



HAL
open science

Predicting pathologic venous invasion before pancreatectomy with venous resection: When does radiology tell the truth?

Pietro Addeo, Jeanne Charton, Pierre de Marini, Arnaud Trog, Vincent
Noblet, Pierre de Mathelin, Gerlinde Averous, Philippe Bachellier

► To cite this version:

Pietro Addeo, Jeanne Charton, Pierre de Marini, Arnaud Trog, Vincent Noblet, et al.. Predicting pathologic venous invasion before pancreatectomy with venous resection: When does radiology tell the truth?. 17ème congrès de chirurgie digestive et hépato-bilio-pancréatique (SFCD-ACHBT), Paris, November 24–26, 2021, Nov 2021, Paris, France. 10.1016/j.surg.2021.12.012 . hal-03594851

HAL Id: hal-03594851

<https://hal.science/hal-03594851>

Submitted on 22 Jul 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

1 **Title Page**
2 **Predicting pathologic venous invasion before pancreatectomy with venous resection: when**
3 **does radiology tell the truth?**

4 Pietro Addeo^{1,2}, Jeanne Charton³, Pierre de Marini³, Arnaud Trog², Vincent Noblet², Pierre De
5 Mathelin¹, Gerlinde Avérous⁴, Philippe Bachellier¹

6 1. Hepato-Pancreato-Biliary Surgery and Liver transplantation, Pôle des Pathologies Digestives,
7 Hépatiques et de la Transplantation, Hôpital de Hautepierre-Hôpitaux Universitaires de Strasbourg,
8 Université de Strasbourg, Strasbourg, France

9 2. ICube, Université de Strasbourg, CNRS UMR 7357, Illkirch, France.

10 3. Department of Radiology, Hôpital de Hautepierre University of Strasbourg, Strasbourg, France.

11 4. Department of Pathology, University of Strasbourg, Hôpital de Hautepierre-Hôpitaux Universitaires
12 de Strasbourg, Université de Strasbourg, Strasbourg, France

13 **Type of study:** Original Study

14 **Reprints:** Reprints will not available from the authors

15 Presented to the 17ème congrès de chirurgie digestive et hépato-bilio-pancréatique (SFCD-ACHBT), Paris 24-26
16 november 2021

17 **Correspondence to:**

18 **Pietro Addeo MD, MPH, PhD, FACS**

19 Hepato-Pancreato-Biliary Surgery and Liver transplantation, Pôle des Pathologies Digestives, Hépatiques et de la
20 Transplantation, Hôpital de Hautepierre-Hôpitaux Universitaires de Strasbourg, Université de Strasbourg, Strasbourg,
21 France 1, Avenue Moliere, 67098, Strasbourg **Email:** pietrofrancesco.addeo@chru-strasbourg.fr **Telephone number:**
22 0033-0388127265; **Fax Number:** 0033-0388127286

23 **Running Head:** Venous invasion in pancreatic cancer
24
25
26
27
28

ABSTRACT

29

30 *Background:* Patients factors in addition to radiological characteristics could predict the presence of

31 pathologic venous invasion (PVI) in patients undergoing pancreatectomy with venous resection.

32 *Methods:* We tested the predictive value of six radiological classification methods for predicting

33 PVI: the Nakao, Ishikawa, MD Anderson, Lu, Raptopoulos and NCCN methods on a cohort of 198

34 pancreatectomies (160 pancreaticoduodenectomies and 38 total pancreatectomies) with venous

35 resection for pancreatic adenocarcinomas. Radiological and clinical factors determining PVI were

36 identified by multivariable logistic analysis.

37 *Results:* PVI was detected in 124 patients (63.2%). The multivariable logistic regression analysis

38 identified LU classification (OR=1.77, 95CI%=1.34-2.35; $p<0.0001$), elevated serum CA19-9

39 values (OR=1.97, 95CI%=1.00-3.90; $p=0.04$), and preoperative neoadjuvant chemotherapy

40 (OR=0.38, 95CI%=0.18-0.79; $p=0.009$) as independent factors associated with PVI. Radiological

41 tumor-vessel contact greater than 50% of the circumference or venous wall deformity were

42 associated with a significantly higher rate of pathological venous invasion (80% vs. 52%;

43 $p<0.0001$), deeper(media-intima) venous invasion (47% vs. 25%; $p<0.0001$), R1 resection (58% vs.

44 41%; $p=0.03$), higher transfusions (84% vs.66%; $p=0.005$) and arterial resection rates (43% vs.

45 27%; $p<0.0001$). Tumor-vein circumference contact of $> 50\%$ and/or venous wall deformity was

46 still associated with significantly higher rates of PVI, regardless of whether neoadjuvant

47 chemotherapy was used or not and CA19-9 normalized or not under preoperative treatment.

48 *Conclusions:* Preoperative radiological detection of tumor-vein circumference contact $>50\%$ and/or

49 venous wall deformity is associated with up to 80% of cases of pathological venous invasion. The

50 combination of radiologic features with biological (CA19-9) and clinical (presence of preoperative

51 chemotherapy) factors could better refine preoperatively the need for venous resection.

52

53

Introduction

54
55 Direct invasion of the portal venous system is a common finding in pancreatic cancer. Venous
56 invasion is not a contraindication for surgical resection in selected patients who are being treated
57 with neoadjuvant chemotherapy if a radical resection could be reasonably expected.^{1,2} After
58 resection, pathological venous invasion represents a poor prognostic factor, particularly in the
59 presence of tumoral invasion up to the venous intima.^{3,4} In the era of modern pancreatic surgery,
60 planning for the need for venous resection preoperatively helps to anticipate surgical difficulties and
61 to choose the type of venous reconstruction.⁵ Preoperatively planned venous resections have been
62 associated with clearer resection margins than unplanned venous resections.⁶ Moreover, attempting
63 to separate tumors from the venous axis in presence of pathologic invasion carries the risk of
64 opening the tumoral plane with the potential for tumor spillage.

