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Predictors of Survival and Positive Surgical Margins in Pancreatic Ductal Adenocarcinoma: a Single Center Retrospective Study

Preditores de Sobrevivência e Margens Cirúrgicas Positivas em Doentes com Adenocarcinoma Ductal do Pâncreas: um Estudo Retrospetivo num Único Centro

Rita Ribeiro[1], João Amorim[2,3,4], Nuno Jorge Lamas[3,4,5], João Carvalho[2], Bruno Giesteira[2], Manuela França[2,6,7]

[1]Escola de Medicina, Universidade do Minho, Braga, Portugal.
[2]Serviço de Radiologia, Departamento de Imagiologia, Centro Hospitalar Universitário do Porto, Porto, Portugal.
[3]Instituto de Investigação em Ciências da Vida e Saúde (ICVS) e Escola de Medicina, Universidade do Minho, Braga, Portugal.
[4]ICVS/3B's, Laboratório Associado do Governo PT, Braga/Guimarães, Portugal.
[5]Serviço de Anatomia Patológica, Departamento de Patologia, Centro Hospitalar Universitário do Porto, Porto, Portugal.
[6]Instituto de Ciências Biomédicas de Abel Salazar, Universidade do Porto, Porto, Portugal.
[7]i3S, Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Porto, Portugal.

Address

João Amorim
Serviço de Radiologia
Departamento de Imagiologia
Centro Hospitalar Universitário do Porto
Largo Professor Abel Salazar
4099-001, Porto, Portugal
email: joaoamorim@med.uminho.pt

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Abstract

Introduction: Pancreatic ductal adenocarcinoma is one of the most common causes of cancer-related death. The overall survival is short even in the small proportion of patients who are eligible for surgical resection. The aims of our study were to assess the value of preoperative CT scan in the prediction of the surgical margin status and to identify imaging features that predict the survival of patients with resectable pancreatic adenocarcinoma.
Methods: Our study included 62 patients with histologically confirmed pancreatic adenocarcinoma, who underwent surgery between January 1st 2010 and June 30th 2019. Medical records and preoperative CT images were reviewed in order to collect clinical and imaging data. Data was analyzed with the Chi-square test and binary logistic regression. Kaplan-Meier estimates, Log-Rank test, and multivariate Cox proportional hazards regression were used for the survival analysis.
Results: From the 62 patients who underwent surgery, negative surgical margins were achieved in 35 of them and 27 patients had positive surgical margins. In the multivariate analysis, vascular contact was a predictor of positive surgical margins. The mean survival was 26,3 months, being significantly different between the two groups of surgical margins. In survival analysis, tumor density on CT (HR=0,985, p-value=0,035) and imaging signs of extra-pancreatic perineural involvement (HR=2,324, p-value=0,048) were identified as predictors of survival.
Conclusion: Preoperative CT is a useful tool to predict positive surgical margins and survival. It helps to identify patients with resectable tumors but worse prognosis who can benefit from different therapeutic strategies.

Keywords

Pancreas; Survival analysis; Computer tomography.

Resumo

Introdução: O adenocarcinoma ductal do pâncreas é uma das principais causas de morte por cancro. Apresenta uma baixa sobrevivência mesmo na pequena proporção de doentes submetidos a cirurgia. O objetivo deste estudo foi avaliar o valor da TC pré-operatória na previsão do envolvimento das margens cirúrgicas e identificar características imagiológicas preditoras de sobrevivência nos doentes com adenocarcinoma pancreático ressecável.
Métodos: Foram avaliados retrospetivamente 62 doentes com adenocarcinoma pancreático confirmado histologicamente e submetidos a ressecção cirúrgica entre 1 de janeiro de 2010 e 30 de junho de 2019. Os registos clínicos e as TC pré-operatórias foram revistos para recolha de dados clínicos e imagiológicos. Os dados foram avaliados com o teste do Qui-quadrado e regressão logística binária. A análise de sobrevivência realizou-se com recurso ao método de Kaplan-Meier, ao teste de Log-Rank e à regressão de Cox.
Resultados: Dos 62 doentes incluídos no estudo, identificaram-se 35 com margens negativas e 27 com margens positivas. Na análise multivariada, o contacto vascular revelou-se preditor de margens cirúrgicas positivas. A sobrevivência média foi de 26,3 meses, sendo significativamente diferente entre os grupos com margens positivas e negativas. Na análise de sobrevivência, a densidade tumoral na TC (HR=0,985, p-value=0,035) e sinais imagiológicos sugestivos de envolvimento perineural extra-pancreático (HR=2,324, p-value=0,048) foram identificados como preditores de sobrevivência.
Conclusão: A TC pré-operatória é uma ferramenta útil na previsão das margens cirúrgicas positivas e sobrevivência, podendo ajudar na identificação de doentes com tumores ressecáveis com pior prognóstico que possam beneficiar de outras estratégias terapêuticas.

