IMPACT OF VISCERAL OBESITY ON OUTCOMES OF PERIAMPULLARY CANCER SURGERY

IMPACTO DA GORDURA VISCERAL NO PROGNÓSTICO DA CIRURGIA DO CANCRO PERI-AMPOLAR

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ABSTRACT

Periampullary cancers are located up to a maximum distance of 2 cm from the duodenal papilla, with pancreatic cancer being the most common. Despite advances in surgical technique, survival rates remain low, making it essential to identify prognostic factors. Visceral obesity has been identified as a risk factor for cancer development, but its influence on the morbidity and mortality of operated patients remains controversial. This study aims to identify an association between the presence of preoperative visceral obesity and an increased risk of postoperative morbimortality in patients with periampullary cancers at Hospital de Braga. The sample includes 44 patients with periampullary cancers who underwent surgery with a curative intention between January/2011 and April/2018. The area of visceral fat was measured using the ImageJ *software*. Statistical analysis was performed using the SPSS software version 25. Visceral fat was not implicated in longer hospital stay or postoperative complications. The survival analysis showed no differences in disease-free survival at 1 year ($p = 0.121$) and 5 years ($p = 0.222$) or in overall survival at 1 year ($p = 0.163$) and 5 years ($p = 0.053$) between groups. Our data suggest that preoperative visceral obesity is not a risk factor for greater postoperative morbidity and mortality in individuals with periampullary cancers. Despite the reduced sample, this study evaluates visceral obesity in four types of tumors with many similar characteristics. Additional studies with larger samples are needed to confirm our observations.

Key Words: *Visceral fat, Periampullary cancers.*

RESUMO

Os tumores periampulares estão localizados a uma distância máxima de 2 cm da papila duodenal, sendo a neoplasia mais comum do pâncreas. Apesar dos avanços da técnica cirúrgica, as taxas de sobrevivência permanecem baixas, sendo fundamental a identificação de fatores determinantes do prognóstico. A obesidade visceral tem sido identificada como fator de risco para o desenvolvimento do cancro, mas a sua influência na morbimortalidade pós-operatória permanece controversa. Este estudo teve como objetivo explorar a associação entre a presença de obesidade visceral pré-operatória e o risco de morbimortalidade pós-operatória em indivíduos com cancro periampular no Hospital de Braga. A amostra é constituída por 44 indivíduos com

cancro periampular, submetidos a cirurgia com intenção curativa, entre janeiro de 2011 e abril de 2018. A área de gordura visceral foi medida com recurso ao *software* ImageJ. A análise estatística foi realizada com o *software* SPSS versão 25. A gordura visceral não se associou ao maior tempo de internamento ou complicações pós-operatórias. A análise de sobrevivência não revelou diferenças no tempo livre de doença a 1 ano (p = 0,121) ou a 5 anos (p = 0,222), nem na sobrevida global a 1 ano (p = 0,163) ou a 5 anos (p = 0,053) entre os grupos. Os dados sugerem que a obesidade visceral pré-operatória não é fator de risco para maior morbimortalidade pós-operatória em indivíduos com cancro periampular. Apesar da amostra reduzida, este estudo avalia a obesidade visceral em quatro tipos de tumores com muitas características semelhantes. Estudos adicionais com amostras maiores são necessários para confirmar as nossas observações.

Palavras-chave: *gordura visceral, tumores periampulares.*

INTRODUCTION

Periampullary cancers are a group of tumours that are located up to a maximum distance of 2 cm from the duodenal papilla[1]. Within this group, pancreatic cancer is the most frequent (3% of gastrointestinal neoplasms), followed by ampullary cancer (1%) and duodenal cancer (0.5%)[2]. Concerned prognosis, survival at 5 years is superior in ampullary and duodenal cancers, being substantially lower in pancreatic cancers. The 5-year survival rates of periampullary cancers remain low, with a rate of 15% for pancreatic, ampullary 39%, distal bile duct 27%, and duodenal 59%[3]. Therefore, it is essential to identify prognostic factors, in order to recognize which patients submitted to surgery will develop high postoperative morbidity and mortality.