65 Venous invasion can be identified and graded based on preoperative computed tomography
66 (CT) scan classifications. Several radiological classifications have been described based on the type
67 of tumor-venous axis contact.⁷⁻¹¹ The extent of longitudinal and circumferential contact between the
68 tumor and the venous axis, the type of venous edge deformities, and the presence of venous
69 thrombosis have been correlated with pathological venous invasion.⁷⁻¹¹ However, the predictive
70 values of these classifications in foreseeing pathological venous invasion remain variable,
71 particularly after neoadjuvant treatment.^{12,13}

72 There is a lack of general agreement on which radiological classification should be used to
73 anticipate venous resection, and the classifications used vary between institutions and countries. In
74 addition, clinical and biological factors predicting pathological venous invasion have been scarcely
75 correlated with radiological aspects.¹⁴ The National Comprehensive Cancer Network (NCCN)
76 guidelines use the cut-off of less of more 180 degrees contact between the tumor and the vein
77 coupled with vein deformations to define the resectability status for pancreatic tumors but
78 correlation with pathology are not extensively reported¹⁵. Hence, we aimed to evaluate the

79 following in a large cohort of pancreatectomies with venous resection: 1) the predictive value of
80 several available radiological classifications for pathological venous invasion 2) whether clinical
81 and biological factors are helpful in anticipating pathological venous invasion.

82 **Methods**

83 *Data selection*

84 This retrospective cohort study was conducted at the Hepato-Pancreato-Biliary Surgery and Liver
85 Transplantation Center of the University of Strasbourg in France under IRB approval. Data were
86 collected and retrospectively analyzed for all patients who underwent a pancreaticoduodenectomy
87 (PD) or a total pancreatectomy (TP) with venous resection for pancreatic ductal adenocarcinomas
88 between January 1, 2010, and December 31, 2019.

89 *Data collection and study definitions*

90 The collected data included demographics, preoperative imaging data, and operative variables such
91 as the operation time, transfusion requirement, and 90-day morbidity and mortality rates. Details
92 were collected on the type of venous resection, the resected venous segment, and the type of venous
93 reconstruction performed. Pathological data included tumor characteristics and resection margin
94 assessment including the resected venous edges. Preoperatively several biologic tests were recorded
95 including serum value of CA19-9 (normal values < 37U/ml). Morbidity was graded according to the
96 Dindo-Clavien classification with major morbidity including complications classified as IIIA or
97 above.¹⁶ Pancreatic-specific complications were all defined according the recommendation of the
98 International Study group for pancreatic surgery, including pancreatic fistula, delayed gastric
99 emptying, and postpancreatectomy haemorrhage.¹⁷⁻¹⁹

100 PDs with venous resection were performed according to a previously described standardized
101 technique as en-bloc procedures without the need for venous graft interposition.⁵ The classes of
102 venous involvement included the following: 1) Type 1: resection of the portal vein, 2) Type 2:
103 resection of the splenomesentericoportal (SMP) confluence, and 3) Type 3: resection of the superior

104 mesenteric vein or its branches.²⁰ Pancreaticogastrostomy was our preferred reconstruction
105 method.²¹ In cases of venous resection, no systemic anticoagulation was given intraoperatively, and
106 patients were placed on low-weight subcutaneous heparin during the postoperative period until day
107 30 postoperatively at prophylactic dosage, but no long-term anticoagulation was given. In cases of
108 synchronous arterial resection,²² long-term antiaggregant treatment (aspirin at 100 mg/day) was
109 given beginning from the first postoperative day until 3 months.

110

111 ***Radiological and pathological data***

112 In all cases, the preoperative evaluation of patients included multidetector contrast-enhanced
113 CT of the abdomen. Only patients having an available CT-scan performed within six weeks before
114 resection were selected. For patients undergoing neoadjuvant treatment only preoperative CT scan
115 were analyzed. Two senior radiologists who are experts in pancreatic disease (JC and PDM) and
116 were blinded to the results of pathology retrospectively reviewed all preoperative CT scans.
117 Assessment of venous invasion were evaluated on dedicated console after having reconstructed
118 images of CT scan of venous phases and/or on maximum intensity projection (MIP)²³. The
119 radiologists classified venous involvement according to the Nakao⁸, Ishikawa⁷, MD Anderson¹⁰,
120 Raptopoulos⁹, and LU¹¹ methods.

121 The Nakao⁸ classification includes no venous contact (A), unilateral vein narrowing (B),
122 bilateral vein narrowing (C), and venous thrombosis with cavernoma development (D). The
123 Ishikawa⁷ classification includes normal (1), smooth shift (2), unilateral narrowing (3), bilateral
124 narrowing (4), and bilateral narrowing with collateral vein (5). The MD Anderson¹⁰ classification
125 includes no tumor-venous interface (A), tumor-venous interface $\leq 180^\circ$ (B), tumor-venous interface
126 $> 180^\circ$ (C), and venous occlusion (D). The Raptopoulos⁹ classification includes normal (0), loss of
127 fat between the tumor and vessel (1), flattening or slight irregularity of one side of the vessel (2),
128 encased vessel with tumor extending around at least two sides altering its contour and producing

129 concentric narrowing the lumen (3), and occluded vessels (4). Finally, the LU¹¹ classification
130 includes <25% of vein circumference contiguous with tumor (1), 25-50% of vein circumference
131 contiguous with the tumor (2), 50-75% of vein circumference contiguous with the tumor (3), and
132 >75% of vein circumference contiguous with the tumor or any focal narrowing regardless of the
133 degree of contiguity (4).

