients receiving adjuvant treatment were not reported.

SURVIVAL

Median overall survival was 17.6 mo. One-year and 5-year survival rates were not always reported and varies among different series; at that point it is important to keep in mind that different reports consider different surgical indications. One-year survival rates range from 50% to 75.7%, while 5-year survival rates range from 0% to 46% (Table 5). When considering only those studies focusing on pancreatic adenocarcinoma, median overall survival is 15.4 mo. Melis et al[14] reported a 1-year and 5-year survival rate of 68.2% and 4.5% respectively. Turrini et al[19] reported a 1-year survival rate of 75.7% while 5-year survival rate was 0%.

Table 3 Perioperative outcomes after pancreatic resection

| Ref. | Mortality % (n) | Morbidity % (n) | Mean length of stay (d) |
|------|----------------|----------------|------------------------|
| Chen et al[24] | 13.0 (2) 51.8 (8) | 25.0 | |
| Makary et al[9] | 4.0 (8) 53.1 (109) | 11.0 | |
| Finlayson et al[10] | 15.5 (452) NR | 20.4 | |
| Riall et al[9] | 11.4 (24) NR | 15.0 | |
| Hardacre et al[11] | 0 (3) 66.2 (21) | 11.0 | |
| Tani et al[12] | NR 44 (13) | 25.0 | |
| Lee et al[13] | 5.4 (4) 47.3 (35) | 10.5 | |
| Khan et al[14] | 2.0 (1) 51.2 (7) | 13.5 | |
| Stauffer et al[15] | 0 50 (16) | 13.3 | |
| Hatzaras et al[16] | 3.7 (1) 52.1 (14) | 12.0 | |
| Melis et al[17] | 4.0 (1) 68.1 (17) | 20.0 | |
| Oguro et al[18] | 4.5 (1) 27.6 (6) | 31.5 | |
| Turrini et al[19] | 4.7 (3) 56.3 (36) | 24.9 | |
| Belyaev et al[20] | 11.4 (4) NR | 15.0 | |
| Beltrame et al[21] | 0 (0) 43 (10) | 13.5 | |
| Kinoshita et al[22] | 0 (0) 8 (2) | 25.8 | |
| Total | 13.2 (501) 34.9 (506) | 18.0 | |

NR: Not reported. 1Clavien-Dindo classification ≥ III; 2Riall et al[9] excluded, because only severe complications were reported.
PROGNOSTIC FACTORS

Six authors [5,10,13,15,16,19] examined clinical variables and risk factors that could be associated with poorer survival in octogenarian patients. Hatzaras et al [13] reported lymphovascular invasion as the only predictor of survival. Oguro et al [13] found that pancreatic cancer was an independent poor prognostic factor in the multivariate analysis with a hazard ratio of 4.398. Turrini et al [16] identified 4 independent prognostic indicators of overall survival: Venous invasion, arterial invasion, positive lymph nodes and adjuvant treatment. In their multivariate analysis, Kinoshita et al [19] indicated that distant metastasis and the conclusion of the planned adjuvant therapy were independent prognostic factors of surgical resection. Lee et al [11] reported female gender, non-caucasian race and positive lymph nodes as factors associated with shorter survival time in the multivariate model. In none of the aforementioned studies, age 80 or more resulted to be a significant predictor of long-term survival. On the contrary, Riall et al [20] in a population-based study used logistic regression models to assess the independent effect of age group on mortality. When compared with patients < 69 years of age, age group was an independent predictor of mortality after pancreatic resection.

QUALITY OF LIFE AFTER RESECTION

Although quality of life (QoL) is an important aspect of surgical result, this point is not evaluated in most of the studies. Gerstenhaber et al [20] firstly assessed QoL after pancreaticoduodenectomy in 70 elderly patients (aged 70 years and older). Fatigue was the most common symptom for the first 6 mo after surgery, but QoL quickly improved to normal scores. However, it has been reported that patients 80 years or older required discharge to a nursing facility more frequently when compared to younger patients [21]. This is obviously due to the need of rehabilitation program both in the physical activity and digestive function.