In 2003, the International Agency for Research on Cancer (IARC) identified a causal relationship between obesity and the increased risk of various cancers[4-5], including periampullary cancers[11]. While the accumulation of visceral adiposity is, also a risk factor of poor prognosis in several types of cancers[6-8], the influence of visceral obesity on survival after surgery remains poorly comprehended[11]. In order to assess visceral obesity, several methods can be considered. The most used are the Body Mass Index (BMI), the electrical bioimpedance (BIA), the densitometry – Dual-Energy X-Ray Absorptiometry (DEXA), the ultrasound, the Computed Tomography (CT) or the Nuclear Magnetic Resonance (NMR). These different measurement methods vary in terms of availability, specificity, reliability, reproducibility, radiation exposure and whether quantitative assessment is allowed or not[9]. When available, CT and MRI are the most reliable means: they are the most specific, with the greatest reproducibility and allow a quantitative assessment of visceral adiposity[10].

This study aimed to evaluate the impact of visceral obesity on morbidity and mortality of patients diagnosed with periampullary cancer, who underwent curative surgical treatment.

METHODS AND MATERIAL

The study population focused on patients with histological diagnosis of periampullary cancer, who underwent curative surgical resection in the General Surgery Service of Braga Hospital, from January 2011 to April 2018. The study excluded: patients with a histological diagnosis different from that previously mentioned; patients undergoing surgical treatment for palliative purposes and patients who died within 30 days after surgery.

For each patient, demographic and clinical data were collected in the preoperative, hospitalization and post-operative follow-up: age, gender, weight, American Society of Anesthesiologists – Physical Status (ASA-PS), date of surgery, date of hospital

discharge, complications at 30 days, mortality at 30 days, disease recurrence and respective date of diagnosis and date of death.

The postoperative morbidity at 30 days was analyzed by the Clavien-Dindo classification[12] and patients grouped in: patients without complications or with postoperative complications mild (grade I and II) and patients with moderate to severe complications (grade III, IV and V).

Days of hospitalization were calculated by the date of surgery and the date of hospital discharge; disease-free survival was calculated based on the date of surgery and the date of recurrence; overall survival was calculated based on the date of surgery and the date of death.

Visceral fat area (VFA) was evaluated in the cross-section of L3 in the preoperative CT by ImageJÒ *software*[13] (Figure 1).

Visceral obesity was defined according to the values described in the literature: visceral fat area of 80 cm^2 for females and 160 cm^2 for males[14] and the sample was divided into two groups: Visceral Fat group (VF) and Visceral Fat Free group (VFF).

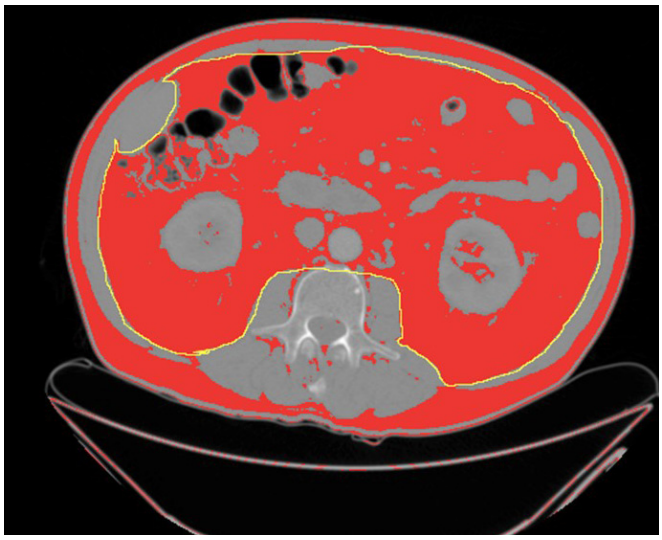

FIGURE 1 – **Visceral fat area (VFA) evaluation in the cross-section of L3 in the preoperative CT by ImageJÒ software.**

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences software version 25.0.

