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SARCOPENIA AS A PREDICTOR OF POSTOPERATIVE COMPLICATIONS IN PATIENTS WITH PANCREATIC CANCER

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Abstract. Sarcopenia as a predictor of postoperative complications in patients with pancreatic cancer. Kopchak V.M., Pererva L.O., Shkarban V.P., Trachuk V.I., Lynnyk S.V. *Several studies showed that sarcopenia is associated with an increase of postoperative complications, with worse postoperative results in patients with pancreatic cancer. According to European Working Group on Sarcopenia, it is a "progressive and generalized skeletal muscle loss" characterized by both loss of skeletal muscle mass and strength (Cruz-Jentoft AJ et al., 2019). Aim of our work*

was to evaluate the effect of sarcopenia on the occurrence of postoperative complications after pancreatic resections in patients with pancreatic and periampullary cancer. We performed a retrospective analysis of treatment of 152 patients who underwent radical pancreatic resections. Sarcopenia was determined by preoperative computed tomography using the Hounsfield Unit Average Calculation (HUAC). In our investigation we measured the psoas area and density (Hounsfield Units) at the level of the third lumbar vertebral body (L3). Sarcopenia was diagnosed in 66 (43.4%) patients. Among patients with sarcopenia complications occurred in 41 (62.1%), mortality was 4 (6.1%). In the group of patients without sarcopenia, complications occurred in 29 (33.7%) of 86 patients, mortality was 2 (2.3%). The level of postoperative complications in patients with sarcopenia was significantly higher (χ^2 =12.1, p=0.0005). Postoperative mortality in patients with sarcopenia was higher without significant difference (χ^2 =1.3, p=0.24). Sarcopenia significantly affects the level of postoperative complications and its detection can be used to improve the selection of patients before pancreatic resections in patients with pancreatic cancer.

Реферат. Саркопенія як фактор прогнозування розвитку післяопераційних ускладнень у хворих зі злоякісними пухлинами підшлункової залози. Копчак В.М., Перерва Л.О., Шкарбан В.П., Трачук В.І., Линник С.В. *Ряд досліджень показав, що саркопенія може асоціюватись з підвищенням кількості післяопераційних ускладнень та з гіршим прогнозом у пацієнтів з аденокарциномою підшлункової залози. Згідно з даними Європейської робочої групи по саркопенії, саркопенія – це «прогресивна та генералізована втрата скелетної м'язової маси», яка характеризується втратою скелетної м'язової маси та функції. Метою нашого дослідження стало визначення впливу саркопенії на виникнення післяопераційних ускладнень після резекційних оперативних втручань на підшлунковій залозі (ПЗ) у пацієнтів зі злоякісними пухлинами ПЗ та періампулярної зони. Був проведений ретроспективний аналіз результатів лікування 152 пацієнтів, яким були виконані радикальні оперативні втручання. Саркопенія визначалась за допомогою передопераційної комп'ютерної томографії при розрахуванні середнього значення Hounsfield Unit Average Calculation (HUAC) великого поперекового м'яза на рівні третього поперекового хребця. Саркопенія була діагностована в 66 (43,4%) хворих. Із них ускладнення виникли в 41 (62,1%), летальність становила 6,1%, померло 4 хворих. У групі хворих без саркопенії ускладнення виникли в 29 (33,7%) із 86 хворих, летальність становила 2 (2,3%). Рівень після-операційних ускладнень у хворих з саркопенією був достовірно вищим (χ^2=12.1, p=0.0005). Післяопераційна летальність у хворих з саркопенією була вищою з недостовірною різницею (χ^2=1.3, p=0.24). Згідно з нашими даними, саркопенія достовірно впливає на рівень післяопераційних ускладнень та може бути використана для покращення селекції пацієнтів перед виконанням резекцій ПЗ при злоякісних новоутвореннях ПЗ.*

Radical pancreatic resection remains the main method of treatment of patients with pancreatic cancer [3]. In recent decades, the improvement of surgical techniques and perioperative treatment of this category of patients has led to better treatment outcomes with a decrease in postoperative complications and mortality.

A decrease in mortality to less than 5% is observed in high-volume centers. Despite a significant reduction in postoperative mortality, the level of postoperative complications remains high up to 40-60% [4].

Postoperative complications have an impact on survival of patients after pancreatic resections since bad general condition of the patient in the postoperative period affects the timely appointment of chemotherapy [4, 5].

Occurrence of pancreatic fistulas, bleeding, infectious complications after pancreatic surgery can lead to fatal results. Thus, it is very important not only to recognize and treat complications, but also to improve methods aimed at preventing of postoperative complications before surgery [2].

