Surgery Open Science 7 (2022) 58–61

Contents lists available at ScienceDirect

Surgery Open Science

journal homepage: https://www.journals.elsevier.com/surgery-open-science

Octogenarians undergoing pancreaticoduodenectomy: Assessing outcomes, disposition, and timing of chemotherapy

Sean E. Kisch, BS [a], Elizabeth R. Nussbaum, MS [a], M. Alyssa Varsanik, MD [a], Alexander O'Hara, BS [a], Jacob J. Pozin, BS [a], Michael J. Littau, BA [a], Xuanji Wang, MD [b], Erin Carollo, BA [a], Lawrence M. Knab, MD [b,*], Gerard Abood, MD, MS [b]

[a] Loyola University Chicago Stritch School of Medicine, 2160 S 1st Ave, Maywood, IL 60153, USA
[b] Department of Surgery, Division of Surgical Oncology, Loyola University Medical Center, 2160 S 1st Ave, Maywood, IL 60153, USA

ARTICLE INFO

Article history:
Received 7 October 2021
Received in revised form 17 November 2021
Accepted 30 November 2021
Available online 04 December 2021

ABSTRACT

Background: Inclusion of pancreaticoduodenectomy has demonstrated higher rates of curative treatment in pancreatic cancer, yet prior research has suggested increased postoperative complications in octogenarians (patients older than 80 years). This study aimed to understand the impact of age on patients undergoing a pancreaticoduodenectomy, focusing on postoperative outcomes and return to intended oncologic treatment.
Materials and Methods: We conducted a single-institution retrospective cohort study for patients undergoing pancreaticoduodenectomy from 2007 to 2018. Collected data included demographics, preoperative comorbidities, and postoperative data (length of stay, 30-day mortality, 1-year mortality, infection, discharge location). Data were separated into 2 cohorts: octogenarians (≥80 years) and nonoctogenarians (<80). χ^2 and independent-sample *t* tests were used for analysis.
Results: A total of 649 patients underwent pancreaticoduodenectomy from 2007 to 2018; 63 (9.7%) were octogenarians. No differences were found in infectious complications (P = .607), 30-day mortality (P = .363), or 1-year mortality (P = .895). Octogenarians had a longer length of stay (P = .003) and were more likely to be discharged to skilled nursing facilities (P < .001). There was no significant difference in neoadjuvant chemotherapy administration, although octogenarians were less likely to receive adjuvant chemotherapy (P = .048) and declined adjuvant therapy at a higher rate (P = .003).
Conclusion: Performing a pancreaticoduodenectomy in octogenarians can be safe and effective in a properly selected cohort. Although postoperative morbidity and mortality are similar to younger patients, elderly patients are more likely to be discharged to nursing facilities and less likely to receive adjuvant chemotherapy. This study suggests that age alone should not be a discriminating factor when discussing surgical therapy for pancreatic cancer treatment in octogenarians.

INTRODUCTION

Pancreatic adenocarcinoma is the fourth leading cause of cancer death in the United States, with 45,050 deaths estimated in 2020 and a 5-year relative survival rate of 10% [1]. Inclusion of pancreaticoduodenectomy (PD) is the standard of care for pancreatic head and periampullary malignancies when feasible and confers the highest chance of curative treatment [2]. Advanced age is a well-known risk factor for pancreatic cancer [3,4]. Given that the elderly population in the United States is expanding, determining if this population can safely undergo pancreatic surgery is of particular clinical relevance, and the ability to deliver appropriate and safe perioperative care is critical [5,6].