Nominal qualitative variables were described through frequency and percentage, while quantitative variables were expressed through minimum and maximum.

Chi-square test (x^2) and *Fisher's exact test* were used to find out if there were significant differences between the VF group and VFF group, concerning gender, tumour location, tumour differentiation, staging, presence of vascular invasion and lymphatic invasion, ASA-PS classification and postoperative complications.

Mann-Whitney U test was used to compare means of age, weight and length of stay between the VF group and VFF group, and *r* was reported as an effect size measure.

Cramér's V test was used to indicate how strongly visceral fat was associated with clinicopathological characteristics and morbidity. The magnitude of the association was classified as week (>0.05), moderate (>0.10), strong (>0,15) or very strong (>025) (REF).

Kaplan-Meier analysis were performed to find out if there were significant differences in overall survival and disease-free survival between the two groups, 1 and 5 years after surgery.

A value of $p < 0.05$ was considered significant.

RESULTS

Baseline characterization of the total sample

Sample characterization is described in Table 1. This study evaluated 44 patients, 31 (70%) male and 13 (30%) female. The minimum age observed was 42 years and the maximum was 83 years, with a median of 72 years. The median weight measured at the date of surgery was 70 kg, the minimum was

Table 1 – **Sample characterization: sociodemographic, clinicopathological characteristics and surgical outcome**

		Sample (n=44)	VF group (n=27)	VFF group (n=17)
Age (years)		72 (69.19±9.54)	73 (72.48±6.94)	65 (63.88±10.86)
Gender				
	Male	31 (70%)	17 (63.0%)	14 (82.4%)
	Female	13 (30%)	10 (37.0%)	3 (17.6%)
Weight (kg)		70 (70.30±13.47)	74 (73.96±13.52)	65 (64.47±11.47)
Localization				
	Pancreas	20 (45.5%)	14 (51.9%)	6 (35.3%)
	Ampulla of Vater	14 (31.8%)	8 (29.6%)	6 (35.3%)
	Duodenal	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Biliary / Principal biliary tree	10 (22.7%)	5 (18.5%)	5 (29.4%)
Stage				
	I	7 (15.9%)	6 (22.2%)	1 (5.9%)
	II	14 (31.8%)	9 (33.3%)	5(29.4%)
	III	20 (45.5%)	12 (44.4%)	8 (47.1%)
	IV	3 (6.8%)	0 (0%)	3 (17.6%)
Differentiation				
	Well differentiated	27 (61.4%)	20 (74.1%)	7 (41.2%)
	Moderately differentiated	15 (34.1 %)	7 (25.9%)	8 (47.1%)
	Undifferentiated	2 (4.5%)	0 (0%)	2 (11.8%)
Vascular invasion		11 (25%)	4 (14.8%)	7 (41.2%)
Lymphatic invasion		24 (54.5%)	16 (59.3%)	8 (47.1%)
ASA				
	I	3 (6.8%)	1 (3.7%)	2 (11.8%)
	II	28 (63.6%)	18 (66.7%)	10 (58.8%)
	III	12 (27.3%)	7 (25.9%)	5 (29.4%)
	IV	1 (2.3%)	1 (3.7%)	0 (0.0%)
Operatory morbidity				
	without /mild postoperative complications	28 (63.6%)	18(66.7%)	10 (58.8%)
	Moderate/severe complications	16 (36.4%)	9 (33.3%)	7 (41.2%)
Days of hospitalization		11 (15.30±13.21)	10 (15.74±16.20)	13 (14.59±6.42)
Disease relapse		28 (63.6%)	19 (70.4%)	9 (52.9%)
Disease-free survival (months)		8.9 (16.5±16.7)	11.8 (20.2±17.5)	7.7 (10.5±14.01)
Mortality		29 (65.9%)	17 (63.0%)	12 (70.6%)
Overall survival (months)		17.2 (23.2±19.7)	21.7 (28.5±20.8)	8.9 (14.7±14.5)
VFA (cm^2)		167.4 (186.1±101.2)	206.7 (238.6±90.7)	120.0 (102.8±46.4)

Variables: gender, localization, staging, differentiation, vascular and lymphatic invasion, ASA, operatory morbidity, disease relapse and mortality were described through frequency (n) and percentage (%).
Variables: age, weight, days of hospitalization, overall and disease-free survival and VFA were described through median and standard deviation.