In 1989, Irwin Rosenberg proposed the term "sarcopenia" (Greek for "sarx" or muscle + "penia" or loss) to describe a decrease in age-related muscle mass and function. Sarcopenia has since been defined as the loss of skeletal muscle mass and strength that occurs with age [15].

The European Working Group on Sarcopenia (EWGSOP) in the elderly developed the first consensus European definition of sarcopenia in 2010 with the latest update in 2019. According to it, sarcopenia was defined as "progressive and generalized skeletal muscle loss" characterized by both loss of skeletal muscle mass and strength with the associated increased risk of adverse postoperative consequences.

Sarcopenia can be both a primary syndrome and a secondary one associated with the presence of a malignant neoplasm. Sarcopenia is an objective indicator of the nutritional status of the patient's diet and level of physical fitness [14].

A number of studies showed that sarcopenia may be associated with a poor prognosis in patients with pancreatic cancer [11, 14]. According to world studies, sarcopenia is an important patient-specific factor that adversely affects the level of postoperative complications, recovery and survival of patients after pancreatic resection and adversely affects the specific outcome of pancreatic tumors treatment using

multimodal anticancer therapy and the prognosis of treatment in cancer patients [1, 8, 11, 12].

According to these data, patients with sarcopenia have an increasing number of both common postoperative complications and severe surgical complications, as well as complications of Grade III and higher according to the Clavien-Dindo classification. Patients with sarcopenia not only have more postoperative complications, but also an increased number of postoperative pancreatic fistulas [3, 12] and postoperative infectious complications [8].

The International Study Group of Pancreatic Surgery recommends evaluating the presence of sarcopenia during preoperative diagnosis of all patients before pancreatic resections as a prognostic factor for both short-term and long-term surgical outcomes [13, 14].

CT images can be used for determining sarcopenia by different methods. According to the literature, HUAC is a measure of the degree of sarcopenia, which is a significant factor in the development of postoperative complications after pancreatic resection in patients with pancreatic cancer. Data on the presence of sarcopenia can be easily obtained by preoperative patient's examination using CT.

Diagnosing of sarcopenia can be widely used to predict postoperative complications, and can potentially affect management tactics, improve patients selection before pancreatic resection and decision – making for adjuvant and neoadjuvant chemotherapy.

Timothy M. Pawlik and co-authors described measurements of sarcopenia using the Total Psoas Index (TPI), which measured the area of the right and left psoas muscles at the level of the third lumbar vertebra and correlated it with the patient's height [8]. Savita Joglekar and co-authors determined sarcopenia, also, depending on TPI parameters, using additionally muscle density in Hounsfield units when calculating HUAC values [11]. In our work, we also calculated the HUAC index for CT, using the program OsiriX 9.

MATERIALS AND METHODS OF RESEARCH

During 2011-2019 period we retrospectively evaluated 152 patients for the presents of sarcopenia. All patients underwent radical surgery for pancreatic adenocarcinoma and adenocarcinoma of periampullary region; we performed distal pancreatectomy in 23 (15.1%) patients, modified Appleby operation – in 2 (1.3%), pancreatoduodenectomy – in 122 (80.3%), total pancreatectomy – in 5 (3.3%).

All patients underwent preoperative examination which included mandatory abdominal ultrasound (US), multidetector spiral computed tomography with intravenous contrast (MSCT) no later than 4 weeks before surgery. Magnetic resonance imaging (MRI) and endosonography were performed if necessary. According to preoperative examination methods we assessed resectability of the primary tumor. We performed computed tomography not earlier than 4 weeks before surgery. The diagnosis was confirmed by postoperative morphological examination.

Postoperative complications were assessed and graded according to the Clavien-Dindo international classification. Complications requiring surgical, endoscopic or radiological intervention were defined as Grade III, complications that threatened the patient's life and required intermediate care or treatment in the intensive care unit were defined as Grade IV (major Grade III-IV complications).

Pancreatic fistula was defined according to the International Study Group of Pancreatic Fistula (ISGPS definition and grading of postoperative pancreatic fistula, 2016). The presence of delayed gastric emptying and bleeding were determined according to the consensus of the International Study Group of Pancreatic Surgery (ISGPS). The presence of a positive result of a culture of microorganisms in the microbiological test confirmed the infectious complications.

The sarcopenic profile included the area of the psoas muscle on both sides and its density. The area of the psoas muscle was measured in cm^2, and the density of muscle tissue was measured in Hounsfield Units.

Sarcopenia was calculated using the Hounsfield Units Average Calculation (HUAC).

We performed measurements in a semi-automated mode with manual outlining of the psoas muscles borders at the third lumbar vertebra and defining the density of muscle tissue between -30 and 110 Hounsfield Units (HU) Fig. 1 and 2, which allowed to automatically calculate the area of the lumbar muscles (Fig. 1, 2).