134 Finally, patients were divided into the two class according to the NCCN guidelines: 1) type
135 1 less or equal to 50% vessels circumference contact without deformity; type 2) more than 50%
136 tumor contact and/or presence of venous deformity¹⁵. All resected specimens were analyzed
137 according to a standardized pathological protocol using multicolor inking of the resection margins
138 as reported previously.²⁴ The resection was defined as R1 based on the presence of tumor cells
139 within 1.0 mm of any of the three margins or on the margins of the resected vein. The same
140 pathologist (GA) assessed the pathological involvement of the resected vein and was blinded to the
141 results of the radiologists. The degree of pathological venous involvement (no invasion, adventitia,
142 media, and intima) and length of resected veins were recorded as well.³

143 ***Statistical analysis***

144 The results for continuous data were expressed as the mean \pm standard deviation or the
145 median and range as appropriate, whereas categorical variables are presented as numbers and
146 percentages. Differences between groups were assessed by the chi-squared or Fisher's exact test for
147 categorical variables as appropriate. In the case of continuous variables, the Wilcoxon rank sum test
148 or the student *t* test was used as appropriate. Univariate logistic regression analysis was conducted
149 for variables associated with the presence of pathological venous invasion. Only the variables with
150 $p < 0.20$ were included in the multivariable analysis. A backward Wald method was used to select
151 the most relevant variables for the definitive multivariable model. The level of significance was set
152 at 0.05, and two-sided *P* values were computed. Statistical analyses were carried out using SAS
153 software (release 9.4, SAS institute, Cary, NC).

154 **Results**

155 *Operative procedures and postoperative outcomes*

156 During the study period, 300 consecutive pancreatectomies (252 PDs and 48 TPs) with
157 venous resection were performed at our institution. Only 198 pancreatectomies (160 PDs and 38
158 TPs) with a final diagnosis of pancreatic adenocarcinomas and available clinical, radiological, and
159 pathological data met the inclusion criteria. Reasons for excluding the remaining cases were
160 pancreatic resection performed for diseases other ductal adenocarcinomas (n=50) and a lack of
161 preoperative radiological data performed at our institution and available for analysis at the time of
162 this study (n=52). The median age was 64 years (range 32-86 years) with a gender ratio of 1.38
163 (115 men and 83 women).

164 Preoperative chemotherapy was administered to 122 patients (61.6%), mostly according to
165 the FOLFIRINOX protocol (n=100, 81.9%) with a median number of 9 preoperative cycles (range
166 2-24 cycles). Neoadjuvant chemotherapy was statistically more common after the year 2016 (71.1%
167 vs. 51.1%; p=0.005). Elevated CA19-9 was present in 166 patients (61.5%) with a median of 63.5
168 U/mL (mean 426 U/mL, range 1-2354 U/mL). Resected venous segments included the Spleno-
169 Mesenterico-Portal (SMP) venous confluence (n=150, 75.7%), the superior mesenteric vein (SMV)
170 (n=41, 20.7%), and the portal vein (PV) (n=7, 3.54%). Seventy patients had an associated arterial
171 resection (35.3%).

172 In cases of SMP confluence resection (n=150), the management of the splenic vein (SV)
173 stump included: 1) ligation with preservation of the natural confluence between the inferior
174 mesenteric vein (IMV) and the SV (n=37); 2) anastomosis between the IMV and the SV (n=11); 3)
175 a splenorenal end-to-side anastomosis (n=67); and 4) reimplantation of the SV into the SMV-PV
176 anastomosis (n=3) (32 patients had a total pancreatectomy). The median operation time was 540
177 minutes (median 345-1145 minutes) with a transfusion rate of 73.2% (n=145). The overall 90-day
178 mortality and morbidity rates were 4.55% (n=9) and 42.9 % (n=85), respectively, and the rate of

179 major morbidity (Clavien grades 3 A/B, 4, 5) was 34%. The overall reoperation rate was 7.5%
180 (n=15).

181 Overall, a median of 45 lymph nodes (range 15 -116 nodes) were harvested and analyzed.
182 Positive resected lymph nodes were present in 156 patients (79%) and the median number of
183 positive lymph nodes was 3 nodes (range 1-50 nodes). Pathological venous invasion was detected in
184 124 patients (63.2%). The depth of venous invasion was at the level of the adventitia (n=46), media
185 (n=33), intima (n=45), or not specified (n=2). Tumoral thrombosis was present in five patients. The
186 overall rate of R0 resection was 51.2% (n=102) according to the 1-mm rule and four patients had
187 positive margin on venous edges. Complete information about postoperative treatment was
188 available for the entire cohort, and 149 patients (75.2%) received adjuvant chemotherapy.