Palavras-chave

Pâncreas; Análise de sobrevivência; Tomografia computorizada.

Introduction

Pancreatic cancer is a major cause of cancer related death, both in men and women.[1,2] Pancreatic ductal adenocarcinoma (PDAC) corresponds to 80% of pancreatic cancer cases, followed by neuroendocrine tumors.[1] PDAC has a survival rate of only 5% in 5 years,[3] as in 80% of patients, at diagnosis, the disease is already locally advanced or with metastases,[4,5] invalidating the hypothesis of a surgical resection, the only potentially curative treatment.[6]

For the diagnosis and staging of PDAC, computed tomography (CT) is the preferred imaging modality.[7] As a rule, the pancreatic tumor is visible on CT as a hypovascular mass or nodule, when compared to the normal parenchyma.[8]

Currently, the most accepted staging rating for the PDAC is that of the National Comprehensive Cancer Network, which is based on the TNM[9] system. In addition, tumors are divided into unresectable, resectable and borderline tumors, according to the presence/ absence of metastases and vascular invasion, which conditions the therapeutic approach.[3,10]

Traditionally, the first therapeutic option for patients with resectable tumors was upfront surgical resection with adjuvant chemotherapy. Similarly, patients classified as borderline were often treated with surgery, depending on the experience of the center and occasionally resorting; to more extensive surgical resections.[5] However, there is an increasing tendency for neoadjuvant chemotherapy or chemoradiotherapy prior to surgery, particularly in tumors classified as borderline. Nevertheless, it is currently unclear which of these patients will benefit most from this approach.[3] Advances in the field of Radiology have allowed a better diagnosis and staging of PDAC and, thus, a better selection of patients with resectable disease who benefit from surgery.[11]

This study aims to evaluate the value of preoperative CT in predicting the involvement of surgical margins and to identify clinical and/or imaging characteristics that predict survival in patients with pancreatic ductal adenocarcinoma.

Method

Retrospective study approved by the Health Ethics Committee of Centro Hospitalar Universitário do Porto. The study focused on the population of patients who underwent resection of pancreatic ductal adenocarcinoma between January 1st 2010 and June 30th 2019. All patients with tumors considered to be resectable/ borderline by multidisciplinary assessment and with an anatomopathological diagnosis of pancreatic ductal adenocarcinoma were included. Cases in which the preoperative CT was not available for consultation, had technical limitations or the images were of poor quality were excluded. Also excluded were all cases in which there was absence of follow-up or the patient underwent neoadjuvant therapy.

Clinical data

The following variables of interest were recorded for each individual: gender, age at diagnosis, preoperative CA 19.9 analytical value, type of surgical resection performed, AJCC stage, status of the surgical margin (R0, R1 or R2), time interval between diagnosis and surgery and survival (defined as the time between the date of surgery and the date of death). Deaths were updated on November 19th 2019.

R0 corresponds to a negative surgical margin. R1 represents the presence of tumor cells ≤ 1 mm of the surgical margin. R2 denotes macroscopic involvement of the margin. R1 and R2 were classified as positive surgical margins.[10]

Imaging data

For all 62 patients, CT images were reviewed by the same radiologist in the Picture Archiving and Communication System. The examinations were performed on 16 or 64-cut CT equipment, with some equipment variability as some tests were performed outside the institution.

In order to collect relevant imaging data in a systematic way, a structured imaging report was used, adapted from the report resulting from the consensus between the Society of Abdominal Radiology and the American Pancreatic Association.[9,12,13] This report has been simplified and other imaging features with prognostic value identified in the literature were added.

Thus, the following imaging characteristics were evaluated: location and size of the tumor, average density value and ratio between the tumor mass and normal pancreatic tissue, signs of metastasis, invasion of the lymph nodes; vascular contact, involvement of the retroperitoneal margin, duodenal invasion and perineural involvement (extrapancreatic).