46 kg and the maximum was 118 kg. Three patients (6.8%) were classified as ASA I, 28 patients (63.6%) were ASA II, 12 patients (27.3%) were ASA III and 1 patient (2.3 %) was ASA IV.

Regarding the presence of visceral obesity, 17 patients (38.6%) had lower visceral fat values than reference value, while 27 patients (61.4%) had a higher established value. The mean of VFA was 186, 1 cm2 (median, 167.4 cm2), with a minimum of 27.8 cm2 and a maximum of 473.51 cm2.

Twenty patients (45.5%) were diagnosed with pancreatic cancer, 14 patients (31.8%) with ampullary cancer and 10 patients (22.7%) with gallbladder or bile duct cancer. In the matter of staging, 7 (15.9%) were in stage I, 14 (31.8%) in stage II, 20 (45.5%) in stage III and 3 (6.8%) in stage IV. With regard to differentiation, 27 (61.4%) were well differentiated, 15 (34.1%) moderately differentiated, and 2 (4.5%) undifferentiated. Twenty-four patients (54.5%) had lymphatic invasion and 11 patients (25%) had vascular invasion.

Postoperative outcomes in the total sample

The median length of stay was 11 days, with a minimum stay of 6 days and a maximum stay of 70 days. Twenty-eight patients (63.6%) had no postoperative complications or had mild complications, while 16 (36.4%) had moderate to severe complications.

The total sample had a median follow-up of 17.2 months, with a minimum follow-up of 1.6 months and a maximum follow-up of 73.4 months. The median disease-free survival was 8.9 months, in which the earliest recurrence occurred 1.6 months after surgery, while the latest recurrence occurred 62.6 months after surgery. The median overall survival was 17.2 months, with the shortest overall survival being 1.6 months and the longest overall survival being 73.4 months. Patients with pancreatic cancer had the lowest rates of disease-free survival and overall survival, while those with ampullary cancer had the best overall survival and disease-free survival.

Baseline characterization and postoperative outcomes in patients stratified by visceral fat

Patients from the VF group were older (U = 119, p = 0.008, r = –0.40) and presented a greater average weight (U = 125, p = 0.012, r = –0.38) than those from VFF group. No correlation was found between the two groups in regard to the length of hospital stay (U = 169, p = 0.142, r = –0.23).

Table 2 shows the association between visceral fat and clinicopathological characteristics and morbidity. A significant and "very strong" association was observed between the VF group and the VFF group for tumour differentiation (p =0.032). No significant association was observed for the remaining characteristics.

The Kaplan-Meier survival analysis showed that there were no differences in disease-free survival (DFS) at 1 and 5 years (p = 0.121, p = 0.222) (Figure 2) nor in the global survival at 1 and 5 years (p = 0.163; p = 0.053) (Figure 3) between the VF group and the VFF group.

TABLE 2 – **Relation between VF and VFF groups by clinicopathological characteristics**

Variable	X^2	*p-value*	Φ / φ_C
Gender	1.884	0.170	Φ = -0.207
Tumour location	1.279	0.528	φ_C = 0.170
Tumour staging	6.582	0.087	φ_C =0.387
Tumour differentiation*	6.383	**0.032**	φ_C = 0.381
Vascular invasion*	3.866	0.075	Φ =-0.296
Lymphatic invasion	0.626	0.429	Φ =0.119
ASA-PS	1.771	0.621	φ_C = 0.201
Morbidity	0.277	0.598	Φ = -0.709

x^2 – *Chi-square test*; **X Φ – Phi (crosstab 2x2)**; **φ_C – *V de Cramer***; * - *Fisher's exact test*

