

## Postoperative functional results of older patients after pancreas and liver surgery

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In clinical observational studies, overall survival and cancer-specific survival are usually considered the gold standard endpoints. Equally or even more important for older patients are patient-reported outcomes, defined as a set of patient-centered measures that evaluate physical, mental, and social health.

This is particularly important due to the complexity of surgical treatment and the higher risk of postoperative morbidity and mortality. The studies showed that after these operations, the quality of life (QoL) decreases and that is improving with time. After 6 months there was no difference in QoL between younger and older patients. Nevertheless, the results refer mostly to the group of patients who survived the follow-up period and had no recurrence. Therefore, age itself should not be a contraindication for pancreatic or liver surgery. QoL of patients not qualified for surgery decreased constantly.

**Key words:** older patients, frailty, functional results, quality of life

Chronological age alone is a poor predictor of cancer treatment outcomes and toxicities [1]. Therefore, chronological age alone should not be a contraindication for radical oncological treatment in older patients. As was mentioned in our previous publications, the population of the elderly is very heterogeneous in terms of co-morbidity, physical reserve, psycho-cognitive function, and social support [2]. Current routine pre-operative assessments cannot adequately identify older patients at risk. The frailty (surrogate of the biological age) evaluation should be the basis for the discussion on treatment planning. At present, it is one of the most reliable factors predicting outcomes in the geriatric population [3]. Therefore, the comprehensive geriatric assessment (CGA) was introduced to help to determine the primary status of the older patient, to diagnose frailty syndrome and to identify how to optimize the patient's condition before the start of treatment [4]. Subsequently, more and more organisations, including

the International Society of Geriatric Oncology, the National Comprehensive Network, the European Organisation for the Research and Treatment of Cancer, the American College of Surgeons' National Surgical Quality Improvement Program, and the American Geriatric Society have called for the routine use of the Geriatric Assessment. Before treatment begins, the following questions should be discussed:

- Is the currently planned treatment strategy correct? Are there alternative treatment options?
- What is the result of the comprehensive geriatric assessment?
- Can frailty syndrome be diagnosed in the patient?
- What is the risk of complications?
- What would be the patient's lifespan be without treatment?
- What are the goals, preferences and expectations of the patient?

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- What effect might the treatment have on these goals, particularly in terms of quality of life?
- Is it possible to improve the patient's state prior to the surgical procedure? [4].

Fit and prefrail patients, according to the comprehensive geriatric assessment, should be qualified for the same treatment as younger patients. Frail patients should be discussed in the oncogeriatric meeting [5]. The goal of the modifications is to reduce surgical stress. In older patients (aged 75 years or older), pathological outcomes and postoperative complications are predictors of survival, whereas pathological outcomes and chemotherapy are predictors of survival in younger population (aged 74 years or less). Thus, prevention of postoperative morbidity may contribute to an improved prognosis for older patients with cancer [6, 7]. However, we still need better designed studies on a larger group of patients using frailty evaluations – not only chronological age and comorbidity. Existing studies on this topic are limited, too small, lack important details with unsatisfactory statistical power. In clinical observational studies, overall survival or cancer-specific survival are usually considered the gold standard endpoint because it is simple and reliable to measure. Equally or even more important for older patients are patient-reported outcomes, defined as a set of patient-centered measures that evaluate physical, mental, and social health [8]. This is particularly important in the case of older patients with pancreas or liver cancer due to the complexity of surgical treatment and the higher risk of postoperative morbidity and mortality.

### Quality of life after pancreatectomy

Although there are many studies on postoperative morbidity and mortality in older patients, there are only few on how this population's quality of life is affected by pancreas resection. The most important are presented below.

The aim of the study conducted by Gestenhaber et al. was to observe long-term outcomes in a group of  $\geq 70$  patients who underwent a pancreatoduodenectomy (PD) (96%) or total pancreatectomy (TP) (4%). Patients with metastatic disease or incomplete data were excluded. 168 patients met the inclusion criteria. Patients were interviewed with EORTC QLQ C-30 questionnaire 3, 6, and 12 months after surgery. 96% of patients underwent PD, while the remaining 4% TP. In 76% of patients, cancer was depicted as invasive and the most common histology was ductal adenocarcinoma (49%). There were no intraoperative deaths. The 30- and 60-day postoperative mortality was 5.9% and 6.5%, while the most common cause of death was sepsis leading to multi-organ failure. The overall postoperative complication rate accounted for 39% and the most frequent were septic complications. The median follow-up lasted 32 months. QoL evaluation was performed in 70 individuals who were free of disease in the first year after surgery. Results of the QoL assessment were compared with the results of 20 matched (sex, age, comorbidities) patients

who underwent a laparoscopic cholecystectomy (LC). After 3 months PD group more frequently than LC group reported:

