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 DOI: 10.4251/wjgo.v9.i1.30

World J Gastrointest Oncol 2017 January 15; 9(1): 30-36
 ISSN 1948-5204 (online)
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MINIREVIEWS

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

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

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Manuscript source: Invited manuscript

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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

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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 octogenarians 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

Table 1 Type of periampullary neoplasms

Ref.	n	Age (mean)	Benign disease	Malignant disease	Pancreatic adenocarcinoma
Chen <i>et al</i> ^[6]	16	82.3	1	15	5
Makary <i>et al</i> ^[7]	207	82	30	177	96
Finlayson <i>et al</i> ^[8]	2915	NR	0	2915	NR
Riall <i>et al</i> ^[9]	214	NR	50	164	NR
Hardacre <i>et al</i> ^[3]	32	82	2	30	25
Tani <i>et al</i> ^[2]	25	82.3	3	22	10
Lee <i>et al</i> ^[10]	74	82.6	16	58	45
Khan <i>et al</i> ^[11]	53	NR	0	53	53
Stauffer <i>et al</i> ^[12]	32	82.1	11	21	18
Hatzaras <i>et al</i> ^[13]	27	83.4	0	27	24
Melis <i>et al</i> ^[14]	25	83	0	25	25
Oguro <i>et al</i> ^[15]	22	81.5	0	22	8
Turrini <i>et al</i> ^[16]	64	83	0	64	64
Belyaev <i>et al</i> ^[17]	38	82	NR	NR	NR
Beltrame <i>et al</i> ^[18]	23	82.6	1	22	20
Kinoshita <i>et al</i> ^[19]	26	82	0	26	26
Total	3793	82.2	114	3641	419

NR: Not reported.

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*^[8] 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

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

Ref.	Type of surgical procedure			Vascular resections % (n)	ASA SCORE	
	PD	DP	TP		1-2	3-4
Chen <i>et al</i> ^[6]	16	0	0	NR	NR	NR
Makary <i>et al</i> ^[7]	197	0	10	2.4 (5)	NR	NR
Finlayson <i>et al</i> ^[8]	NR	NR	NR	NR	NR	NR
Riall <i>et al</i> ^[9]	155	48	NR	NR	NR	NR
Hardacre <i>et al</i> ^[3]	26	5	1	12.5 (4)	8	24
Tani <i>et al</i> ^[2]	25	0	0	4 (1)	NR	NR
Lee <i>et al</i> ^[10]	74	0	0	14.9 (11)	NR	NR
Khan <i>et al</i> ^[11]	18	10	4	6.25 (2)	7	46
Stauffer <i>et al</i> ^[12]	20	5	0	NR	NR	NR
Hatzaras <i>et al</i> ^[13]	53	0	0	NR	NR	NR
Melis <i>et al</i> ^[14]	25	0	0	4 (1)	7	17
Oguro <i>et al</i> ^[15]	22	0	0	23 (5)	21	1
Turrini <i>et al</i> ^[16]	56	8	0	11 (7)	37	23
Belyaev <i>et al</i> ^[17]	27	3	8	NR	NR	NR
Beltrame <i>et al</i> ^[18]	21	2	0	8.7 (2)	5	18
Kinoshita <i>et al</i> ^[19]	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.

tumor (74.6% of malignant cases, $n = 419$), followed by periampullary 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 (20.3%, $n = 13$) and neuroendocrine tumors (9.4%, $n = 6$). A total of 3793 resections were performed, with data on 751 pancreatoduodenectomy, 90 distal pancreatectomy and 24 total pancreatectomy (TP). A vascular resection was reported in 48 cases (Table 2).

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)

Table 3 Perioperative outcomes after pancreatic resection

Ref.	Mortality % (n)	Morbidity % (n)	Mean length of stay (d)
Chen <i>et al</i> ^[6]	13.0 (2)	51 (8)	25.0
Makary <i>et al</i> ^[7]	4.0 (8)	53 (109)	11.0
Finlayson <i>et al</i> ^[8]	15.5 (452)	NR	20.4
Riall <i>et al</i> ^[9]	11.4 (24)	NR	15.0
Hardacre <i>et al</i> ^[3]	0	66 (21)	11.0
Tani <i>et al</i> ^[2]	NR	44 (11)	25.0
Lee <i>et al</i> ^[10]	5.4 (4)	47 (35)	10.5
Khan <i>et al</i> ^[11]	2.0 (1)	51 (27)	13.5
Stauffer <i>et al</i> ^[12]	0	50 (16)	13.3
Hatzaras <i>et al</i> ^[13]	3.7 (1)	52 (14)	12.0
Melis <i>et al</i> ^[14]	4.0 (1)	68 (17)	20.0
Oguro <i>et al</i> ^[15]	4.5 (1)	27 (6)	31.5
Turrini <i>et al</i> ^[16]	4.7 (3)	56 (36)	24.9
Belyaev <i>et al</i> ^[17]	11.4 (4)	NR	15.0
Beltrame <i>et al</i> ^[18]	0 (0)	43 (10)	13.5
Kinoshita <i>et al</i> ^[19]	0 (0)	8 (2) ¹	25.8
Total	13.2 (501)	34.9 (306) ²	18.0

NR: Not reported. ¹Clavien-Dindo classification \geq III; ²Riall *et al*^[9] excluded, because only severe complications were reported.

or required other inpatient acute care hospitals.