Generally speaking, patients older than 80 years (octogenarians) have more comorbidities and present higher operative risks when compared to younger patients [2]. It has been reported that octogenarians may also have more postoperative complications, longer length of stay (LOS), higher morbidity and mortality, and increased likelihood of discharge to skilled nursing facilities (SNF) or rehabilitation centers [2,3,7–9]. In contrast, several other studies have shown similar postoperative outcomes when comparing patients by age, resulting in some

* Corresponding author at: 2160 S 1st Ave, Maywood, IL 60153. Tel.: +1 708-327-2667 (Business phone), 814-880-8808 (Home phone); fax: +1 708-327-2835.
E-mail addresses: skisch@luc.edu (S.E. Kisch), enussbaum1@luc.edu (E.R. Nussbaum), alyssavarsanik@gmail.com (M.A. Varsanik), aohara2@luc.edu (A. O'Hara), jpozin@luc.edu (J.J. Pozin), mlittau@luc.edu (M.J. Littau), xuanji.wang@lumc.edu (X. Wang), ecarollo@luc.edu (E. Carollo), Lawrence.Knab@lumc.edu (L.M. Knab), gabood@lumc.edu (G. Abood).

https://doi.org/10.1016/j.sopen.2021.11.008

ambiguity [6,10]. Studies have also shown that elderly patients with pancreatic adenocarcinoma are less likely to receive adjuvant chemotherapy, which negatively impacts overall survival [11].

The aim of this study was to evaluate if age alone impacts postoperative outcomes in octogenarians who have undergone a PD at Loyola University Medical Center (LUMC) from 2007 to 2018. In addition, we aimed to determine the effect of age on administration of systemic chemotherapy in those patients with pancreatic adenocarcinoma. The goal of this study was to understand what factors should be considered when evaluating octogenarian patients for pancreatic surgery.

MATERIALS AND METHODS

We conducted an Institutional Review Board–approved retrospective review of patients who underwent a PD at LUMC from 2007 to 2018. Data were collected and managed using Research Electronic Data Capture (REDCap) tools hosted at LUMC [12,13]. REDCap is a secure, Web-based software platform designed to support data capture for research studies.

PD was generally performed in a standard fashion by 4 different surgeons at the medical center. An antrectomy was performed in most cases. A standard lymphadenectomy was performed in all cases, and if the portal vein or superior mesenteric vein was involved, a vein resection was performed with appropriate reconstruction using either primary repair or autologous graft. Generally, anastomotic stents were not used. Closed-suction drains were routinely placed in close proximity to the anastomoses.

Collected data included patient demographics (age, sex), preoperative comorbidities (hypertension, hyperlipidemia, history of smoking, and diabetes mellitus), and body mass index. Postoperative data included LOS, 30-day mortality, 1-year mortality, postoperative infection, and discharge location (home, home health, or SNF). Home and home health discharge locations were also analyzed in the grouped category "total home."

Demographic information and preoperative and postoperative variables were compared between octogenarians and nonoctogenarians. Differences were evaluated using χ^2 for categorical variables and independent-sample t tests and Wilcoxon rank-sum tests for continuous variables, respectively.

Primary end points were LOS, 30-day mortality, 1-year mortality, infections, and discharge location (home, home health, or SNF).

RESULTS

A total of 649 patients underwent PD at Loyola University Medical Center from 2007 to 2018. There were 63 patients (9.7%) in the octogenarian group (≥80 years of age) and 586 patients (90.3%) in the nonoctogenarian group (<80 years old). The demographic and preoperative data of the two groups are compared in Table 1. Octogenarians were more likely to have comorbid atrial fibrillation (14.3% vs 6.0%, $P = .013$), coronary artery disease (22.2% vs 10.8%, $P = .008$), hyperlipidemia (41.3% vs 21.6%, $P = .011$), and hypothyroidism (15.3% vs 6.0%, $P = .003$) compared to nonoctogenarians.

The postoperative outcomes in the octogenarian group compared to the nonoctogenarian group are shown in Table 2. There was a significant difference between nonoctogenarians and octogenarians in median LOS (8 vs 9 days, $P = .003$). There were no significant differences in 30-day mortality (2.7% vs 4.7%, $P = .363$) and 1-year mortality (21.5% vs 22.2%, $P = .895$). Upon discharge from the hospital, nonoctogenarian patients were more likely to be discharged home with or without home health care (84.1% vs 55.6%, $P < .001$) and less likely to be discharged to skilled nursing facilities (9.4% vs 31.7%, $P < .001$) compared to octogenarians.