189

190 *Comparison between radiological and pathological venous invasion*

191 As expected, there was a linear increase in the rate of pathological invasion of the venous
192 wall with the different classes of each radiological classification (**Table 1**). Bilateral venous
193 narrowing and venous occlusion had the highest rates of pathological venous invasion (ranging
194 from 78% to 100% according to the different classifications) and the deepest pathological invasions
195 (intima, up to 50%). Multivariable logistic regression analysis (**Table 2**) identified LU classification
196 (OR=1.77, 95CI%=1.34-2.35; p<0.0001), elevated serum CA19-9 (OR=1.97, 95CI%=1.00-3.90;
197 p=0.04) and preoperative neoadjuvant chemotherapy (OR=0.38, 95CI%=0.18-0.79; p=0.009) as
198 independent risk factors associated with the presence of pathological venous invasion. The
199 combination of these three factors was able to predict venous invasion with an area under the curve
200 (AUC) of 0.72. According to the Lu classification, grade 1, grade 2, grade 3, and grade 4 were
201 characterized by pathological venous invasion in 46%, 57%, 100%, and 77% of patients,
202 respectively. When dividing the patient population in the two categories according to NCCN
203 classification (Figure 1 and Table 3), tumor-vessel circumference contact greater than 50% or

204 venous wall deformity was associated with a significantly higher rate of pathological venous
205 invasion (80% vs. 52%; $p<0.0001$), deeper venous invasion (47% vs.25%; $p<0.0001$), R1 resection
206 (58% vs. 41%; $p=0.03$), higher transfusions (84% vs.66%; $p=0.005$) and arterial resection rates (43
207 vs.27; $p<0.0001$) despite lower median serum CA19-9 levels (295 vs. 521; $p<0.0001$), similar
208 lymph nodes positive rates (78% vs.79%) and the higher rate of preoperative use of neoadjuvant
209 chemotherapy (72% vs. 49%; $p=0.006$).

210 Patients undergoing neoadjuvant chemotherapy before venous resection had a significantly
211 lower rate of pathological venous invasion (57 vs. 72%; $p=0.04$), R1 resection rate (40% vs. 61%;
212 $p=0.003$), lymph node involvement rate (73% vs. 88%; $p=0.01$), and number of involved lymph
213 nodes (4.7 ± 6.5 vs. 7.3 ± 86 ; $p=0.01$) compared with those that underwent upfront venous resection.

214 Under neoadjuvant chemotherapy in patients with radiological tumor-vessel circumference
215 contact $\leq 50\%$, 27% (17/63) had normalization of CA19-9 and 54 % (34/63) had reduction $\geq 50\%$ of
216 the preoperative values. In patients with radiological tumor-vessel circumference contact $\geq 50\%$ of
217 the circumference or venous deformity, 27% (16/59) had normalization of CA19-9 and 51 %
218 (30/59) had reduction $\geq 50\%$ of the preoperative values. Interestingly, the use of neoadjuvant
219 chemotherapy was associated with a lower rate of venous invasion only when the degree of
220 radiological tumor-vein circumference involvement was less than 50% (38% vs. 67%; $p=0.001$),
221 while similar venous invasion rates were seen when tumor-vein contact was more than 50% or
222 when venous wall deformity was present (78% vs. 85%; $p=1.00$), despite having similar length of
223 resected veins (26.9 mm vs. 29.8 mm; $p=0.44$). Finally, when considering patients having
224 preoperative chemotherapy and having normal CA19-9 before resection the rate of PVI was
225 statistically higher in presence of radiological tumor-vessel circumference contact greater than 50%
226 or venous wall deformity (78% vs 21%; $p=0.0001$) (**Figure 1**).

227

228

229

230 **Discussion**

231 The present study confirmed that the degree of radiological tumor-vessel circumference
232 involvement predicts pathological venous invasion. Tumor-contact > 50% of the vein
233 circumference and the presence of venous wall deformity were associated with pathological venous
234 invasion in more than 80% of cases. The rate of venous invasion was higher in absence of
235 preoperative chemotherapy and in patients with persistently high CA19-9 values. The combination
236 of radiology features with these biological and clinical factors refines preoperatively the need for
237 venous resection.

238 Preoperative detection of venous invasion is of paramount importance before planning major
239 pancreatic resection. Recent studies suggest that tumor detachment from arterial mesenteric vessels
240 could be an alternative to classical en-bloc arterial resection to reduce the mortality of extended
241 pancreatectomies.²⁵⁻²⁷ In contrast, tumor detachment from the venous wall in the presence of venous
242 invasion can be a source of massive bleeding or tumor spillage. Therefore, venous resection remains
243 the most preferred surgical technique when contact is present.

244 Preoperative prediction of venous involvement based on CT examination has traditionally
245 shown poor accuracy. In the current study, the six radiological classifications examined showed
246 high levels of correlation between radiological aspects and pathology in the presence of venous wall
247 deformity. In fact, bilateral venous wall narrowing and venous occlusion predicted almost 80% of
248 pathological venous invasions, thus confirming previous observations by Nakao et al.⁸ A recent
249 large multicenter study found that in the presence of radiological tumor-vessel contact of less than
250 180 degrees, the rate of pathological venous invasion was only of 36.2% (84 of 232). This suggests
251 that the portal vein should be resected only when needed after surgical exploration.²⁸

252 In the current study, the LU classification¹¹ was identified as the most sensible radiological
253 classification for predicting pathological venous invasion. In contrast to other classifications, Lu et

254 al. consider contact and venous wall deformity separately and regroup patients with contact of more
255 than 75 degrees of the vessel wall and any venous deformity (bilateral or unilateral) in the same
256 class (class 4), which has a venous invasion rate of almost 80% . This probably simplifies previous
257 classifications, which tried to correlate the extent of contact with pathological venous invasion.
258 Extensive contact and venous deformity seldom coexist, which should help explain the high rate of
259 venous invasion found in class 4 of the Lu classification in our study. One of the major
260 shortcomings of the Lu classification is the less simple usage that can result when considering
261 several classes. The NCCN classification, which divides venous involvement according to only 2
262 classes, appears easier to be adopted. In fact, tumor-vein circumference contact > 50% or the
263 presence of venous wall deformity were associated with 80% of pathologic venous invasion even in
264 presence of neoadjuvant therapy. This confirms the high predictive value and the validity of the
265 NCCN guidelines when classifying patients for surgery.