The size of the lesion used in the study models was taken from CT images using the highest measurement value (in centimeters) obtained in one of the three orthogonal planes. The tumor density was calculated in Hounsfield units (HU) in the portal phase, using a circular region of interest (ROI), located on the tumor mass. For the calculation of the referred ratio, a ROI was also placed on the normal pancreatic tissue. Metastasis was considered positive when there were metastatic liver lesions or peritoneal carcinomatosis on CT. The invasion of lymph nodes was considered by dimensional criteria (short axis greater than 10mm) or the presence of central necrosis. Vascular contact was considered positive when there was contact with SMA, SMV or PV, regardless of the degree of involvement. The involvement of the retroperitoneal margin was considered when there was a densification of the fat layers of the retroperitoneum adjacent to the pancreatic tissue. The duodenal invasion was considered to be present on CT when the tumor tissue had continuity with the wall of the duodenum, being this tumor infiltrate of a similar density to that of the primary tumor. Extra-pancreatic perineural involvement was considered when there was invasion of small peri-pancreatic vessels at CT arterial phase.

Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS)®, version 25.0. A descriptive analysis of the variables of interest was carried out. The association among qualitative variables was tested with the Chi-square test. The phi coefficient (Φ) was used as a measure of the effect magnitude, considering a low effect for values between 0.10-0.30; an average effect for values of 0.30-0.50; and high effect for values equal to or greater than 0.50 (14). Regarding the quantitative variables, the groups were compared with the Mann-Whitney test.

A predictive model of surgical margins was created, using binary logistic regression.

For the survival analysis, the Kaplan-Meier method and the Log-Rank test were used. After a univariate analysis, significant prognostic factors were included in a Cox regression model. For all tests, the results were considered statistically significant at $p \leq 0.05$.

Results

In this study, 62 patients, 30 men and 32 women, between 37 and 85 years of age (median 69 years, Range: 62-76) were analyzed. The median tumor size on preoperative

CT is 3.0 cm (Range: 2.2-3.8). The mean follow-up time was 20.5 ± 23.7 (0.2-114.9) months. During the time of the study, 48 patients died, corresponding to 77.4% of the cases. The 90-day postoperative mortality rate is 8.1%. Of the 62 surgical interventions, 4 of them with vascular resection, 35 had R0, 24 had R1 and 3 had R2 margins.

The clinicopathological (Table 1) and imaging (Table 2) characteristics of the patients were summarized, grouped according to the result of pancreatic tumor resection (negative versus positive surgical margins).

In patients with positive surgical margins, there was vascular contact on preoperative CT in 20 (74.1%) patients and involvement of the retroperitoneal margin in 18 (66.7%). In the 35 patients where surgical margins were negative, 10 (28.6%) had vascular contact on CT and 12 (34.3%) patients had signs of involvement of the retroperitoneal margin.

Predictive model of surgical margins

A statistically significant association was found between vascular contact and positive surgical margins ($\chi 2$ (1, n = 62) = 12.636, p = 0.001), being classified as a medium effect association (Φ = 0.451, p = 0.001). The association between involvement of the retroperitoneal margin on CT and positive surgical margins is also statistically significant ($\chi 2$ (1, n = 62) = 6.399, p = 0.011), being classified as a medium effect association (Φ = 0.321, p = 0.011). Regarding the quantitative variables, the differences between the two groups were tested, being statistically significant only regarding size (U = 2.93; p = 0.011; r = 0.32).

Based on the previous results, the impact of the vascular contact, retroperitoneal involvement and size variables on the positive surgical margins result were tested.

As shown on Table 3, only one of the variables was considered statistically significant in the model: vascular

Table 1 – Clinicopathological characteristics of the 62 patients with pancreatic ductal adenocarcinoma, who underwent surgical resection between January 1, 2010 and June 30, 2019 and were included in the study. The groups were divided according to the status of the surgical resection (negative versus positive surgical margins).