DISCUSSION

The higher incidence of morbidity, risk of mortality and of a prolonged recovery in an extended care facility following hospital discharge, made in past years pancreatic surgery a rare indication for older patients. The improved outcomes after pancreatic resections performed in high-volume centres have allowed to broaden the selection criteria for surgery and to include more elderly patients. The first study considering octogenarian patients and pancreatic surgery was published by Sohn et al [22]: Authors compared postoperative outcome of octogenarian patients undergoing pancreaticoduodenectomy with patients younger than 80 years, and reported similar morbidity and mortality rates in the two different age groups. This observation was then confirmed in other subsequent studies, showing similar results in postoperative outcome in elderly patients [2,7,11]. On the contrary, two large population-based studies [10,11] showed high mortality rates after pancreatic surgery in octogenarians with a high rate of discharge to health facilities. Sukharamwala et al [23] performed a systematic review and meta-analysis comparing the results of four studies [7,11,13,22] and showed that patients 80-years or older had a higher incidence of postoperative mortality, morbidity and pneumonia in comparison to younger patients. A recent meta-analysis by Casadei et al [24], showed a higher postoperative mortality rate in patients 80 years or older when compared to younger patients. These conflicting results may have different possible explanations. First of all, it...
has to be considered that the presence of an increased prevalence of preoperative comorbidities, represents a potential selection bias in those studies comparing outcome of elderly to younger patients. Therefore, preoperative studies play a major role in recognizing high-risk patients and in selecting the most appropriate treatment. The identification of modifiable preoperative risk factors for morbidity and mortality would improve the surgical outcome of patients\(^\text{[25]}\). Several scoring systems are available in the clinical practice to assess the surgical risk of old patients: Adult Comorbidity Evaluation-27 (ACE-27)\(^\text{[26]}\), Charlson Comorbidity index\(^\text{[27]}\) and G8 geriatric screening tool\(^\text{[28]}\). These tools allow a risk stratification in order to evaluate the impact of age in the surgical management of elderly patients. Old patients require a multidisciplinary evaluation (geriatric assessment) in order to identify those individuals who are at high-risk of complication\(^\text{[29]}\). Another reason of difference in postoperative outcome may be the hospital load for pancreatic resections. In fact, the importance of hospital volume for improving outcome after pancreatic surgery has already been demonstrated\(^\text{[30]}\) and better prognosis after centralization of pancreatic cancer resection is reported\(^\text{[31]}\). Riall et al\(^\text{[32]}\) reported a mortality rate following surgery in octogenarians nearly doubled at low-volume facilities compared to high-volume centres. Management of elderly patients requires a multidisciplinary evaluation prior to surgery in order to have a precise risk stratification and a selection of patients undergoing surgery. Moreover, postoperative care requires a specialized staff (surgeons, anaesthesiologists, interventional radiologists, endoscopists, etc.) and specialized facilities commonly available in high-volume centres. Finally, only few reports\(^\text{[3,16,18,19]}\) in the literature reported the patients’ rate undergoing adjuvant treatment after surgery and their specific outcome. It is increasingly recognized that elderly patients are underrepresented in cancer trials and that elderly patients are less likely to receive adjuvant chemotherapy\(^\text{[32,33]}\). Reluctance to administer postoperative treatment is often based on the presence of comorbidities in elderly patients and by the perception that there is an increased risk of non-cancer-related cause of death, limiting the overall benefit of adjuvant treatment. Nagrial et al\(^\text{[33]}\) showed that this is not the case, being cancer the predominant cause of death in older patients. Given the role of adjuvant therapies in prolonging overall survival and delaying time to recurrence in resectable pancreatic cancer\(^\text{[34,35]}\), the advancing age alone should not preclude the use of adjuvant treatment. Although these limitations, most Authors reported that overall survival after resection for pancreatic cancer in octogenarians is not statistically different from younger patients\(^\text{[10,21,36,37]}\).