266 The low sensitivity value of CT scans in predicting pathological venous invasion seems
267 more apparent after neoadjuvant treatment because of the dense fibrotic stroma of pancreatic
268 adenocarcinomas.^{12,13,29} In fact, the persistence of perivascular fibrotic tissue around the vein could
269 be associated with a major response of cancerous cells, even with minor changes of the radiological
270 findings. In the current study, the presence of neoadjuvant chemotherapy was found as an
271 independent factor associated with a lesser rate of pathologic venous invasion. Nevertheless, the
272 rate of venous invasion was significantly lower in presence of neoadjuvant chemotherapy only
273 when the tumor-vessel contact was less than 50% of the circumference but similar rates of
274 pathological venous invasion were seen when tumor-vessel contact was more than 50% as already
275 noticed in a previous study.³⁰ This was because we only studied preoperative CT scans with the
276 group of patients with tumor-vein contact less than 50% of the circumference there were probably
277 more patients having good response to preoperative treatment.

278 While few radiologic changes are generally seen under neoadjuvant treatment, biological
279 serial assessment of CA19-9 values is emerging as a reliable and low-cost marker of good response
280 to preoperative treatment. CA19-9 normalization or consistent drop ($\geq 50\%$) has been identified as
281 one of the strong prognostic factors after neoadjuvant treatment³¹⁻³³. In the current study elevated
282 CA19-9 was identified as an independent prognostic factor predicting venous invasion and this can
283 potentially guide clinical decision and orient surgical exploration. In our study patients with
284 normalized CA19-9 after neoadjuvant chemotherapy showed higher PVI rate in presence of
285 venous contact $> 50\%$ or venous deformity (78%). On the contrary, patients with venous contact less
286 than 50% and normalized CA 19-9 had only 21% of pathological venous invasion. Therefore the
287 normalization of CA19-9 after neoadjuvant chemotherapy in presence of venous contact $< 50\%$
288 could indicate a potential lower need for venous resection preoperatively and the need for careful
289 perioperative exploration to guide operative decision.

290 In our study, preoperative chemotherapy was administered to 62% of patients, and the rate
291 was significantly higher after the year 2016. Patients undergoing resection after neoadjuvant
292 chemotherapy showed improved pathological outcomes in terms of reduced pathological venous
293 invasion, less lymph node involvement, and better margin resection status. This confirms data from
294 a recent systematic review,³⁴ which showed that neoadjuvant treatment was associated with a higher
295 R0 resection rate and less lymph node involvement compared with cases of upfront resection,
296 leading to higher overall survival rates. The recent results of the PREOPANC trial also showed
297 that preoperative radio-chemotherapy in cases of borderline tumors is associated with better margin
298 resection status, less lymph node involvement, and less venous invasion compared with cases of
299 upfront surgery.³⁵

300 While tumor contact $> 50\%$ of the vein diameter is currently considered as a borderline
301 criteria and indication for neoadjuvant chemotherapy, tumor contact $< 50\%$ of the vein diameter
302 continues to be considered as resectable disease.³⁶ Venous invasion represents a poor prognostic

303 factor in resected pancreatic adenocarcinoma associated with inferior recurrence-free and overall
304 survival.^{3,4,37} In the current study, we have shown that in the presence of tumor-vein contact less
305 than 50% of the diameter 52% of patients have pathologic venous invasion. These rates of venous
306 invasion are reduced when neoadjuvant chemotherapy is used (38% vs. 67%; p=0.001), suggesting
307 that even the presence of tumor contact < 50% of the vein diameter could be considered as an
308 indication for neoadjuvant treatment.

309 Patients with tumor contact > 50% of the vein diameter or vein deformity showed similar
310 rates of pathological venous invasion regardless of whether or not neoadjuvant treatment was used
311 (78% vs. 85%; p=1.00). The presence of this extensive contact or venous deformity identified a
312 population of patients who had a rate of pathological venous invasion of 80% and were
313 characterized by other poor pathological prognostic factors (R1 resection, intimal invasion). The
314 presence or persistence of these radiological signs in combination with elevated serum values of
315 CA19-9 at the end of preoperative treatment could orient clinical decisions in planning surgery for
316 patients and evaluating the response to preoperative treatment.

317 This study has several limitations that deserve discussion. First, the retrospective nature and
318 limited size are potential sources of bias. However, the retrospective review by expert radiologists
319 and a dedicated pathologist contributed to increasing the quality of the study. Second, the setting of
320 a specialized tertiary center for pancreatic surgery could have resulted in potential selection bias
321 toward more advanced cases. However, the poor pathological factors associated with venous
322 invasion found in our study are similar to that found in other studies by large-volume centers. Third,
323 the changes of radiological equipment over the years could have led to lower sensitivity for venous
324 invasion in the first year of this study. Review by a specialized radiologist contributed to improving
325 the sensitivity power.

326

327

328 **Conclusions**

329 Preoperative presence of tumor-vein circumference contact more than 50% in radiological findings
330 and venous wall deformity are associated with a rate of 80% of pathological venous invasion
331 despite the use of neoadjuvant chemotherapy. Tumor-vein circumference contact of > 50% of the
332 circumference and/or venous wall deformity were associated with significantly higher rates of PVI,
333 regardless of whether neoadjuvant chemotherapy was used or not and CA19-9 normalized or not.
334 The combination of radiology features with biological (CA19-9) and clinical (presence of
335 preoperative chemotherapy) factors could better refine preoperatively the need for venous resection.

336 **Figure legends**

337 **Figure 1:** Illustration of pathological venous invasion according to the type of venous contact (\leq or
338 $> 50\%$).

