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Histopathological correlation of preoperative MRI findings for local staging of resectable pancreatic adenocarcinoma: A pilot study with matched histopathology validation of MRI features

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Introduction:

Pancreatic ductal adenocarcinoma (PDAC) is the most common epithelial exocrine pancreatic malignancy, accounting for 90% of the malignant neoplasm of the pancreas (1). PDAC is a very aggressive tumor with a poor 5-year survival of less than 10%. It is characterized by early lymphatic and vascular spread, as well as aggressive local infiltration. The current standard treatment for resectable tumors is surgery followed by adjuvant chemotherapy(2).

According to the NCCN definition, a tumor is considered to be resectable if no distant metastasis, no local signs of invasion or abutment of major vessels are seen on preoperative CT or MRI(2). The tumor is classified as borderline resectable when no distant metastasis is to be seen, the invasion of the superior mesenteric vein or portal vein allows safe resection and reconstruction, the invasion of the superior mesenteric artery does not exceed 180° of the circumference and the tumor does not invade the celiac trunk(2). The tumor is seen as not resectable when the conditions for clearly or borderline resectable are not fulfilled(2).

In the literature, 16 to 85% of the resected tumors have an incomplete tumor resection (R1 status) (3), whereby the large range is related to the pathological processing and the used definition for R1. This means that an important number of patients will undergo an operation with an increased risk for early tumor recurrence, and subsequently, a shortened long-term survival.

The best way to increase survival in patients at risk for an incomplete tumor resection would be to offer them a neoadjuvant treatment in order to increase the R0 resection rate, as such therapy has proven to be effective to downstage locally advanced PDAC (4). However, it remains difficult to preoperatively predict the R status; consequently, it would be crucial to find preoperative criteria to precisely predict surgical resection margins in order to select patient for neoadjuvant treatments.

R classification for pancreas cancer:

The R classification of the Union for International Cancer Control (UICC) describes the presence or absence of residual tumor after resection. A complete resection is defined as R0 meaning no residual tumor is to be detected after treatment. R1 means that microscopic but not macroscopic residual tumor is to be found, and in case of R2 resection, macroscopic tumor residues are left behind in situ during the operation(5).

The prognostic value of an incomplete (R1) resection has been unclear for a long time (6). Nowadays, using standardized pathological procedures for pancreaticoduodenectomy specimen examination, it has been demonstrated that the R status is among the most relevant prognostic factors for long-term survival (7–9). This statement is true using the definition of R1 as presence of the tumor at margin(9) according to UICC and American Joint Committee on Cancer (AJCC) guidelines(10), as well as for the

definition of R1 as presence of tumor within 1mm to the margin(11), as proposed by the Royal College of Pathologists(12).

There is good evidence that the survival of patients with an R1 is similar to patients who were not at all operated but only underwent a palliative radio-chemotherapy (11)(2). The predominance of local recurrences after pancreas cancer resection also outlines the importance of the R status (11,16).

Imaging of pancreatic cancer:

Resectability criteria of PDAC are based on Computed Tomography (CT) which allows to analyze the relationship of the primary tumor with the surrounding tissues, in particular the major intestinal vessels (portal vein, superior mesenteric artery)(14).

Magnetic Resonance Imaging (MRI) is frequently performed as the superiority of MRI over CT to assess tumor conspicuity in the pancreas has been proven(15). MRI is successfully used nowadays for many cancer staging, e.g. for rectal cancer. The Beets-Tan group has performed several studies to show that MRI was able or even superior to predict tumor-free resection margins of rectal cancers(16). This has brought a much better management and survival to rectal cancer patients. Transposing the results of these studies for pancreas would be of great interest, however this kind of work couldn't be done until now for the pancreatic cancer for different reasons.

The main problem with the pancreas is the anatomopathological processing. Until recently, the reproducibility of the pancreas histopathological processing has been very poor. In 2007, the Verbeke et al. group proposed a new standardized protocol giving more robust data than before. The production of reproducible studies has only started since then.

Aim of the study:

The aim of the present study is to develop a new standardized method for comparison of MRI measurements with anatomopathological specimen of PDAC. The method will be used on a small number of cases to assess the feasibility.

The correlations looked at are later to be used as tests to predict the preoperative probability of an R1 resection, and to decide whether or not a neoadjuvant treatment would be indicated for an individual patient.

Methods:

Concept:

The background of this study was to get clinically relevant information for the surgeon's daily practice. Therefore, a consensus between radiologists and pathologists with the participation of the surgeons had to be found.

The concept was to assess as precisely as possible the tumor size and it's relation to the surrounding structures on both histopathological slides and MR images.

This study has been restricted to tumors localized in the pancreas head, as these represent the majority of the pancreas adenocarcinoma and as the tail and body adenocarcinoma represent a different surgical and radiological challenge.

Definitions:

Definition of tumor size:

For the assessment of the tumor size, only the greatest tumor dimensions were measured.