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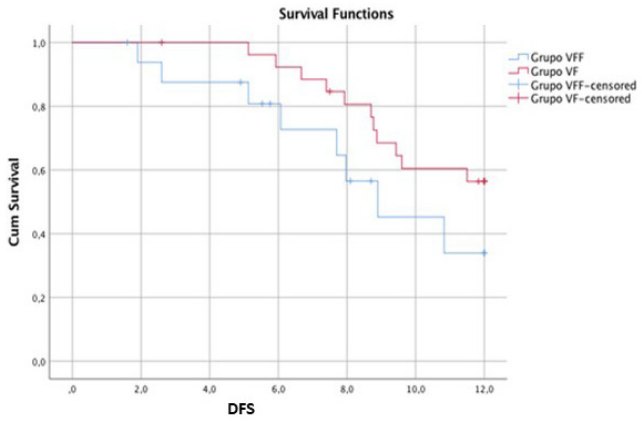

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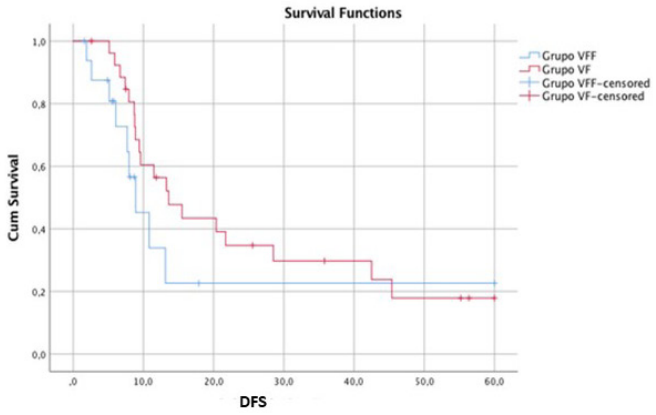

FIGURE 2 – **Disease free survival (DFS) at 1 and 5 years.**

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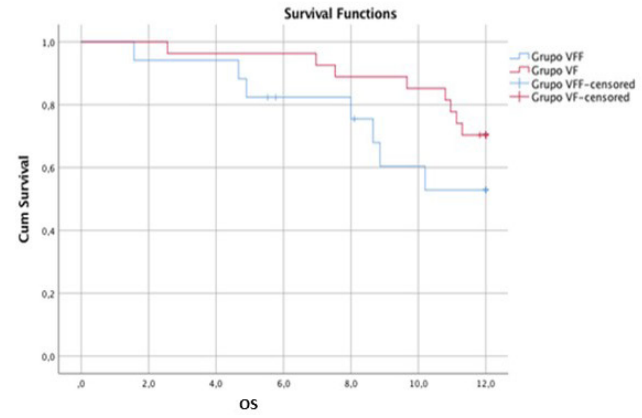

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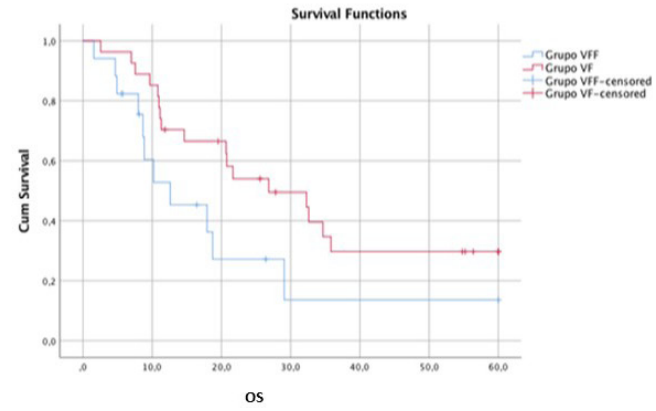

FIGURE 3 – **Overall survival (OS) at 1 and 5 years.**

DISCUSSION

Periampullary cancers, despite having a low incidence rate, maintain high mortality rates[15-18]. Therefore, the identification of risk factors for greater morbidity and mortality is extremely important in order to be able to stratify patients and institute an individualized treatment. Thus, it was our purpose to evaluate the impact of visceral obesity on morbidity and mortality of patients diagnosed with periampullary cancer, who underwent curative surgical treatment. Our data suggests that visceral fat was not associated with longer hospital stay, postoperative complications, disease-free survival poor survival or global survival.