339

340

341 **Conflicts of interest/ Disclosure:** the authors have no conflict of interest to disclose

342

343 **Funding/ Financial Support:** No funding.

344

345

346

347

348

349

350

351

352

353 **References**

354

355 1. Delpero JR, Boher JM, Sauvanet A, et al. Pancreatic adenocarcinoma with venous
356 involvement: is up-front synchronous portal-superior mesenteric vein resection still justified?
357 A survey of the Association Francaise de Chirurgie. *Ann Surg Oncol* 2015;22:1874-83.

358 2. Raptis DA, Sanchez-Velazquez P, Machairas N, et al. Defining Benchmark Outcomes
359 for Pancreatoduodenectomy With Portomesenteric Venous Resection. *Ann Surg*
360 2020;272:731-7.

361 3. Addeo P, Velten M, Averous G, et al. Prognostic value of venous invasion in resected
362 T3 pancreatic adenocarcinoma: Depth of invasion matters. *Surgery* 2017;162:264-74.

363 4. Belfiori G, Fiorentini G, Tamburrino D, et al. Vascular resection during
364 pancreatotomy for pancreatic head cancer: A technical issue or a prognostic sign? *Surgery*
365 2020.

366 5. Addeo P, Bachellier P. Pancreaticoduodenectomy with Segmental Venous Resection:
367 a Standardized Technique Avoiding Graft Interposition. *J Gastrointest Surg* 2021.

368 6. Kim PT, Wei AC, Atenafu EG, et al. Planned versus unplanned portal vein resections
369 during pancreaticoduodenectomy for adenocarcinoma. *Br J Surg* 2013;100:1349-56.

370 7. Ishikawa O, Ohigashi H, Imaoka S, et al. Preoperative indications for extended
371 pancreatotomy for locally advanced pancreas cancer involving the portal vein. *Ann Surg*
372 1992;215:231-6.

373 8. Nakao A, Kanzaki A, Fujii T, et al. Correlation between radiographic classification
374 and pathological grade of portal vein wall invasion in pancreatic head cancer. *Ann Surg*
375 2012;255:103-8.

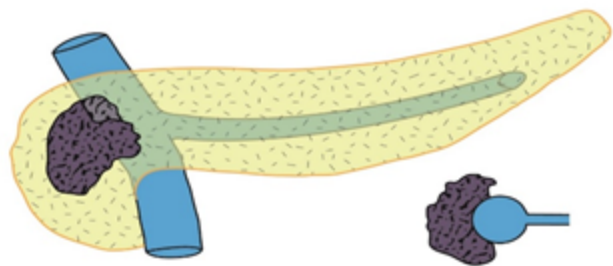
376 9. Raptopoulos V, Steer ML, Sheiman RG, Vrachliotis TG, Gougoutas CA, Movson JS.
377 The use of helical CT and CT angiography to predict vascular involvement from pancreatic
378 cancer: correlation with findings at surgery. *AJR Am J Roentgenol* 1997;168:971-7.

- 379 10. Tran Cao HS, Balachandran A, Wang H, et al. Radiographic tumor-vein interface as a
380 predictor of intraoperative, pathologic, and oncologic outcomes in resectable and borderline
381 resectable pancreatic cancer. *J Gastrointest Surg* 2014;18:269-78; discussion 78.
- 382 11. Lu DS, Reber HA, Krasny RM, Kadell BM, Sayre J. Local staging of pancreatic
383 cancer: criteria for unresectability of major vessels as revealed by pancreatic-phase, thin-
384 section helical CT. *AJR Am J Roentgenol* 1997;168:1439-43.
- 385 12. Cassinotto C, Mouries A, Lafourcade JP, et al. Locally advanced pancreatic
386 adenocarcinoma: reassessment of response with CT after neoadjuvant chemotherapy and
387 radiation therapy. *Radiology* 2014;273:108-16.
- 388 13. Cassinotto C, Sa-Cunha A, Trillaud H. Radiological evaluation of response to
389 neoadjuvant treatment in pancreatic cancer. *Diagn Interv Imaging* 2016;97:1225-32.
- 390 14. Shen YN, Guo CX, Pan Y, et al. Preoperative prediction of peripancreatic vein
391 invasion by pancreatic head cancer. *Cancer Imaging* 2018;18:49.
- 392 15. Oncology NCPGi. Pancreatic Adenocarcinoma Version 2-2021. 2021.
- 393 16. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new
394 proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*
395 2004;240:205-13.
- 396 17. Bassi C, Marchegiani G, Dervenis C, et al. The 2016 update of the International Study
397 Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After.
398 *Surgery* 2017;161:584-91.
- 399 18. Wente MN, Veit JA, Bassi C, et al. Postpancreatectomy hemorrhage (PPH): an
400 International Study Group of Pancreatic Surgery (ISGPS) definition. *Surgery* 2007;142:20-5.
- 401 19. Wente MN, Bassi C, Dervenis C, et al. Delayed gastric emptying (DGE) after
402 pancreatic surgery: a suggested definition by the International Study Group of Pancreatic
403 Surgery (ISGPS). *Surgery* 2007;142:761-8.

