Impact of nutritional status on outcome of pancreatic resections for pancreatic cancer and periampullary tumors

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The high complication rate of pancreatic resections and the poor oncologic outcome of pancreatic and periampullary malignancies cannot be explained by just a single factor. There are, however, some underlying elements that affect both surgical outcomes and cancer prognosis. Nutritional status and nutritional support/therapy are among these factors, as they strongly impact on both surgical recovery (1) and cancer survival (2). Additionally, pancreatic cancer entails specific nutritional and metabolic derangements (3) that can lead to immunological deterioration and further enhance tumor aggressiveness (4). Approximately 66% of the patients with pancreas cancer are malnourished (5). Nutritional assessment, support, and therapy are all recommended in pancreatic surgery (1).

In a recent article Seika and coworkers reported on the outcome of 1,384 open pancreatoduonectomies for pancreatic and periampullary cancer. Results were reported based on patients' body mass index (BMI). BMI was found to predict early outcome and long-term survival. In detail, obesity (BMI >30.0 kg/m^2) was associated with increased frequency of post-pancreatectomy hemorrhage, postoperative pancreatic fistula (POPF), bile leakage, wound infection, SIRS/sepsis, and need for reoperation. Underweight (BMI <18.5 kg/m^2), on the other hand, was shown to have higher 30- and 90-day mortality and inferior long-term survival, despite lower incidence of post-operative complications and similar histopathology parameters (6). Higher mortality in underweight patients, despite lower incidence of postoperative complications, means high failure to rescue. Failure to rescue is a relatively new quality metric indicating the proportion of patients who are not rescued following potentially treatable complications (7). In the context of uniform postoperative management policy, higher failure to rescue clearly demonstrates the frailty of underweight patients.

BMI is recommended by the World Health Organization to assess nutritional status, mainly in the assumption that it defines the excess of fat storage. In adults, a BMI <18.5 kg/m^2 corresponds to underweight, a BMI ≥25 kg/m^2 to overweight, and a BMI ≥30 kg/m^2 to obesity (8). BMI, however, can miss important nutritional conditions, such as sarcopenia, thus providing only a rough picture of nutritional status.

Underweight, in cancer patients, is associated with low performance status (5), and often means cachexia. Cachexia is a complex syndrome, including weight loss, marked by muscle wasting, increased muscle protein catabolism, insulin resistance and inflammation (5). Cachexia was associated with poor outcome after pancreatoduodenectomy (9).

Obesity, at the other extreme of BMI spectrum, is also a complex syndrome characterized by type 2 diabetes, coronary artery disease, hypertension, dyslipidemia, non-alcoholic fatty liver disease, and increased risk for development of several cancers (10). Actually, some patients may be metabolically obese despite normal weight making metabolic profile potentially more relevant than BMI in defining the risks associated with obesity. Patients who are metabolically obese, despite normal weight phenotype, show most of the negative medical features of obesity such as high cardiovascular risk profile, high proportion of visceral fat, low insulin sensitivity, hyperinsulinemia, dyslipidemia and high plasma level of proinflammatory cytokines (11). From the specific point of view of the pancreatic surgeon, high BMI correlates with fatty infiltration of the pancreas which, in turn, is associated with higher rates of POPF (12). Additionally, visceral obesity can make the procedure more technically demanding.

In 2015 approximately 39% of the world's adult population was either overweight (1.9 billion persons) or obese (609 million persons), with a generally higher prevalence in women and an age-related increase peaking between the ages of 50 to 65 years. By the year 2030 approximately 58% of the world population is anticipated to be overweight or obese (13). At the same time, pancreatic cancer is estimated to become the second leading cause of cancer-related mortality (14). Considering that a high BMI is associated with increased risk of pancreatic cancer (15) in the next years patients with pancreatic cancer are expected to be frequently obese.

When making an overall assessment on the impact of obesity on the outcome of pancreatic resections, despite conflicting data (9) the global picture shows that obesity increases surgical risk especially concerning POPF (12). A minimally invasive approach could mitigate the impact of obesity on the outcome of pancreatic resections but, unfortunately, just few studies have investigated this key issue.