- fatigue (75% vs. 13%),
- loss of efficiency (70% vs. 20%),
- weight loss (51% vs. 0%),
- pain (35% vs. 10%)
- nausea and vomiting (68% vs. 10%),
- diarrhea (29% vs. 5%)

– all these differences were statistically significant. Comparing results 6 months postoperatively in the following domains:

- physical (73% vs. 78%),
- psychological (69% vs. 67%),
- global health (79% vs. 84%),
- global quality of life (73% vs. 79%)

– the differences were not statistically significant. In patients after PD results in functional, symptoms and global QoL domains indicated constant improvement in subsequent time intervals. Comparing PD subgroups results in all domains were being slightly higher in patients with benign or premalignant pathology than in the group with malignant pathology (physical 75% vs. 72%; psychological 70% vs. 69%; global health 83% vs. 78%; global quality of life 77% vs. 72%), but none of the differences were statistically significant. The study revealed that the quality of life in patients after a pancreatoduodenectomy is improving with time from the period of surgery. The limitation of the study is that the results only refer to patients who survived at least a year after the operation and who in this time did not have a recurrence of the disease [9].

The research of Kim et al. analyzed QoL in 154 patients  $\geq 65$ , operated due to periampullary neoplasms with regard to the stage of nutrition. Patients undergoing palliative resection, with metastases or recurrence, treated with neoadjuvant therapy, with a history of other abdominal operations, after cerebrovascular accident or with ASA score  $>III$  were excluded from the study. The primary outcome was postoperative morbidity related to nutritional status and the secondary outcomes were: Clavien-Dindo classification, rate of postoperative pancreatic fistula, cognitive score and quality of life. According to a preoperatively performed Mini Nutritional Assessment, patients were divided into three groups: well-nourished (13%), at risk of malnutrition (59.7%), and malnourished (27.3%); this resulted in statistically significant differences in body mass index (mean values respectively: 25.6 kg/m<sup>2</sup>, 23.4 kg/m<sup>2</sup> and 21.1 kg/m<sup>2</sup>). Types of operations included in the study were: pancreatoduodenectomy with pylorus resection (12.3%) and pylorus-preserving pancreatoduodenectomy (87.7%) performed due to malignant (79.2%) or benign (22.8%) neoplastic disease of the periampullary area. Patients were also dichotomized based on age, into 65–74 (n = 117) and 75–85 (n = 37) years old groups. Overall morbidity was 41.6%. It was more frequent in patients with a poorer stage of nutrition, with statistically significant difference between well-nourished and malnourished groups. There were no significant differences in morbidity between the

younger and older group. A cognitive evaluation was performed with the use of 4-point scale of cognitive function, based on the EORTC QLQ-C30 questionnaire. Cognitive function was evaluated preoperatively, the results were higher in patients with better nutrition, but not significantly. There were also no significant differences in cognitive score between age groups. Quality of life was assessed using global health status from EORTC QLQ-C30. Questionnaires were completed before the operation and 3, 6, and 12 months after surgery. Preoperatively, QoL was higher in patients with better nutrition and in the older group, but the differences were not significant. After 12 months, across all nutrition groups, an increase of QoL was observed, compared to preoperative results. The intergroup differences in QoL 12 months after surgery were not significant, but in the evaluation after 6 months it was significantly higher in the well-nourished and at-risk of malnutrition group than in the malnourished group [10].

Parray et al. investigated perioperative, long-term, and quality of life results of elderly patients undergoing pancreatoduodenectomy. 94 patients  $\geq 70$  years old operated on due to a malignant or non-malignant pathology between January 2007 and December 2019 were included. Distal pancreatic resections, median pancreatectomies, enucleations or palliative procedures were excluded. The average age was 73 years (70–85) with male prevalence (71%). The majority of the patients underwent surgery due to the adenocarcinoma of periampullary region (63%), the second most common was pancreatic ductal adenocarcinoma (22%). Based on the histopathological results, 46 patients had tumors described as T1 or T2 stage, while 39 had T3 or T4. The 30- and 90-day postoperative mortality was 3.1% and 5.3% respectively. Median follow-up lasted 25 months (0–108 months) and it was completed in 95% ( $n = 89$ ) of patients. 53% ( $n = 47$ ) were alive at the end of the median follow-up. The QLQ-PAN26 questionnaire was used to evaluate patients' long-term quality of life at the end of the follow-up period.