ADJUVANT THERAPY

Only few studies reported data on adjuvant therapy after pancreatic resections for cancer (Table 5). Kinoshita *et al*^[19] 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*^[18] reported 30% of resected patients who received adjuvant treatment, while in the study by Turrini *et al*^[16] the patients' rate receiving postsurgical treatment was as low as 23.4%. Finally, Hardacre *et al*^[3] 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*^[16] reported a 1-year survival rate of 75.7% while 5-year survival rate was 0%.

Table 4 Postoperative complications and reoperation rates

Ref.	Pancreatic Fistula	Delayed gastric emptying	Postpan-createctomy haemorrhage	Reoperation rate % (n)
Chen <i>et al</i> ^[6]	2	3	3	NR
Makary <i>et al</i> ^[7]	21	32	0	5.6 (11)
Finlayson <i>et al</i> ^[8]	NR	NR	NR	NR
Riall <i>et al</i> ^[9]	NR	NR	NR	NR
Hardacre <i>et al</i> ^[3]	3	4	5	22.0 (7)
Tani <i>et al</i> ^[2]	1	6	0	NR
Lee <i>et al</i> ^[10]	3	NR	NR	5.4 (4)
Khan <i>et al</i> ^[11]	6	9	5	1.9 (1)
Stauffer <i>et al</i> ^[12]	NR	NR	NR	6.2 (2)
Hatzaras <i>et al</i> ^[13]	3	0	NR	4.0 (1)
Melis <i>et al</i> ^[14]	NR	NR	NR	NR
Oguro <i>et al</i> ^[15]	11	5	4	4.5 (1)
Turrini <i>et al</i> ^[16]	10	NR	10	10.9 (7)
Belyaev <i>et al</i> ^[17]	NR	NR	NR	13.1 (5)
Beltrame <i>et al</i> ^[18]	4	0	1	13.0 (3)
Kinoshita <i>et al</i> ^[19]	5	3	1	NR
Total	69	62	29	7.5 (43)

NR: Not reported.

PROGNOSTIC FACTORS

Six authors^[9,10,13,15,16,19] 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*^[15] 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*^[10] 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*^[9] 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

Table 5 Long-term results

Ref.	Adjuvant therapy % (NR)	Median overall survival (mo)	1-yr survival rate (%)	5-yr survival rate (%)
Chen <i>et al</i> ^[6]	NR	17.6	NR	NR
Makary <i>et al</i> ^[7]	NR	19	59.1	24.4
Finlayson <i>et al</i> ^[8]	NR	NR	NR	11.3
Riall <i>et al</i> ^[9]	NR	NR	NR	NR
Hardacre <i>et al</i> ^[3]	31.2 (10)	14.4	57.0	24.0
Tani <i>et al</i> ^[2]	NR	NR	NR	NR
Lee <i>et al</i> ^[10]	NR	11.6	NR	NR
Khan <i>et al</i> ^[11]	22	13.5	NR	NR
Stauffer <i>et al</i> ^[12]	NR	NR	67.0	42.0
Hatzaras <i>et al</i> ^[13]	NR	33.3	NR	33.1
Melis <i>et al</i> ^[14]	NR	17.3	68.2	4.5
Oguro <i>et al</i> ^[15]	0 (0)	13.0	NR	46.0
Turrini <i>et al</i> ^[16]	23.4 (15)	30.0	75.7	0
Belyaev <i>et al</i> ^[17]	NR	NR	NR	NR
Beltrame <i>et al</i> ^[18]	30.0 (7)	19.0	NR	NR
Kinoshita <i>et al</i> ^[19]	50.0 (13)	12.4	50.0	NR

NR: Not reported.

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^[8,9] showed high mortality rates after pancreatic surgery in octogenarians with a high rate of discharge to health facilities. Sukhramwala *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^[25]. Several scoring systems are available in the clinical practice to assess the surgical risk of old patients: Adult Comorbidity Evaluation-27 (ACE-27)^[26], Charlson Comorbidity index^[27] and G8 geriatric screening tool^[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^[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^[30] and better prognosis after centralization of pancreatic cancer resection is reported^[31]. Riall *et al*^[9] 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^[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^[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*^[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^[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^[18,21,36,37].

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^[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.

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Sperti C *et al.* Pancreatectomy in octogenarians

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P- Reviewer: Fu D, Peng B, Ramia JM **S- Editor:** Qiu S
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