Postoperatively, there were no differences between rates of overall infection (24.1% vs 27.0%, $P = .607$) or superficial versus deep infections ($P = .222$).

When pathologies were compared between groups, the octogenarian group was found to have significantly higher rates of ampullary adenocarcinoma (15.9% vs 8.0%, $P = .036$) and significantly lower rates of chronic pancreatitis (0.0% vs 6.0%, $P = .046$). Other pathologies were similar.

Systemic chemotherapy has been shown to prolong survival in patients with pancreatic cancer. Table 3 shows that there was a trend toward fewer octogenarians with pancreatic cancer receiving chemotherapy in either the neoadjuvant or adjuvant setting compared to their younger counterparts, although this did not reach statistical significance (50% vs 68%, $P = .08$). When the timing of chemotherapy was analyzed between groups, several differences were observed. There was no difference between octogenarians and nonoctogenarians in receipt of neoadjuvant chemotherapy (15% vs 18%, $P = .718$), although there was a significant difference between octogenarians and nonoctogenarians in receipt of adjuvant chemotherapy (39% vs 59%, $P = .048$). A significantly higher percentage of octogenarians refused adjuvant chemotherapy compared to younger patients (15% vs 2%, $P < .01$). None of the octogenarians received fluorouracil (5-FU)-based chemotherapy (FOLFIRINOX or FOLFOX) pre- or postoperatively compared to 17% of younger patients.

DISCUSSION

Despite significant improvements in the perioperative care for PD patients, PD remains a morbid operation even for young, healthy patients. However, the operative risk must still be considered because it confers the highest rates of long-term survival in patients with periampullary and pancreatic head malignancies. Given the aging population and the associated increased incidence of malignancy with age, pancreatic adenocarcinoma and periampullary malignancies are increasingly identified in the older patient population, including octogenarians. There have been multiple population-based studies using representative national databases, as well as single-institution series examining outcomes of octogenarians undergoing PD with varying results. As one of the largest, single-institution studies, we aimed to evaluate single-institution data with a relatively high number of octogenarians compared to past studies to evaluate the safety of PD in this at-risk population. We found that while octogenarians had increased comorbidities and LOS compared to younger patients, they had similar infectious complications and mortality rates. Octogenarians were discharged to rehabilitation institutions more frequently and were less likely to receive adjuvant systemic chemotherapy.

There is conflicting evidence regarding early and long-term outcomes of octogenarians undergoing PD. Sperti et al reviewed multiple studies that included all types of pancreatic resections and found overall morbidity and mortality rates of 35% and 13%, respectively. The overall LOS was 18 days [2]. Melis et al reviewed 6 studies that included PD in octogenarians. They found mixed results, with most studies demonstrating similar morbidity and mortality rates between younger and older patients, although the largest study did demonstrate a difference between the age groups. In addition to the variability between reported differences in age groups, there is a wide range in overall morbidity and mortality rates. The mortality rates of octogenarians in examined series range from 0% to 13% [9]. In addition, a single-institution multivariate analysis by Huang et al concluded that age alone was not proven to be a prognostic factor on morbidity or mortality [14]. Our octogenarian data, which were similar to those of Liang et al, demonstrated an infectious complication rate of 27%, median LOS of 9.0 days, and 30-day mortality rate of 4.7%, with no significant differences between octogenarians and nonoctogenarians in infectious complications or mortality [15]. There were significant differences between the 2 age groups in comorbidities, LOS, and discharge disposition, with a greater percentage of octogenarians being discharged to rehabilitation facilities and a greater percentage of nonoctogenarians being discharged to home. Data demonstrating when octogenarians were discharged home from rehabilitation facilities were unfortunately not available for analysis. When examining LOS, 30-day mortality, and

complications in octogenarians, our results align with the low end of the published ranges.