The questionnaire included answers: "not at all", "a little", "quite a bit" and "very much". For symptoms-based questions answers: "quite a bit" or "very much" were reported most commonly for weakness (94%) and backache (78%). 100% of patients reported "very much" in health care support, while 97% of patients chose the answer "not at all" for frequency of stools. 61% of patients answered "not at all" about weight loss. The most common answer for: abdominal pain (57%), food restriction (74%), and activity restriction (97%) was "a little". The postoperative complication appeared in 76.6% of patients  $\geq 70$  years old and in 63% of patients  $< 70$ , but the differences were not statistically significant. The differences in mortality between the study group and the control group were also not statistically significant. The conclusion of the authors was that age alone should not be a contraindication for PD [11].

In turn, Torphy et al. compared the QoL results in the open and laparoscopic approach groups of patients undergoing

pancreatic resection. Patients after pancreatoduodenectomy or distal pancreatectomy in either the open or laparoscopic approach were included. There were no age restrictions for the inclusion. The only exclusion criteria for undergoing a laparoscopic procedure was receiving neoadjuvant therapy or vessel involvement. 159 patients were included in the study, 60.4% in the open approach group and 39.6% in laparoscopic. 71.7% of all procedures were PD and DP accounted 28.3%. Patients were also dichotomized depending on age. There were 80 patients  $\leq 65$  and 79  $> 65$  years old. 52 patients  $> 65$  underwent laparotomy, while remaining 27 laparoscopy. The overall complication rate was 66.7%. All participants were asked to complete the FACT-Hep questionnaire preoperatively and 2 weeks, 1 month, 3 months, and 6 months after surgery. Response rates were the highest preoperatively (96.6%) and decreased to 69.2% at the last evaluation. The internal consistency of the questionnaire assessed with standardized Cronbach alpha at subsequent time intervals were respectively: 0.80, 0.76, 0.81, 0.81, and 0.86. Quality of life in comparison with age groups was emphasized with the estimated beta coefficient, with a 95% confidence interval. Evaluated in physical, emotional, social, functional, hepatobiliary domains, and FACT-Hep Total, there were no significant differences in either postoperative period, or in the long-term recovery between  $\leq 65$  and  $> 65$  patients. The conclusion for the whole group of included patients is that there is no significant difference in QoL after pancreatic surgery when compared to the open and laparoscopic surgical approach [12].

Watanabe et al. was to observe long-term outcomes of patients after a total pancreatectomy. The study group comprised 44 consecutive patients between 1990–2013. At the time of the study there were 25 survivors who were assessed cross-sectionally. Their body weight and blood chemical parameters were evaluated. They also completed an institutional questionnaire about sociodemographic data, ambulatory care, exocrine and endocrine function. To collect QoL results, 25 survivors completed the SF-36v2 questionnaire – a tool consisting of 36 questions on eight different domains:

- physical functioning (PF),
- role physical (RP),
- body pain (BP),
- general health perceptions (GH),
- vitality (VT),
- social functioning (SF),
- role emotional (RE),
- mental health (MH).

The separate domain results were calculated into three summarized component scores (SCS): physical component score (PCS), mental component score (MCS), and the role-social component score (RCS). The SF-36v2 standard values were determined based on general Japanese population results. To assess the influence of age, patients were divided into  $< 70$  ( $n = 21$ ) and  $\geq 70$  ( $n = 23$ ) groups. Median age was 71 (46–88),

with a prevalence of males (29 vs. 15). The indications for total pancreatectomy were pancreatic ductal adenocarcinoma (PDAC) (45%), intraductal papillary mucous neoplasm (IPMN) or mixed PDAC and IPMN etiology (10%). Overall morbidity rate was 32%, while postoperative mortality was 5%. There were no significant differences in histological diagnoses, length of stay or surgical procedure between the younger and older group, but the postoperative complications were more frequent in the older group (48% vs. 14%;  $p = 0.02$ ). Median follow-up lasted 21 months (2–222). Apart from 2 patients (5%) who died postoperatively, another 17 died during the follow-up period. The majority of deaths were caused by underlying pancreatic disease. The 3- and 5-year survival rate was 64% and 48% respectively. From 25 survivors, 5 patients had a recurrence during the follow-up. Their PF, RP, RE, and SCS scores were significantly lower than in the non-recurrence group ( $n = 16$ , without octogenarians). For accurate evaluation, patients who experienced recurrence were excluded from the comparison with national population. In two domains (PF and GH) and one SCS (PCS), the QoL results were significantly lower than the reference values. Patients who complained about diarrhea ( $n = 5$ ) had significantly lower results in VT and MCS than those without such symptoms ( $n = 16$ ). Due to the large group of young people in the national population, patients aged 60–69 and 70–79 were compared with their age-matched with individuals of a similar age. As a result, no significant differences between study and general population individuals were found in any QoL domain or SCS. Results among 60–69, 70–79, and the octogenarians groups did not reveal any significant differences in QoL. Comparing  $<70$  ( $n = 9$ ) and  $\geq 70$  ( $n = 11$ ) patients, the outcomes were almost indistinguishable with the exception of the mental component score, which was significantly lower in the younger group. In conclusion, QoL after total pancreatectomy is satisfactory even in the elderly and age itself should not be a contraindication for surgery. However, the complication rate is more often higher in the older group and the study was conducted on a very small population [13].