Patient characteristics	Negative surgical margins N=35	Positive surgical margins N=27
Gender Male, n (%) Female, n (%)	 14 (40.0) 21 (60.0)	 16 (59.3) 11 (40.7)
Age (in years)	69 (Range: 63-77)	70 (Range: 60-76)
Analytical values CA 19.9 (U/mL) Not available CEA (ng/mL) Not available	 114,8 (Range: 26.8-360.4) 2 3,1 (Range: 1.4-4.2) 3	 167,9 (Range: 42.5-1372.5) 5 3,4 (Range: 2.3-5.3) 7
Type of surgery Cephalic duodenum pancreatectomy, n (%) Distal pancreatectomy, n (%)	 30 (85.7) 5 (14.3)	 24 (88.9) 3 (11.1)
Time between CT and surgery (days)	10 (Range: 6-27)	10 (Range: 5-21)
Unless otherwise indicated, values in parentheses are percentages.		

Table 2 – Imaging characteristics of preoperative CTs of patients undergoing surgical resection for pancreatic ductal adenocarcinoma. The groups were divided according to the status of the surgical resection (negative versus positive surgical margins).

Patient characteristics	Negative surgical margins N=35	Positive surgical margins N=27
Tumor location Head Head and body Body Tail	 27 (77.1) 1 (2.9) 5 (14.3) 2 (5.7)	 23 (85.2) 0 2 (7.4) 2 (7.4)
Size (cm)	2,5 (Range: 1.9-3.2)	3,3 (Range: 2.5-4.0)
Stage* IA IB IIA IIB III IV	 3 (8.6) 8(22.9) 6 (17.1) 10 (28.6) 6 (17.1) 2 (5.7)	 1 (3.7) 5(18.5) 2 (7.4) 12 (44.5) 5 (18.5) 2 (7.4)
Tumor density (UH)	60.0(Range: 40.0-72.0)	51.0 (Range: 30.0-66.0)
Tumor density/pancreatic density ratio	0.59 (Range: 0.43-0.76)	0.50 (Range: 0.41-0.62)
Vascular contact	10 (28.6)	20 (74.1)
Involvement of the retroperitoneal margin	10 (28.6)	18 (66.7)
Extra-pancreatic peri-neural involvement	4 (11.4)	6 (22.2)
Duodenal invasion	13 (57.1)	12 (44.4)
Presence of metastases	3 (8.6)	1 (3.7)
Lymphatic invasion	18 (51.4)	16 (59.3)
Unless otherwise indicated, values in parentheses are percentages. *According to AJCC 8th edition.		

Table 3 – Predictive model of positive surgical margins in patients with pancreatic ductal adenocarcinoma, undergoing surgical resection.

Variable	p-value	Exp(B)	95% CI for Exp (B)
Vascular contact	0.008	5.207	1.533-17.687
Extra-pancreatic retroperitoneal involvement	0.068	2.997	0.922-9.740
Size (cm)	0.317	1.398	0.726-2.691

contact. Thus, patients with visualized vascular contact on preoperative CT are more likely to have positive margins on tumor resection.

Survival analysis

An analysis of survival of the population being studied was performed, obtaining an average survival of 26.3 ± 4.6 months. The 5-year survival rate is 6.5%. The survival of the 2 groups of patients under study was also assessed (Fig. 1). Patients with negative surgical margins had an average survival of 32.9 (95% CI: 19.2-46.7) months, while patients with positive surgical margins had an average survival of 16.5 (95 % CI: 9.3-711) months.

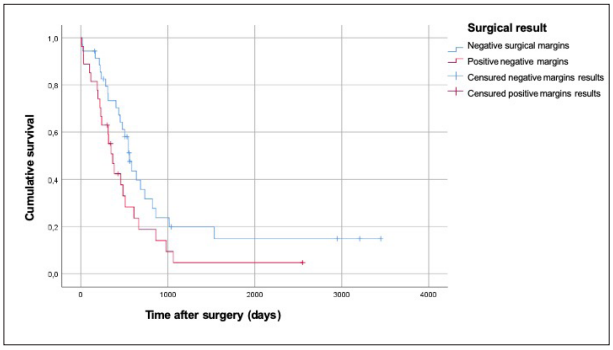

Figure 1 – Kaplan-Meier survival curve of the two groups under study: patients with pancreatic ductal adenocarcinoma who underwent surgical resection, separated according to the surgical result (positive versus negative surgical margins). The overall mean survival was 26.3 ± 4.6 months. Patients with negative surgical margins had an average survival of 32.9 (95% CI: 19.2-46.7) months and, in cases where the surgical margins were positive, the average survival was 16.5 (95% CI: 9.3-711) months.