In contrast to the similarities in postoperative outcomes between octogenarians and younger patients, there were differences between the 2 groups in the likelihood of receiving systemic chemotherapy [16–19]. Systemic chemotherapy has been shown to improve survival in pancreatic cancer, and this study showed that significantly fewer octogenarians received adjuvant chemotherapy compared to younger patients. In addition, none of the patients older than 80 years received 5-FU–based regimens (FOLFOX or FOLFIRINOX), which tend to be more difficult chemotherapy regimens to tolerate compared to gemcitabine-based therapies. A SEER study of Medicare patients (older than 65 years) undergoing upfront PD for pancreatic adenocarcinoma demonstrated that only 35% of patients went on to initiate any adjuvant chemotherapy and only 7% completed it [11]. Of the octogenarians in the study, 27% received chemotherapy of any kind/duration. Similarly, Hue et al conducted a National Cancer Database study on patients with pancreatic adenocarcinoma and found that 42.2% of octogenarians received adjuvant therapy. The median survival of octogenarians with PD alone was 12 months, but in patients with PD and chemotherapy, the survival was increased to more than 20 months [20]. This is important given the recommendation that all patients with pancreatic cancer should receive systemic chemotherapy if able because it has been shown to prolong survival.

Our data demonstrated that 39% of octogenarians received adjuvant chemotherapy, which suggests that octogenarians were unable to recover at the same rate as younger patients after PD. An additional factor is the rate of patients declining recommended chemotherapy. We found a significantly higher rate of octogenarian patients refusing adjuvant chemotherapy compared to younger patients, 15% vs 2%, respectively. This raises an important question of chemotherapy sequence in pancreatic cancer, specifically in the elderly population. If an elderly patient is willing and able to tolerate chemotherapy, perhaps administering it in the preoperative setting would be advantageous knowing that they are less likely to receive it postoperatively compared to younger patients. The use of neoadjuvant chemotherapy in resectable pancreatic cancer is currently not standard of care, although it is currently being evaluated in randomized trials. The results of these trials will further elucidate the topic and may be extrapolated to octogenarians.

Given that several large series of octogenarians undergoing PD, including this study, have demonstrated similar morbidity and mortality compared to younger patients, this suggests that age alone does not dictate postoperative outcomes and survival. Multiple studies have recently investigated the concept of *frailty*, defined as a "multidimensional syndrome of loss of reserves (energy, physical ability, cognition, health) that gives rise to vulnerability" [21]. Most studies investigating frailty and surgical outcomes after pancreatic surgery have used a "modified frailty index" or mFI, which can be calculated using retrospective databases [22–24]. This index is calculated using factors including history of diabetes, myocardial infarction, hypertension, functional status, and congestive heart failure, among others. Most of these studies have used large national databases. Studies have found that the mFI was more predictive of postoperative morbidity and mortality than age alone [22,23]. In future studies, we aim to investigate frailty in octogenarians and its relationship to postoperative outcomes and receipt of chemotherapy. This could have practical implications including the development of additional frailty indices to enable a more sophisticated risk stratification for elderly patients.

There are several limitations in the study. As with any retrospective study, it is subject to bias. Despite being one of the largest single-institution cohorts of octogenarians, the overall cohort size remains relatively low, and the actual true denominator of potential patients that were not offered surgery limit further insights. Due to the retrospective nature, variables such as detailed functional status and activities of daily living, home support, and attitudes about health were unable to be analyzed. In addition, this study focused on the immediate postoperative period and did not consider the extended postoperative period or quality of life scores which can certainly have significant impacts on outcomes, particularly in the elderly population. Finally, long-term follow-up to accurately determine survival differences was unfortunately unable to be obtained, which would have been an asset to the study.