- 404 20. Addeo P, De Mathelin P, Averous G, et al. The left splenorenal venous shunt
405 decreases clinical signs of sinistral portal hypertension associated with splenic vein ligation
406 during pancreaticoduodenectomy with venous resection. *Surgery* 2020;168:267-73.
- 407 21. Addeo P, Rosso E, Fuchshuber P, et al. Double purse-string telescoped
408 pancreaticogastrostomy: an expedient, safe, and easy technique. *J Am Coll Surg*
409 2013;216:e27-33.
- 410 22. Bachellier P, Addeo P, Faitot F, Nappo G, Dufour P. Pancreatectomy With Arterial
411 Resection for Pancreatic Adenocarcinoma: How Can It Be Done Safely and With Which
412 Outcomes?: A Single Institution's Experience With 118 Patients. *Ann Surg* 2020;271:932-40.
- 413 23. Al-Hawary MM, Francis IR, Chari ST, et al. Pancreatic ductal adenocarcinoma
414 radiology reporting template: consensus statement of the Society of Abdominal Radiology
415 and the American Pancreatic Association. *Radiology* 2014;270:248-60.
- 416 24. Delpero JR, Bachellier P, Regenet N, et al. Pancreaticoduodenectomy for pancreatic
417 ductal adenocarcinoma: a French multicentre prospective evaluation of resection margins in
418 150 evaluable specimens. *HPB (Oxford)* 2014;16:20-33.
- 419 25. Cai B, Lu Z, Neoptolemos JP, et al. Sub-adventitial divestment technique for resecting
420 artery-involved pancreatic cancer: a retrospective cohort study. *Langenbecks Arch Surg*
421 2021;406:691-701.
- 422 26. Diener MK, Mihaljevic AL, Strobel O, et al. Periarterial divestment in pancreatic
423 cancer surgery. *Surgery* 2021;169:1019-25.
- 424 27. Habib JR, Kinny-Koster B, van Oosten F, et al. Periadventitial dissection of the
425 superior mesenteric artery for locally advanced pancreatic cancer: Surgical planning with the
426 "halo sign" and "string sign". *Surgery* 2021;169:1026-31.

- 427 28. Kishi Y, Nara S, Esaki M, Hiraoka N, Shimada K. Feasibility of resecting the portal
428 vein only when necessary during pancreatoduodenectomy for pancreatic cancer. *BJS Open*
429 2019;3:327-35.
- 430 29. Wagner M, Antunes C, Pietrasz D, et al. CT evaluation after neoadjuvant
431 FOLFIRINOX chemotherapy for borderline and locally advanced pancreatic adenocarcinoma.
432 *Eur Radiol* 2017;27:3104-16.
- 433 30. Chun YS, Milestone BN, Watson JC, et al. Defining venous involvement in borderline
434 resectable pancreatic cancer. *Ann Surg Oncol* 2010;17:2832-8.
- 435 31. Truty MJ, Kendrick ML, Nagorney DM, et al. Factors Predicting Response,
436 Perioperative Outcomes, and Survival Following Total Neoadjuvant Therapy for
437 Borderline/Locally Advanced Pancreatic Cancer. *Ann Surg* 2019.
- 438 32. van Veldhuisen E, Vogel JA, Klompmaker S, et al. Added value of CA19-9 response
439 in predicting resectability of locally advanced pancreatic cancer following induction
440 chemotherapy. *HPB (Oxford)* 2018;20:605-11.
- 441 33. Hackert T, Sachsenmaier M, Hinz U, et al. Locally Advanced Pancreatic Cancer:
442 Neoadjuvant Therapy With Folfirinox Results in Resectability in 60% of the Patients. *Ann*
443 *Surg* 2016;264:457-63.
- 444 34. Versteijne E, Vogel JA, Besselink MG, et al. Meta-analysis comparing upfront surgery
445 with neoadjuvant treatment in patients with resectable or borderline resectable pancreatic
446 cancer. *Br J Surg* 2018;105:946-58.
- 447 35. Versteijne E, Suker M, Groothuis K, et al. Preoperative Chemoradiotherapy Versus
448 Immediate Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Results of
449 the Dutch Randomized Phase III PREOPANC Trial. *J Clin Oncol* 2020;38:1763-73.

- 450 36. Bockhorn M, Uzunoglu FG, Adham M, et al. Borderline resectable pancreatic cancer:
451 a consensus statement by the International Study Group of Pancreatic Surgery (ISGPS).
452 *Surgery* 2014;155:977-88.
- 453 37. Malleo G, Maggino L, Marchegiani G, et al. Pancreatectomy with venous resection for
454 pT3 head adenocarcinoma: Perioperative outcomes, recurrence pattern and prognostic
455 implications of histologically confirmed vascular infiltration. *Pancreatology* 2017;17:847-57.
456



Contact $\leq 50\%$ circumference



Venous Invasion 67%



Venous Invasion 38%



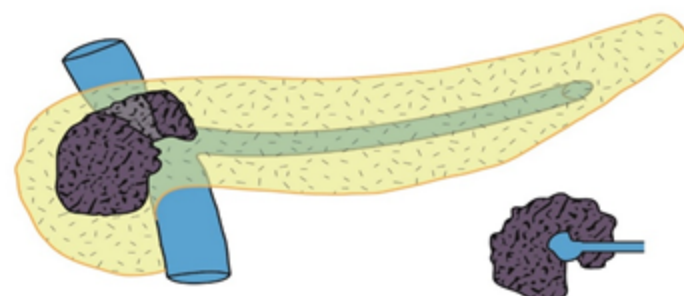
Venous Invasion 21%

Preoperative CT-scan

Upfront surgery

Preoperative
Chemotherapy

Normalized CA 19-9



Contact $>50\%$ circumference/ vein deformity/ occlusion



Venous Invasion 85%



Venous Invasion 78%



Venous Invasion 81%

Table 1: Correlation radiologic venous invasion according to the different classification and pathologic venous involvement.