The analysis of the cranio-caudal size measurement has been abandoned due to the following reasons. During the histopathological processing, the pancreas is cut cranio caudally with an interval of 4mm. The cranio-caudal size can then only be assessed with a precision of ± 4mm. On the other hand, the MRI slices are made with an irregular interval of 3 to 6 mm. It is therefore almost impossible to get a precise correlation.

Definition of the faces:

For the relation of the tumor to the different surrounding structures, the pancreas faces were described as following. The lateral face is in a sagittal plane; it corresponds to the part of the pancreas directly bounded to the Duodenum. The anterior face is in a coronal plane; it is defined as the part of the pancreas covered with peritoneum. The medial face is in a sagittal plane; it starts where the pancreas stops being covered by peritoneum and ends where the retroportal lamina starts.

The posterior face is the posterior part of the pancreas located between the lateral face and the retroportal lamina. The retroportal lamina has been defined as the neuronal and fat tissue pad located posteromedially of the pancreas on the lateral side of the superior mesenteric artery (SMA), surrounded by the SMA, the retroperitoneum, the aorta and the pancreas.

Based on these definitions the following parameters of the tumor were measured on MRI and anatomopathological specimen:

- Greatest anterior-posterior, left-right and greatest overall diameter
- Distance to anterior, posterior, lateral and medial face
- Distance to portal vein / superior mesenteric vein (PV/SMV) and to superior mesenteric artery (SMA)
- Invasion of the duodenal wall by the tumor, common bile duct (CBD), Vater ampulla, main pancreatic duct, retroportal lamina, PV/SMV
- T stage

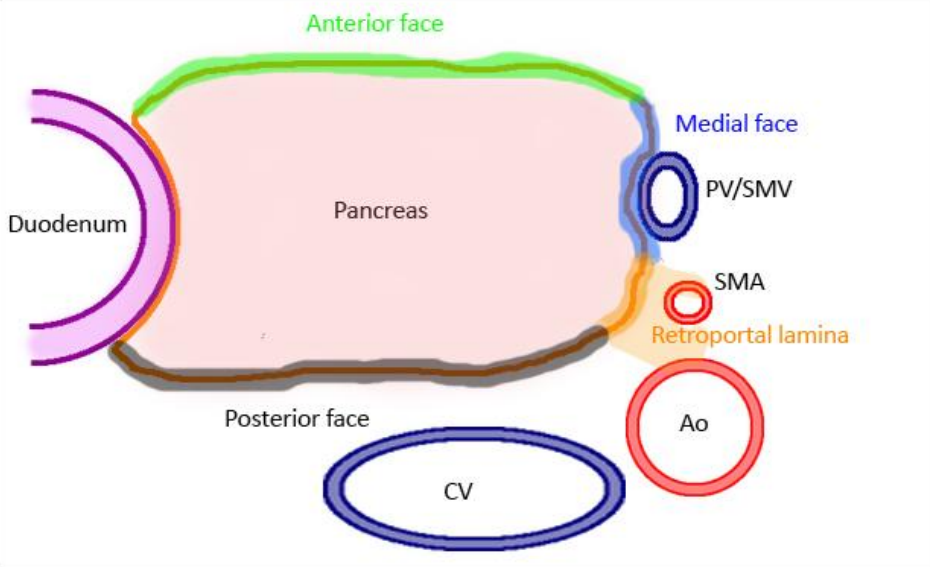


Image 1: Schematic representation of the pancreatic faces as inked at the histopathological department. Caval vein (CV), aorta (Ao), superior mesenteric artery (SMA), portal vein / superior mesenteric vein (PV/SMV).

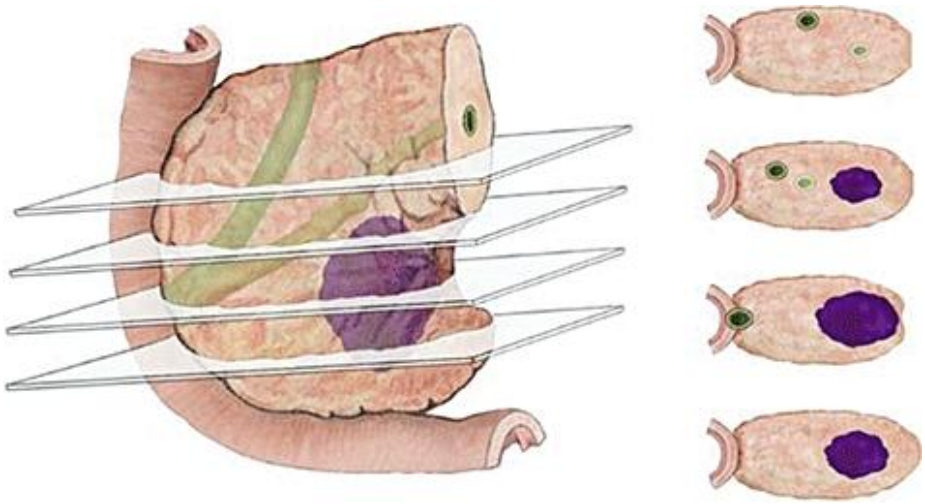


Image 2: Schematic representation of the pancreas as sliced at the histopathological department. Original image from “Resection margins and R1 rates in pancreatic cancer - are we there yet?” C. S. Verbeke (3).