CONCLUSION

Although several authors say that major pancreatic surgery is safe and feasible in very old patients, the risk of postoperative complications and troubled outcome objectively exist, and may explain the reluctance to perform such complex operation in older patients\(^\text{[38]}\). To overcome any prejudice, a careful patient selection is fundamental to avoid or reduce postoperative mortality and morbidity. It seems reasonable to consider elderly patients with 2 or 3 ASA score, with a low rate of comorbidity and good performance status, as good candidate for surgical resection. Even if caution is recommended when treating elderly patients, the morbidity and mortality rates of octogenarians appear within the acceptable range for pancreatic surgery when performed at experienced centres. Geriatric assessment and centralization of pancreatic cancer are key to treatment decisions for patients 80 years and older. Survival after pancreatic resection appears similar in old and young patients, but we are lacking sufficient information about the quality of life of elderly pancreatectomized patients. Additionally, prospective studies are needed in order to determine the quality of life and long-term outcome in this subset of patients, because these features have to be considered in planning of the surgical treatment of octogenarians.

REFERENCES

1. Pratt WB, Gangavati A, Agarwal K, Schreiber R, Lipsitz LA, Callery MP, Vollmer CM. Establishing standards of quality for elderly patients undergoing pancreatic resection. *Arch Surg* 2009; 144: 950-956 [PMID: 19841364 DOI: 10.1001/archsur.2009.107]
2. Tani M, Kawai M, Hirono S, Ina S, Miyazawa M, Nishioka R, Shimizu A, Uchiyama K, Yamaue H. A pancreaticoduodenectomy is acceptable for periampullary tumors in the elderly, even in patients over 80 years of age. *J Hepatobiliary Pancreat Surg* 2009; 16: 675-680 [PMID: 19387530 DOI: 10.1007/s00534-009-0106-6]
3. Hardacre JM, Simo K, McGee MF, Stellato TA, Schulak JA. Pancreatic resection in octogenarians. *J Surg Res* 2009; 156: 129-132 [PMID: 19592032 DOI: 10.1016/j.jss.2009.03.047]
4. Winter JM, Cameron JL, Campbell KA, Arnold MA, Chang DC, Coleman J, Hodgkin MB, Sauter PK, Hruban RH, Riall TS, Schulick RD, Choti MA, Lillennoe KD, Yeo CJ. 1423 pancreaticoduodenectomies for pancreatic cancer: A single-institution experience. *J Gastrointest Surg* 2006; 10: 1199-1210; discussion 1210-1211 [PMID: 17114007 DOI: 10.1016/j.gassur.2006.08.018]
5. Fernández-del Castillo C, Morales-Oyarvide V, McGrath D, Wargo JA, Ferrone CR, Thayer SP, Lillennoe KD, Warshaw AL. Evolution of the Whipple procedure at the Massachusetts General Hospital. *Surgery* 2012; 152: S56-S63 [PMID: 22779061 DOI: 10.1016/j.surg.2012.05.022]
6. Chen JW, Shyr YM, Su CH, Wu CW, Lui WY. Is pancreaticoduodenectomy justified for septuagenarians and octogenarians? *Hepatogastroenterology* 2003; 50: 1661-1664 [PMID: 14571811]
7. Makary MA, Winter JM, Cameron JL, Campbell KA, Chang D, Cunningham SC, Riall TS, Yeo CJ. Pancreaticoduodenectomy in the very elderly. *J Gastrointest Surg* 2006; 10: 347-356 [PMID: 16504879 DOI: 10.1016/j.gassur.2005.12.014]
8. Finlayson E, Fan Z, Birkmeyer JD. Outcomes in octogenarians undergoing high-risk cancer operation: a national study. *J Am Coll Surg* 2007; 205: 729-734 [PMID: 18035254 DOI: 10.1016/j.jamcollsurg.2007.06.307]
9. Riall TS, Reddy DM, Nealon WH, Goodwin JS. The effect of age on short-term outcomes after pancreatic resection: a population-based study. *Ann Surg* 2008; 248: 459-467 [PMID: 18791366 DOI: }
Pancreatic resection in octogenarians.

Speri C et al. Pancreas in octogenarians.
He W, Zhao H, Chan W, Lopez D, Shroff RT, Giordano SH. Underuse of surgical resection among elderly patients with early-stage pancreatic cancer. *Surgery* 2015; 158: 1226-1234 [PMID: 26138347 DOI: 10.1016/j.surg.2015.04.031]

P- Reviewer: Fu D, Peng B, Ramia JM  
S- Editor: Qiu S  
L- Editor: A  
E- Editor: Wu HL