In conclusion, PD can be safely performed in octogenarians that are properly selected. Postoperative morbidity and mortality are similar to those of younger patients, although elderly patients are more likely to be discharged to nursing facilities and less likely to receive adjuvant chemotherapy. Age alone should not be a discriminating factor in surgical planning. Further research is needed to determine additional factors to risk-stratify patients for surgery and potential interventions to decrease perioperative risk.

Table 1
Demographic and comorbid conditions in octogenarians versus nonoctogenarians who underwent PD

Variable	*Nonoctogenarian* (n = 586)	*Octogenarian* (n = 63)	P *value*
Age, mean	83.2	61.0	
Male sex, %	51.4	50.8	.931
Body mass index, mean (SD)	26.8 (5.6)	25.5 (2.8)	.084
Comorbidities, %			
Atrial fibrillation	6.0	14.3	.013*
Coronary artery disease	10.8	22.2	.008*
Congestive heart failure	3.4	6.3	.241
Colon cancer history	2.9	6.4	.142
COPD	3.9	4.8	.748
Cerebrovascular accident	3.8	7.9	.114
Diabetes mellitus	29.2	34.9	.343
Deep venous thrombosis	3.8	4.8	.693
Family history of cancer	16.0	22.2	.211
Gastroesophageal reflux	10.9	11.1	.963
Hyperlipidemia	26.1	41.3	.011*
Hypertension	54.4	66.7	.063
Hypothyroidism	6.0	15.3	.003*
History of pulmonary embolism	2.6	1.6	.636
Smoker/previous smoker	44.5	38.1	.327

COPD, chronic obstructive pulmonary disease.
* Statistically significant.

Table 2
Postoperative outcomes in octogenarians vs nonoctogenarians who underwent PD

Variable	*Nonoctogenarian* (n = 586)	*Octogenarian* (n = 63)	P *value*
LOS, median (IQR)	8 (4)	9 (6)	.003*
30-d mortality, %	2.7	4.7	.363
1-y mortality, %	21.5	22.2	.895
Discharge location, %			
Home and home health	84.1	55.6	<.001*
Skilled nursing facility	9.4	31.7	<.001*
Overall infection, %	24.1	27.0	.607
Infectious organisms, %			
S. aureus	2.0	6.4	.036*
Infection location, %			.222
Intra-abdominal abscess	12.6	7.9	
Superficial skin	1.0	1.6	
Other	7.8	15.9	
Pathology, %			
Ampullary adenocarcinoma	8.0	15.9	.036*
Cholangiocarcinoma	3.1	3.2	.964
Chronic pancreatitis	6.0	0.0	.046*
Pancreatic adenocarcinoma	32.1	41.3	.140
Benign mass	4.9	3.2	.457
Other	17.9	11.1	.174

IQR, interquartile range.
* Statistically significant.

Table 3
Systemic therapy in octogenarians versus nonoctogenarians pancreatic adenocarcinoma patients who underwent PD

Variable	Nonoctogenarian (n = 186)	Octogenarian (n = 26)	P value
Systemic therapy, %	68.3	50.0	.075
Neoadjuvant therapy, %			
None	48.4	84.6	<.001*
Declined	0	0	
Radiation	4.4	11.5	.126
Gemcitabine	3.8	3.8	.996
FOLFIRINOX	10.4	0	.085
Other	5.5	15.4	.144
Adjuvant therapy, %			
First line			
None	41.0	61.5	.048*
Declined	1.6	15.4	<.001*
Radiation	11.5	15.4	.565
Gemcitabine	50.3	7.7	<.001*
FOLFIRINOX	1.6	0	.510
Other	9.3	7.7	.791
Second line			
None	71.6	96.1	.007*
Declined	0.5	3.8	.106
Radiation	15.9	0.0	.029*
Gemcitabine	5.5	0.0	.222
FOLFIRINOX	3.8	0.0	.310
Non-gemcitabine	7.6	0.0	.144

* Statistically significant.