Predictive model of survival

A predictive survival model was created to assess the impact of the variables under study on the survival of patients with pancreatic ductal adenocarcinoma. The choice of predictors to be included in the model was based on a univariate analysis, selecting the variables: tumor density (p = 0.032) and extra-pancreatic perineural involvement (p = 0.029). Based on the literature15, the variables tumor size and presence of metastases were also included in the model. As shown in Table 4, the variables tumor density and extra-pancreatic perineural involvement were considered statistically significant in the model.

Table 4 – Predictive model of survival in patients with pancreatic ductal adenocarcinoma, undergoing surgical resection, considering the preoperative CT imaging data.

Variable	p-value	HR	95% CI for HR
Tumor density (UH)	0.035	0.985	0.972-0.999
Extra-pancreatic perineural involvement	0.048	2.324	0.186-0.993
Metastases	0.570	1.383	0.237-2.209
Size (cm)	0.273	0.835	0.605-1.152

For tumor density, the hazard ratio is 0.985 (p = 0.035; 95% CI: 0.972-0.999), so the higher tumor density value is a predictor of greater survival. (Fig. 2 and 3).

As for extra-pancreatic perineural involvement, the hazard ratio is 2.324 (p = 0.048; 95% CI: 0.186-0.993), so patients with extra-pancreatic perineural involvement on CT will have lower survival outcomes.

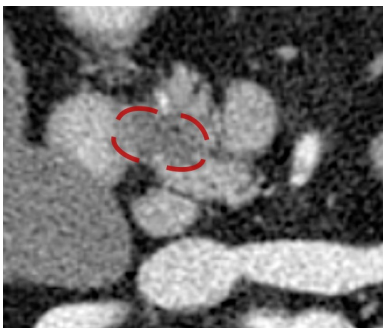

Figure 2 – 77-year-old male patient with pancreatic ductal adenocarcinoma (pT3N1R1) and short survival time after surgery (7 months). CT image shows pancreatic neoplasia with low tumor density.

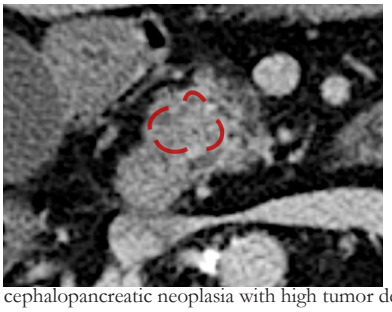

Figure 3 – 81-year-old woman with ductal adenocarcinoma of the pancreas (pT2N0R0), with a long survival time after surgery, currently alive and undergoing clinical follow-up (31 months of follow-up). Axial CT scan in the venous phase shows cephalopancreatic neoplasia with high tumor density, practically isodense in relation to the rest of the pancreatic parenchyma.

Discussion

CT has an essential role in the management of patients with pancreatic ductal adenocarcinoma, allowing their staging and helping to classify patients according to their resectability. However, there is significant variability in the perception of resectability of the tumor[16] and an increasing trend in the use of neoadjuvant therapy, these aspects are changing the way that imaging data are used to optimize the therapeutic strategy decided for each patient. Thus, it is intended that CT imaging data may also help to stratify patients according to their degree of probability of obtaining positive surgical margins, so that patients with greater probability can be considered for neoadjuvant therapy.[3]

According to previous studies, the percentage of R1 resections can vary between 20 to 80%.[15,17] In the present study, 43.5% of the cases submitted to surgery had positive surgical margins, and this definition includes not only R1 but also R2 resections. It should also be noted that, in this study, all patients undergoing surgery as first-line treatment were considered, including some patients initially classified as borderline, who tend to be more likely to have positive margins. In addition, the definition of borderline tumors has been changing over time, and is also somewhat dependent on the experience of different centers.[5]

The presence of signs of vascular contact on CT was a predictor of positive surgical margins, both in univariate and multivariate analysis. The degree of involvement of the vessels and the nature of the affected vessel (arterial or

venous) is extremely important in assessing the resectability of the lesion, according to the criteria defined by the NCCN.[7] This data was also identified in a recent study that shows the involvement of the portomesenteric vein as a predictor of the involvement of the margins, together with the size of the lesions.[10] In our study, vascular contact was considered positive when there was contact with SMA, SMV or PV, regardless of the degree of involvement. Thus, the importance of vascular contact is reinforced in the assessment of the probability of obtaining negative surgical margins, regardless of the classification system used.[18] Also noteworthy are some cases with venous involvement submitted to vascular resection with negative surgical margins, an aspect that should be considered in future studies, as the percentage of patients undergoing this type of resections increases. Despite this, some questions remain open regarding the benefit of this type of surgery as a first-line treatment. Stricter guidelines, namely those of the American Society of Clinical Oncology, do not recommend surgery in patients with venous contact of any degree.[19]