Girgis and coworkers reported the outcome of 474 pancreatoduodenectomies, including 213 robotic pancreatoduodenectomies and 145 procedures performed in obese patients. Compared to non-obese patients, obese patients showed a higher estimated blood loss (EBL), a higher rate of clinically relevant POPF, and a higher rate of wound infections. In the obese group 75 patients underwent open pancreatoduodenectomy and 70 robotic pancreatoduodenectomy. Despite similar baseline characteristics, robotic pancreatoduodenectomy was associated with shorter operating room time (381 *vs.* 428 minutes; P=0.003), lower EBL (250 *vs.* 500 mL, P=0.001), a reduced need for red blood cell (RBC) transfusions (17% *vs.* 33%, P=0.035), a lower rate of clinically relevant POPF, and a decreased incidence of wound infection (19% *vs.* 44%, P=0.001). The robotic approach was associated with a higher incidence of delayed gastric emptying (26% *vs.* 11%, P=0.029), but a multivariate analysis showed that only older age (OR 1.03, P=0.012) and non-pancreatic cancer tumor type (OR 0.46, P=0.014) predicted the occurrence of delayed gastric emptying. Multivariate analysis showed also that the robotic approach did not significantly mitigate for severe postoperative complications, but was the only factor protective against wound infection (OR 0.27, P<0.0005) and was also protective against POPF (OR 0.33, P=0.019) (16).

He and coworkers reported the outcome of robotic pancreatectomies in 44 overweight patients (BMI >25 kg/m^2) in the context of a 1:2 propensity score matched comparison with the open procedure. Overall, 127 patients with a median BMI of 29.9 kg/m^2 [interquantile range (IQR): 27.0–31.8] were included in this study. The two groups (44 *vs.* 83 patients) were matched based on age, gender, ASA classification, type of procedure, histopathology, history of neoadjuvant therapy, and BMI. Overall, there were 67 distal pancreatectomies, 50 pancreatoduodenectomies, and 10 total pancreatectomies. The robotic approach was associated with a lower median EBL [100 (IQR: 75–200) *vs.* 300 (IQR: 200–600) mL; P<0.001) and with a shorter mean length of hospital stay (6.9±3.0 *vs.* 9.2±5.6 days; P=0.19). Patients receiving a robotic procedure did not require intraoperative transfusions of RBC, which were instead required in 5 patients in the open group (6%). This difference was not statistically significant (17).

Sahakyan and coworkers reported on 402 distal pancreatectomies performed in normal weight patients (n=191; mean BMI: 22.3±1.7 kg/m^2), overweight patients (n=155; mean BMI: 27.2±1.4 kg/m^2), and obese patients (n= 56; mean BMI: 33.7±3.8 kg/m^2). The three groups had similar baseline parameters, but hypertension (39.3% *vs.* 27.1% *vs.* 19.4%, P=0.008) and diabetes mellitus (26.8% *vs.* 12.9% *vs.* 10.5%, P=0.007) were more frequently observed in obese patients. Obese patients had longer median operative time [190 (IQR: 61–480) *vs.* 158 (IQR: 56–520) *vs.* 153 (IQR: 29–374) minutes; P=0.009] and median EBL [200 (IQR: 0–2,800) *vs.* 50 (IQR: 0–6,250) *vs.* 90 (IQR: 0–2,000) mL; P=0.01]. Obesity was also associated with more frequent occurrence of postoperative complications (30.9% *vs.* 38.1% *vs.* 48.2%; P=0.04), but a similar rate of severe complications (16.8% *vs.* 22.6% *vs.* 21.4%), and an increased incidence of POPF (27.2% *vs.* 34.2% *vs.* 46.4%; P=0.023), but a similar rate of clinically relevant POPF (15.2% *vs.* 17.4% *vs.* 25.0%). The rate of intraoperative unfavorable incidents was higher in obese patients (7.9% *vs.* 13.5% *vs.* 23.2%; P=0.007), despite similar rates of conversion to open surgery (0.5% *vs.* 3.2% *vs.* 1.8%) (18).

In conclusion, BMI is only a surrogate of body fatness that does not accurately define body composition. As such, it just captures the tip of the iceberg in the complex interplay that involves nutritional status, pancreatic cancer, and pancreatic resections. With this limitation, patients with high BMI do generally worse following pancreatic resections when compared to patients with normal body weight. Difference in outcome, however, is not so relevant as to justify restriction in access to pancreatic resections for obese patients and/or a selection based on BMI alone. Underweight, sarcopenia, and cachexia, on the other hand, are even worse nutritional conditions as compared to obesity. Patients facing these conditions should receive preoperative nutritional support and postoperative personalized nutrition. Studies using more sophisticated nutritional metrics are urgently needed to define the true impact of nutritional status of pancreatic resections performed for cancer and implement tailored therapeutic interventions. The impact of minimally invasive surgery also needs to be better defined. In general, a minimally invasive approach could be beneficial when there is a higher surgical risk, such as in obese patients. However, visceral obesity and fatty infiltration of the pancreas could make minimally invasive pancreatic resections more complex in obese patients. At least in theory, the robotic approach could reduce the impact of these technical hurdles.

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