A comparison between the studies is difficult because of their heterogeneity. The endpoints were evaluated using different questionnaires: EORTC QLQ-C30 [9, 11], EORTC QLQ-PAN26 [12], FACT-Hep [10] and SF-36v2 [13]. Among the studies there were different criteria for inclusion to the QoL evaluation. Two of the studies collected PRO only once, at the end of the follow-up [12, 13]. Multiple postoperative assessments were conducted in three studies: 3-months, 6-months, and 12-months postoperatively [9, 11] and 2-weeks, 1-month, 3-months, and 6-months postoperatively [10].

Concluding, the QoL in older patients decreases after surgery and then is improving with time. Six months post pancreatic surgery, there was no difference in QoL between younger and older patients. Therefore, age itself should not be a contraindication for pancreatic surgery. Nevertheless, the results refer mostly to the group of patients who survived

the follow-up period and had no recurrence. This systematic review revealed a lack of high-quality data in this area and incontestably it undoubtedly indicated the demand for further research in this area.

### Quality of life after liver resection

There are many studies analyzing postoperative outcomes in older patients after liver resection, however, there are only few on how this population's quality of life is affected by liver resection. Most of the studies are retrospective in design. Only a few are prospective, and none of them are randomized control trials [14–17]. Moreover, the tools used to evaluate the QoL is different in each of the studies, which makes metaanalysis impossible. A systemic review on instruments measuring quality of life found that there is no gold standard in the field; these different measures make comparisons between studies difficult if not impossible [18].

Chen et al. compared patients  $\geq 70$  years of age with hepatocellular carcinoma who underwent liver resections with those who did not using European Cooperative Oncology Group (ECOG). Comparing pre- and postoperative performance status scores, ECOG in the conservative group only worsened. All patients received at least 6 months of follow up. In the surgery group, postoperatively 7 patients received a score of 0, 7 a score of 1, and 2 a score of 2. No patient in the resection group received a score of 3–5 [19].

Nomi et al. compared patients  $\geq 75$  undergoing laparoscopic liver resection (LLR) and open liver resection (OLR). In order to minimize selection bias, propensity score-based analysis was performed, after which 155 patients were in the LLR group and 155 in the OLR group. After propensity score matching, 3 patients in the LLR group and 13 in the OLR group were transferred to rehabilitation facilities, 12 in the LLR group and 14 in the OLR group had their comorbidities exacerbated, and 2 patients in the LLR group and 7 in the OLR group developed dementia [20].

Mise et al. used the Short Form-36 questionnaire to assess QoL in 108 patients who underwent liver resection between January 2004 and January 2008. Patients were assessed before surgery, 3 months after surgery, and 6 months after surgery. Physical Component Summaries (PCS) and Mental Component Summaries (MCS) were determined and compared between patients at or above 70 and patients below 70. PCS decreased at 3 months, then increased at 6 months for both groups. Patients  $<70$  experienced a more drastic drop in PCS at 3 months than patients  $\geq 70$ . MCS increased at 3 months and 6 months for patients  $<70$ , while it decreased at 3 months and increased at 6 months for patients  $\geq 70$  [21]. Quality of life appears to either remain stable or improve in the long term in older patients undergoing liver resection. There is still a deficit in high quality studies exploring this issue.

### Conclusions

To conclude, pancreas and liver surgery influence quality of life in the short term. However, after 3–6 months quality of life

level is rising and is comparable with the preoperative time. We have to remember that it was evaluated only in patients that had a radical operation and survived the follow-up time. Moreover, chronological age was the inclusion criteria in all of the studies and not biological age. This is also important, in the context that all patients not qualified for surgery had a QoL that was constantly decreasing.

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