As for retroperitoneal involvement, several studies have demonstrated that it is a relevant predictor of positive surgical margins.[20] In the univariate analysis, retroperitoneal involvement was associated to positive surgical margins, which is explained by the anatomical relationship close to the retroperitoneal surface with the superior mesenteric vessels.[21]

With regard to the lymph nodes, there was no association between their invasion and the surgical margins, nor was it proven to be an indicator of low survival, although this is expected.[21] These results are most likely due to the low acuity of CT for the detection of lymph node metastases.[3]

CA 19.9 is established as a marker of prognosis and resectability.[7] However, no statistically significant differences were found in the value of CA 19.9 or CEA in the two groups, which can be justified by the significant number of patients in which these values were not available (11.3% in the case of CA 19.9). This, despite allowing comparison between the two groups, ended up limiting the inclusion of the value of CA 19.9 in the predictive model of survival.

The 5-year survival rate was 6.5%, which is in agreement with the available literature in which survival in PDAC patients submitted to surgery appears, as a rule, to be less than 10%. For survival analysis, it is essential to mention not only the inclusion of tumors classified as borderline, but also the exclusion of patients with loss of follow-up, which could alter the percentage of survival.[22] Survival was significantly different between the two study groups, where the group with negative margins had an average survival 16.4 months higher than the group with positive margins. This result, despite some controversy surrounding the subject,[15] reinforces the data revealed by several studies that demonstrate that positive surgical margins are an important indicator of poor prognosis.[26-29]

Even so, and as the main objective of this study is related to the assessment of preoperative prognostic markers, the variables studied were also assessed for their influence on patient survival, which is the most important endpoint in the prognostic assessment. Currently, most prognostic markers in these patients include only postoperative findings, including surgical or anatomopathological variables.[24]

In Cox regression, it was concluded that the presence of signs suggesting extra-pancreatic perineural invasion on CT is a predictor of lower survival, corroborating previous studies.[6,25] As for tumor density, a tumor with a higher density value predicts greater survival, attesting results found in other studies regarding isodense tumors, justified by the less aggressive biology of these tumors.[24]

This study, however, has a number of limitations. On the one hand, it includes a low number of patients, who are spread over different stages and different locations within the pancreas. On the other hand, patients were studied for a relatively long period and from a center with a significant volume of hepato-bilio-pancreatic surgery.

The study is retrospective, which also constitutes a difficulty limiting the collection of some important variables. However, this limitation was overcome by the fact that several imaging parameters were collected after reviewing the images and using a structured imaging report. Another limitation to be taken into account is the fact that intra and inter-observer variability for imaging variables has not been assessed, which may be particularly relevant considering the variability found in the assessment of resectability by different radiologists.[16]

It should also be noted that the adjuvant therapies were not considered in this study, which may also have influenced the patients' survival.

Conclusion

Preoperative CT has an established role in deciding the resectability of patients with pancreatic adenocarcinoma. It is also a useful tool in the identification of patients with potentially curable neoplasia with a worse prognosis after surgery, allowing the recognition of patients who are more likely to obtain positive surgical margins and lower survival. Considering the increasing use of neoadjuvant therapy in this context, CT can play an essential role in identifying patients who benefit from this therapeutic strategy.

This study demonstrates that signs of vascular contact are particularly important in predicting surgical margins and that some recently explored imaging data, such as signs suggestive of extra-pancreatic perineural invasion or the value of tumor density, may be crucial to predict the survival of patients. Thus, a detailed description of preoperative CT becomes increasingly urgent. In addition to assessing the resectability of the lesion, it is pertinent to consider the inclusion of other relevant data in the structured reports, even though these need further prospective validation that should be put in motion.

Ethical disclosures / Divulgações Éticas

Conflicts of interest: The authors have no conflicts of interest to declare.

Conflitos de interesse: Os autores declaram não possuir conflitos de interesse.

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Confidentiality of data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Confidencialidade dos dados: Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação dos dados de doentes.

Protection of human and animal subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).
Protecção de pessoas e animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial.

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