In the current study, and concerning post-operative morbidity, 36% of patients had severe complications in the 30 days after surgery, slightly higher than reported by other studies (27.9%)[24]. In respect of disease recurrence, 63.6% of patients presented recurrence of the disease, while Santosh et al described a recurrence rate of 52%[25]. In the matter of overall survival, ampullary cancer was the one with the best overall survival (31.9 months) while

pancreatic cancer had the worst overall survival (16.3 months), values that are also in concordance the literature[26].

Obesity has been described as an important risk factor, both in the development of cancer and as a prognostic factor[19-22]. However, the influence of visceral obesity on the outcome of cancer patients remains controversial[23]. In the our study population with periampullary cancer at Hospital de Braga, visceral obesity was present in 61.4% of patients according to the cut-off used. Bearing in mind that the ideal cut-off value for the diagnosis of visceral obesity is not well established, it is difficult to estimate the prevalence of visceral obesity in the oncology population. Thus, studies that validate the cut-off values determined by Doyle et al[14] for the oncology population are an asset in order to increase the consistency of the research work that links visceral obesity with the cancer prognosis.

Regarding the influence of VF on the postoperative outcomes, we did not observe any association with postoperative complications, length of hospital stay, overall survival, nor disease-free survival. Regarding periampullary cancers, no study was found that related the visceral fat area with the prognosis of patients with this diagnosis, thus not obtaining a term of comparison with the results obtained in our study. We can consider this research innovative, in the sense that it presents itself as the first study to evaluate visceral obesity with, not only one type of tumour, but with four types of tumours with many similar characteristics. Thus, this work may serve as a basis for further studies, including periampular carcinomas, to be carried out with larger samples.

Limitations

As a first limitation of the current work, it is necessary to highlight the small sample size. In addition, the fact that four different types of tumours were evaluated, translates into a very heterogeneous study sample. It would be better to perform studies for each type of cancer in particular, which on the other hand, is not easy having taken into account the low incidence of these cancers. In addition, the fact that it is a retrospective study, results in incomplete clinical processes, which can lead to selection bias: patients were excluded from the study because they did not have preoperative CT and the height of all patients were not available.

CONCLUSION

In this study, visceral fat was not associated with specific tumour characteristics or cancer-related outcome; however, additional studies with larger samples are necessary to better understand this relationship.

REFERENCES

1 Sarmiento JM, Nagomey DM, Sarr MG, Farnell MB. Periampullary cancers: are there differences? Surg Clin North Am. 2001;81(3):543-55.

2 Spalding DR, Pancreatic and periampullary cancers: treatment and outcome. Br J Hosp Med (Lond). 2006;67(1):14-20.

3 Yeo CJ, Sohn TA, Cameron JL, Hruban RH, Lillemoe KD, Pitt HA. Periampullary adenocarcinoma: analysis of 5-year survivors. Ann Surg. 1998;227(6):821-31.

4 Vainio, Harri, et al., editores. International Agency for Research on Cancer Working Group on Evaluation of Cancer-Preventive Strategies. Weight Control and Physical Activity. IARC Press, 2002.

5 Organization, World Health, et al. Diet, Nutrition and the Prevention of Chronic Diseases: Report of a Joint WHO/FAO Expert Consultation. World Health Organization, 2003.

6 Moon, Hyeong-Gon, et al. «Visceral Obesity May Affect Oncologic Outcome in Patients with Colorectal Cancer». Annals of Surgical Oncology. 2008;15(7):1918-22.