We calculated HUAC according to the formulas:

Hounsfield Unit Calculation (RHUC) = (Right Hounsfield Unit*Right Psoas Area) / (Total Psoas Area), left Hounsfield Unit Calculation (LHUC) = (Left Hounsfield Unit*Left Psoas Area) / (Total Psoas Area), and HUAC = (Right Hounsfield Unit Calculation+Left Hounsfield Unit Calculation) / 2.

For men, taking into account HUAC, the presence of sarcopenia was considered when the HUAC value was less than 18.8, for women, the HUAC value should be less than 20.3.
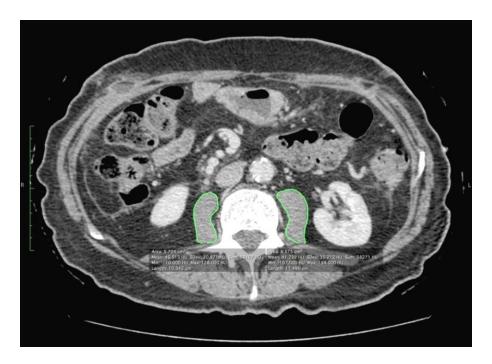
Fig. 1. Contrast enhanced computed tomography in axial projection with manual outlining of the psoas muscles borders at the third lumbar vertebra body

Fig. 2. Contrast enhanced computed tomography, frontal projection, determination of the third lumbar vertebra body

RESULTS AND DISCUSSION

We calculated HUAC in 152 patients with pancreatic cancer and cancer of periampullary region.

All patients underwent radical surgery. We performed distal pancreatectomy in 23 (15.1%) patients, modified Appleby operations – in 2 (1.3%), pancreatoduodenectomy – in 122 (80.3%), total pancreatectomy – in 5 (3.3%).

Pancreatic head cancer was diagnosed in 65 patients, tumors of the papilla Vateri – in 47 patients, tumors of the distal common bile duct – in 10, tumors of the pancreatic body and tail – in 25 patients, total pancreatic cancer was in 5 patients.

We diagnosed sarcopenia in 66 (43.4%) patients. In the patients with sarcopenia, pancreatic head cancer was diagnosed in 32 patients, tumors of

papilla Vateri – in 16 patients, tumors of distal part of common bile duct – in 7, tumors of the pancreatic body and tail – in 9 patients, and total pancreatic tumor – in 2 patients.

All patients underwent radical pancreatic resections: distal pancreatectomy – in 8 (12.1%) patients, modified Appleby operation – in 1 (1.5%) patient, pancreatoduodenalectomy – in 55 (83.3%), total pancreatectomy – in 2 (3.1%) patients.

In patients with sarcopenia postoperative complications occurred in 41 (62.1%) patients, in the group of patients without sarcopenia postoperative complications occurred in 29 (33.7%) patients. The number of postoperative complications in patients with sarcopenia was significantly higher (χ^2 =12.1, p=0.0005).

Mortality in the group of patients with sarcopenia was also higher: in the group of patients with sarcopenia 4 (6.1%) patients died, without sarcopenia – 2 (2.3%) patients (χ^2 =1.3, p=0.24), but the difference was insignificant.

From the group of patients with sarcopenia, infectious complications occurred in 8 (19.5%) patients, pancreatic fistula Grade B or C – in 24 (58.5%) patients, delayed gastric empting – in 3 (7.3%), postpancreatectomy hemorrhage – in 3 (7.3%), lymphorrhea – in 2 (4.9%), colon ulcer – in 1 (2.4%) patient.

Regarding Clavien-Dindo classification of complications, in the group of patients with sarcopenia postoperative complications Grade I occurred in 9 (21.9%) patients, Grade II – in 12 (29.3%) patients, Grade III – in 8 (19.5%) patients, Grade IV – in 8 (19.5%), and Grade V – in 4 (9.8%) patients .

In patients without sarcopenia following complications were observed: infectious – in 7 (24.1%) patients, pancreatic fistula Grade B or C – in 10 (34.5%) patients, postpancreatectomy hemorrhage – in 5 (17.2%), delayed gastric empting - in 3 (10.3%) patients, lymphorrhea – in 2 (6.9%), chyle leak Grade B – in 2 (6.9%) patients.

Regarding Clavien-Dindo classification of complication, in the group of patients without sarcopenia postoperative complications of Grade I occurred in 6 (20.7%) patients, Grade II – in 12 (41.4%) patients, Grade III – in 8 (27.6%) patients, Grade IV – in 1 (3.4%) and Grade V – in 2 (6.9%) patients.