| | PVI +/-tot (%) | Intimal Invasion |
|--------------------|-----------------------|-------------------------|
| Nakao | | |
| A | 45/91(49,4%) | 11(24,4%) |
| B | 23/33(69,6%) | 5(21,7%) |
| C | 28/37(75,6%) | 14(50%) |
| D | 28/35(80%) | 15(53,5%) |
| Ishikawa | | |
| 1 | 38/80(47,5%) | 8(21%) |
| 2 | 10/16(62,5%) | 5(50%) |
| 3 | 20/28(71,4%) | 3(15%) |
| 4 | 26/32(81,5%) | 13(50%) |
| 5 | 30/38(78,9%) | 14(46,7%) |
| MD anderson | | |
| A | 14/34(41,1%) | 4(28,6%) |
| B | 48/84(57,1%) | 11(23%) |
| C | 33/42(78,5%) | 15(45,5%) |
| D | 29/36(80,5%) | 15(51,8%) |
| Raptopoulos | | |
| 0 | 12/29(41,3%) | 4(33,4%) |
| 1 | 34/63(53,9%) | 8(23,6%) |
| 2 | 22/32(68,7%) | 4(18,2%) |
| 3 | 27/36(75%) | 14(51,9%) |
| 4 | 29/36(80,5%) | 15(51,8%) |
| Lu | | |
| 1 | 27/58(46,5%) | 6(22,3%) |
| 2 | 33/58(56,8%) | 9(27,3%) |
| 3 | 7/7(100%) | 1(14,3%) |
| 4 | 57/73(78%) | 29(50,9%) |

PVI=pathological venous invasion; **superficial=** adventitia and media; **deep=**intima.

Table 2: Univariate and multivariate analyses of factors predicting pathological venous invasion

| Variables | Univariate | | | | | | Multivariate | | | | | |
|--------------------------|------------|------|-------|------|--------------|---------------|--------------|--------------|--------------|-------------|--------------------|-------------------|
| | Beta | SE | Wald | OR | CI95% | P | Beta | SE | Wald | OR | CI95% | P |
| Age | -0.001 | 0.01 | -0.07 | 0.99 | (0.96-1.03) | 0.93 | | | | | | |
| Tumoral localisation | 0.07 | 0.17 | 0.41 | 1.07 | (0.76-1.50) | 0.68 | | | | | | |
| Neoadjuvant chemotherapy | -0.71 | 0.32 | -2.17 | 0.48 | (0.25-0.93) | 0.02 | -0.96 | 0.37 | -2.58 | 0.38 | (0.18-0.79) | 0.009 |
| > 8 FOLFIRINOX cycles | -0.14 | 0.32 | -0.44 | 0.86 | (0.45-1.63) | 0.65 | | | | | | |
| CA19-9 >Normal | 0.73 | 0.31 | 2.31 | 2.07 | (1.12-3.85) | 0.02 | 0.68 | 0.34 | 1.97 | 1.97 | (1.00-3.90) | 0.04 |
| CA 19-9>200 | 0.33 | 0.36 | 0.91 | 1.39 | (0.68-2.86) | 0.35 | | | | | | |
| Tumoral size>30mm | 0.29 | 0.32 | 0.88 | 1.33 | (0.70-2.54) | 0.37 | | | | | | |
| NAKAO | 0.46 | 0.14 | 3.17 | 1.58 | (1.19-2.10) | 0.001 | | | | | | |
| ISHIKAWA | 0.34 | 0.10 | 3.38 | 1.41 | (1.15-1.73) | 0.0007 | | | | | | |
| LU | 0.43 | 0.13 | 3.36 | 1.55 | (1.20-2.00) | 0.0007 | 0.57 | 0.144 | 3.99 | 1.77 | (1.34-2.35) | <0.0001 |
| Raptopoulos | 0.41 | 0.12 | 3.33 | 1.50 | (1.18-1.92) | 0.0008 | | | | | | |
| MD anderson | 0.57 | 0.17 | 3.28 | 1.77 | (1.26-2.49) | 0.001 | | | | | | |
| NCCN | 1.08 | 0.44 | 3.18 | 2.96 | (1.26-2.49) | 0.01 | | | | | | |
| Arterial invasion | 0.54 | 0.31 | 1.73 | 1.72 | (0.93-3.19) | 0.08 | | | | | | |
| Venous thrombosis | 1.29 | 0.51 | 2.52 | 3.65 | (1.33-10.03) | 0.01 | | | | | | |

Table 3: Correlation between tumor-vessel circumference degree involvement and pathology.

| | Tumor Vessels circumference contact ≤50% | Vessels circumference >50% or any venous wall deformity | P |
|---|---|---|-------------------|
| Number of patients | 117 | 81 | |
| CA19-9(U/ml) | 521 | 295 | <0.0001 |
| Normal CA19-9 | 36% | 42% | 0.45 |
| Preoperative Chemotherapy | 63(54%) | 59(73%) | 0.007 |
| Normalization CA19-9 | 27%(17/63) | 27%(16/59) | 1.00 |
| Reduction ≥50% preoperative value CA19-9 | 54 %(34/63) | 51 %(30/59) | 0.85 |
| Pathological venous invasion | 60(52%) | 64(80%) | <0.0001 |
| Pathological venous invasion /Neoadjuvant chemotherapy | 24/65(38%) | 46/58(73%) | <0.0001 |
| Deep pathologic invasion (media-intima) | 25% | 47% | <0.0001 |
| R1 | 49(41.8%) | 47(58.0%) | 0.03 |
| Positive lymphnodes | 92(78%) | 64(79%) | 1.00 |
| Number of positive lymph nodes | 5.7±0.7 | 6.0±0.9 | 0.84 |
| Length of resected vein (mm) | 26.9±10.6 | 29.8±10.4 | 0.44 |
| Transfusion | 77(66%) | 68(84%) | 0.005 |
| Arterial resection | 27 | 43 | <0.0001 |