Author Contribution

Lawrence M. Knab: Conceptualization, Methodology, Validation, Writing – original draft, Writing – review & editing, Supervision. **Gerard Abood**: Conceptualization, Methodology, Writing – review & editing. **Sean Kisch**: Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Elizabeth Nussbaum**: Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **M Alyssa Varsanik**: Investigation, Data curation, Writing – review & editing. **Jacob J. Pozin**: Investigation, Data curation, Writing – review & editing. **Alexander O'Hara**: Investigation, Data curation, Writing – review & editing. **Michael Littau**: Investigation, Data curation, Writing – review & editing. **Xuanji Wang**: Writing – review & editing. **Erin Carollo**: Writing – review & editing.

Conflict of Interest

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

Funding Source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics Approval

This retrospective cohort study was Institutional Review Board approved. For this type of study, formal consent is not required.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA: a cancer journal for clinicians*. 2019;69(1):7–34.
[2] 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):30–6. https://doi.org/10.4251/wjgo.v9.i1.30.
[3] Patil S, Chamberlain, Ronald S., MD, MPA, FACS. Whipple procedure in octogenarians and nonagenarians: a United States population-based study analyzing morbidity and mortality following Whipple procedure in elderly patients (National Inpatient Sample Database 1998-2010). *Journal of the American College of Surgeons*. 2015;221(4):e108-e109. . https://www-clinicalkey-es.archer.luhs.org/playcontent/1-s2.0-S1072751515012284. doi: . https://doi.org/10.1016/j.jamcollsurg.2015.08.189.
[4] Ramai D, Ofosu A, Ofori E, et al. Demographics, tumor characteristics, treatment, and clinical outcomes of patients with ampullary cancer: A Surveillance, Epidemiology, and End Results (SEER) cohort study: presidential poster award. The American journal of gastroenterology. 2018;113(Supplement):S46–7. https://doi.org/10.14309/00000434-201810001-00085.
[5] Beltrame V, Gruppo M, Pastorelli D, Pedrazzoli S, Merigliano S, Sperti C. Outcome of pancreaticoduodenectomy in octogenarians: single institution's experience and review of the literature. *Journal of visceral surgery*. 2015;152(5):279–84.
[6] Lee M, DiNorcia J, Reavey P, et al. Pancreaticoduodenectomy can be performed safely in patients aged 80 years and older. *J Gastrointest Surg*. 2010;14(11):1838–46.
[7] Kim SY, Weinberg L, Christophi C, Nikfarjam M. The outcomes of the pancreaticoduodenectomy in patients aged 80 or older. A systematic review and meta-analysis. *HPB (Oxford, England)*. 2017;19(6):475–82.
[8] Haigh PI, Bilimoria KY, DiFronzo LA. Early postoperative outcomes after pancreaticoduodenectomy in the elderly. *Archives of surgery (Chicago. 1960)*. 2011;146(6):715-723. http://dx.doi.org.archer.luhs.org/10.1001/archsurg.2011.115. doi: . https://doi.org/10.1001/archsurg.2011.115.
[9] Melis M, Marcon F, Masi A, et al. The safety of a pancreaticoduodenectomy in patients older than 80 years: risk vs. benefits. *HPB (Oxford, England)*. 2012;14(9):583–8.
[10] Hatzaras, Ioannis, MD, MPH, Schmidt, Carl, MD, FACS, Klemanski, Dori, MS, MS, RN, CNP, et al. Pancreatic resection in the octogenarian: a safe option for pancreatic malignancy. *Journal of the American College of Surgeons*. 2011;212(3):373-377. . https://www-clinicalkey-es.archer.luhs.org/playcontent/1-s2.0-S1072751510011762. doi: . https://doi.org/10.1016/j.jamcollsurg.2010.10.015.