The level of occurrence of Grade B or C pancreatic fistula was significantly higher in the group of patients with sarcopenia (χ^2=3.9, p=0.04). The level of infectious complications was higher in the group of patients with sarcopenia but the difference was insignificant (χ^2=0.04, p=0.8). Regarding the level of delayed gastric empting and postpancreatectomy hemorrhage, a significant difference between

the two groups was not found. The level of delayed gastric empting in both groups was without a significant difference (χ^2=0.2, p=0.6), the level of postoperative hemorrhage was also without a significant difference (χ^2=1.6, p=0.2) too.

According to the Clavien-Dindo classification, we did not find any significant difference in the increase of Grade III complications in patients with sarcopenia. In the group of patients with sarcopenia we observed a significantly higher number of severe complications according to Clavien-Dindo grade IV and grade V, in the group of patients with sarcopenia severe complications occurred in 12 patients, in the group of patients without sarcopenia – in 3 patients, the difference was significant (χ^2=6.4, p=0.01).

According to the literature, sarcopenia affects both the development of postoperative complications and the long-term oncological outcome of treatment of patients with pancreatic cancer [9, 13, 14]. Postoperative complications affect the further course of the patient's disease with pancreatic cancer [10, 11]. Occurrence of postoperative complications often limits us in timely appointment of adjuvant chemotherapy, and in some cases postoperative complications can be the reason for refusing chemotherapeutic treatment.

The ability to predict the level of postoperative complications can potentially improve selections of patients before surgery, especially for borderline resectable pancreatic tumors [10]. Hounsfield Units average calculation (HUAC) is a patient-specific measurement of muscle density and fat infiltration, reflecting the patient's sarcopenia [11].

Our results show that sarcopenia detected by HUAC is a reliable predictor of postoperative complications after pancreatic resection in patients with pancreatic cancer.

Sarcopenia is an atrophy of muscle tissue in the absence of necrosis with a decrease in the size and number of muscle cells and can be a reversible process [3]. Patients at increased risk of complications may receive neoadjuvant chemotherapy while receiving special therapy to improve their sarcopenic profile (nutrition optimization and exercise) before radical surgery [10]. This tactic can ultimately reduce the level of postoperative complications after pancreatic resections, leading to a better outcome and survival [1, 8]. The obtained results are clinically suitable for patients with pancreatic cancer, candidates for radical surgery. In addition, sarcopenia is a feature of the physique that can change over time. Sarcopenia is an indicator of the patient's nutritional status. According to many authors, overall survival and non-recurrent survival in patients with sarcopenia is significantly lower.

Peng and co-authors in their studies showed that patients with sarcopenia even have an increased risk of death in the first 3 years after surgery [8].

In the future, there is a need to develop a therapeutic strategy to increase the patient's muscle mass in order to improve the sarcopenic profile and reduce the risk of postoperative complications.

According to Tosei Takagi and co-authors, sarcopenia is an objective and reliable preoperative predictor of postoperative infectious complications after pancreatic resection [8]. According to our data, there was no significant difference in the occurrence of infectious complications in patients with sarcopenia. According to several world studies, patients with sarcopenia have a significantly higher number of pancreatic fistulas after pancreatic resections. Yasunori Nishida and co-authors showed a significant increase in the incidence of pancreatic fistulas after pancreatoduodenectomy in patients with sarcopenia [3]. Minji Jang and Hyung Woo Park and co-authors also noted an increase in the number of pancreatic fistulas after pancreatic resection in patients with sarcopenia [7].

Jukes P. Namm and his colleagues from US clinics showed an increase in both pancreatic fistulas and the incidence of wound infection and infectious complications of the abdominal cavity [12]. According to the results of our studies in patients with sarcopenia the total number of Grade B and Grade C pancreatic fistulas significantly increased, without increasing the number of infectious complications.

According to Prado and co-authors, the effect of sarcopenia is multifactorial. Skeletal muscles play a fundamental role in protein synthesis and sarcopenia can disrupt the body's immune defenses [6]. According to Savita Joglekar, the assessment of muscle volume as well as its density and fat infiltration give more accurate results in the sarcopenia calculation which is comparable to our results [11].

In some cases, the presence of obesity does not allow for a correct assessment of muscle tissue loss. In such patients, determining the presence of sarcopenia can help assess the patient's condition before surgery. Presence of sarcopenia can help surgeons in predicting the occurrence of postoperative complications and impact on the tactics of perioperative treatment. However, a therapeutic strategy in increasing lumbar muscle mass and improvement of the sarcopenic profile for reducing the risk of complications needs to be further developed.

CONCLUSIONS

Received data indicate that sarcopenia, determined by HUAC in preoperative CT, is an important indicator of surgical outcome and significantly affects not only the level of postoperative complications, but also the level of pancreatic fistula occurrence and can be used to improve the selection of patients with pancreatic cancer before radical resection.

Conflict of interests. The authors declare no conflict of interest.

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