7 Okamura, Akihiko, et al. «Clinical Impact of Abdominal Fat Distribution on Prognosis After Esophagectomy for Esophageal Squamous Cell Carcinoma». Annals of Surgical Oncology. 2016;23(4):1387-94.
8 Fujiwara, Naoto, et al. «Sarcopenia, Intramuscular Fat Deposition, and Visceral Adiposity Independently Predict the Outcomes of Hepatocellular Carcinoma». Journal of Hepatology. 2015;63:131-40.
9 Shuster, A., et al. «The Clinical Importance of Visceral Adiposity: A Critical Review of Methods for Visceral Adipose Tissue Analysis». The British Journal of Radiology. 2012;85:1-10.
10 Gaujoux, Sébastien, et al. «Impact of Obesity and Body Fat Distribution on Survival After Pancreaticoduodenectomy for Pancreatic Adenocarcinoma». Annals of Surgical Oncology. 2012;19(9):2908-16.
11 Okumura, Shinya, et al. «Visceral Adiposity and Sarcopenic Visceral Obesity Are Associated with Poor Prognosis After Resection of Pancreatic Cancer». Annals of Surgical Oncology. 2017;24(2):3732-40.
12 Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240:205-13.
13 Sottier, D., Petit, J.-M., Guiu, S., Hamza, S., Benhamiche, H., Hillon, P., Guiu, B. Quantification of the visceral and subcutaneous fat by computed tomography: interobserver correlation of a single slice technique. Diagnostic and Interventional Imaging. 2013;94(9), 879–884.
14 Doyle, S. L., Bennett, A. M., Donohoe, C. L., Mongan, A. M., Howard, J. M., Lithander, F. E., … Lysaght, J. Establishing computed tomography-defined visceral fat area thresholds for use in obesity-related cancer research. Nutrition Research (New York, N.Y.). 2013;33(3):171-179.
15 Benhamiche, A. M., et al. «Cancer of the Ampulla of Vater: Results of a 20-Year Population-Based Study». European Journal of Gastroenterology & Hepatology. 2000;12(1):75-79.
16 Berberat, P. O., et al. «An Audit of Outcomes of a Series of Periampullary Carcinomas». European Journal of Surgical Oncology (EJSO). 2009;35(2):187-91.
17 Uomo, Generoso. «Periampullary Carcinoma: Some Important News in Histopathology». JOP. Journal of the Pancreas. 2014;15(2).
18 Ilic, Milena, e Irena Ilic. «Epidemiology of pancreatic cancer». World Journal of Gastroenterology. 2016;22(44):9694-705.
19 De Pergola, Giovanni, e Franco Silvestris. «Obesity as a Major Risk Factor for Cancer». Journal of Obesity.2013p. 291546.
20 Pischon, Tobias, e Katharina Nimptsch. «Obesity and Risk of Cancer: An Introductory Overview». Recent Results in Cancer Research. Fortschritte Der Krebsforschung. Progres Dans Les Recherches Sur Le Cancer. 2016 ;208 :1-15.
21 Calle, Eugenia E., et al. «Overweight, Obesity, and Mortality from Cancer in a Prospectively Studied Cohort of U.S. Adults». New England Journal of Medicine.2003;348(17):1625-38.
22 Genkinger, J. M., et al. «Central Adiposity, Obesity during Early Adulthood, and Pancreatic Cancer Mortality in a Pooled Analysis of Cohort Studies». Annals of Oncology. 2015;26(11):2257-66.
23 Xiao, J., Mazurak, V. C., Olobatuyi, T. A., Caan, B. J., & Prado, C. M. Visceral adiposity and cancer survival: a review of imaging studies. European Journal of Cancer Care. 2018;27(2), e12611.
24 Nakeeb, Ayman, et al. «Trends and Outcomes of Pancreaticoduodenectomy for Periampullary Tumours: A 25-Year Single-Center Study of 1000 Consecutive Cases». World Journal of Gastroenterology. 2017;23(38):7025-36.
25 Hatzaras, Ioannis, et al. «Predictors of Survival in Periampullary Cancers Following Pancreaticoduodenectomy». Annals of Surgical Oncology. 2010;17(4):991-97.
26 Santhosh, Sampath, et al. «Diagnostic Accuracy of F-18 FDG PET/CECT vs. CECT for Detecting Recurrence of Periampullary Carcinoma and Its Prognostic Significance». Abdominal Imaging. 2015;40(5):1131-37.

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