[11] Altman A, Wirth K, Marmor S, et al. Completion of adjuvant chemotherapy after upfront surgical resection for pancreatic cancer is uncommon yet associated with improved survival. *Ann Surg Oncol*. 2019;26(12):4108–16.
[12] Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of biomedical informatics*. 2009;42(2):377-381. http://dx.doi.org.archer.luhs.org/10.1016/j.jbi.2008.08.010. doi: . https://doi.org/10.1016/j.jbi.2008.08.010.
[13] Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. *Journal of biomedical informatics*. 2019;95:103208. http://dx.doi.org.archer.luhs.org/10.1016/j.jbi.2019.103208. doi: . https://doi.org/10.1016/j.jbi.2019.103208.
[14] Huang Y, Damodaran Prabha R, Chua TC, et al. Safety and efficacy of pancreaticoduodenectomy in octogenarians. *Frontiers in surgery*. 2021.;8:617286.
[15] Liang DH, Shirkey BA, Rosenberg WR, Martinez S. Clinical outcomes of pancreaticoduodenectomy in octogenarians: a surgeon's experience from 2007 to 2015. *Journal of gastrointestinal oncology*. 2016;7(4):540–6.
[16] Conroy T, Hammel P, Hebbar M, et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. *The New England journal of medicine*. 2018;379(25):2395-2406. http://dx.doi.org.archer.luhs.org/10.1056/NEJMoa1809775. doi: . https://doi.org/10.1056/NEJMoa1809775.
[17] VALLE JW, PALMER D, O'REILLY D, et al. Optimal duration and timing of adjuvant chemotherapy after definitive surgery for ductal adenocarcinoma of the pancreas: ongoing lessons from the ESPAC-3 study. *Journal of clinical oncology*. 2014;32(6):504-512. . http://jco.ascopubs.org.archer.luhs.org/content/32/6/504.abstract. doi: . https://doi.org/10.1200/JCO.2013.50.7657.
[18] Neoptolemos J, Dunn J, Stocken D, et al. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial. *The Lancet (British edition)*. 2001;358(9293):1576-1585. http://dx.doi.org.archer.luhs.org/10.1016/S0140-6736(01)06651-X. doi: . https://doi.org/10.1016/S0140-6736(01)06651-X.
[19] Yeo CJ, Abrams RA, Grochow LB, et al. Pancreaticoduodenectomy for pancreatic adenocarcinoma: postoperative adjuvant chemoradiation improves survival. A prospective, single-institution experience. *Annals of surgery*. 1997;225(5):621–36.
[20] Hue JJ, Bingmer K, Sugumar K, et al. Mortality and survival among octogenarians with localized pancreatic head cancer: a national cancer database analysis. Journal of Gastrointestinal Surgery. 2021;25(10):2582–92.
[21] Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *Canadian Medical Association journal*. 2005;173(5):489–95.
[22] Mogal H, Vermilion SA, Dodson R, et al. Modified frailty index predicts morbidity and mortality after pancreaticoduodenectomy. *Annals of surgical oncology*. 2017;24(6):1714–21.
[23] Augustin, Toms, MD, MPH, Burstein, Matthew D., MD, PhD, Schneider EB, PhD, et al. Frailty predicts risk of life-threatening complications and mortality after pancreatic resections. *Surgery*. 2016;160(4):987-996. https://www-clinicalkey-es.archer.luhs.org/playcontent/1-s2.0-S0039606016303427. doi: . https://doi.org/10.1016/j.surg.2016.07.010.
[24] Velanovich V, MD, Antoine H, MD, Swartz A, BS, Peters D, BS, Rubinfeld, Ilan, MD, MBA. Accumulating deficits model of frailty and postoperative mortality and morbidity: its application to a national database. *The Journal of surgical research*. 2013;183(1):104-110. . https://www-clinicalkey-es.archer.luhs.org/playcontent/1-s2.0-S002248041300019X. doi: . https://doi.org/10.1016/j.jss.2013.01.021.