Radiology technique:

Preoperative MRI imaging was made within 30 days before the operation. The protocol included ingestion by the patient of 200ml of pineapple juice 10 minutes before the examination as a negative oral contrast solution in order to suppress the signal of duodenal and gastric secretion. MRI was done at 3.0 T (Siemens Skyra®). The patient lied in a supine position with a quadrature phased array coil on each side of the abdomen.

Images were placed in order to cover the whole pancreas and liver. The used sequences were: HASTE ("single-shot" turbo spin echo) coronal and transverse 3mm slice thickness, fat sat T2 with respiratory gating (6mm slice thickness), transverse diffusion (b 50,300 and 600) in 6mm slices, fat sat transverse VIBE (Volume interpolated GRE) before and after gadolinium chelate injection (Dotarem Guerbet®, France, 0.1cc/kg of body weight) injection in care bolus/smart prep in arterial, venous and late phase (transverse and coronal plane for the late phase) (slice thickness:3mm, matrix 256/320).

Two experienced radiologists reviewed images in consensus. The following criteria were collected: The greatest antero-posterior (parallel to the duodenum wall), left-right (perpendicular to the duodenal wall) and overall greatest diameter of the tumor. The minimal perpendicular distance from the tumor to the anterior, posterior, lateral and medial surface of the pancreatic parenchyma was equally assessed. The minimal distance from the tumor to the superior mesenteric artery or the superior mesenteric vein was assessed. The invasion status of the following structures by the tumor was assessed by yes or no: Vater ampulla, main pancreatic duct, common bile duct (CBD), duodenal wall, portal vein/superior mesenteric vein (PV/SMV) and retroportal lamina. Additionally, the presence of a T3 stage (tumor extending outside of the pancreas into nearby tissue, but not into a large vessel or nerve) was assessed.

Extension to adjacent organs were as followed. The lesion has been localized using diffusion imaging (high signal at B600 imaging and pre-injection VIBE T1 imaging). Vascular encasement as well as duodenal or gastric wall extension was analyzed on post Gadolinium injection. Basic semiology was as followed. Retroportal lamina has been recognized as the fatty tissue passing behind the mesenterico-portal axis joining the posterior aspect of the pancreatic head to the second portion of the duodenum. This lamina was considered at risk of invasion when it was directly invaded by the tumor or when there was no more normal pancreas visible on the posterior aspect of the tumor of the pancreatic head. Vascular invasion criteria were the standard ones. Anterior extra-pancreatic extension was considered when the tumor was encasing the gastro-duodenal artery and or irregular infiltration of the pre-pancreatic fat was visible either on T1 or on T2 weighted imaging.

Histopathology technique:

The Whipple procedure specimen was received fresh at the pathology department immediately after its resection. The posterior, anterior and medial pancreatic surface, as well as the pancreatic transection margin were inked, in accordance to the NCCN guidelines(2), an additional orange painting for the retroportal lamina has been introduced for the purpose of this study. The pancreas was then serially sliced in a plane perpendicular to the duodenum with an interval of 4mm. After recording the macroscopic size of the tumor and the distances from the margins, the slices were cut in order to fit in the cassettes before being fixed in formalin. Five-micrometer thick sections of the whole tumor and other relevant structures were taken and processed for haematoxylin-eosin staining. Since October 2011 the hospital stopped using big cassettes containing one whole pancreas slice each to use smaller 21x30x4 mm cassettes for logistic reasons. Therefore, the slides of the specimen operated after this date had to be reassembled to get each pancreas slice entirely.

Two pathologists jointly delimited the tumor circumference and the circumference of the pancreatic parenchyma. The greatest antero-posterior (parallel to the duodenum wall), left-right (perpendicular to the duodenal wall) and overall greatest diameter of the tumor could then easily be measured on these slides. The minimal perpendicular distance from the tumor to the anterior, posterior, lateral and medial surface of the pancreatic parenchyma was equally assessed. The minimal distance from the tumor to the superior mesenteric artery or the superior mesenteric vein was assessed if present on the specimen. The invasion status of the following structures by the tumor was assessed by yes or no: Vater ampulla, main pancreatic duct, common bile duct (CBD), duodenal wall, portal vein/superior mesenteric vein (PV/SMV) and retroportal lamina. The invasion of the retroportal lamina has been defined as tumor invading the peripancreatic fat postero-medially. This surface was easily recognizable, as it had been cauterized during the operation and in the prospective cases as it had been inked in orange. We defined an invasion of the duodenal wall as tumor infiltrating the duodenal musculature (lamina muscularis propria).

Beside this, we defined the T stage of the tumor according to the AJCC classification(10). We also recorded the lymphovascular, perineural and lymph node invasion of the tumor to correlate with the survival.

Patients:

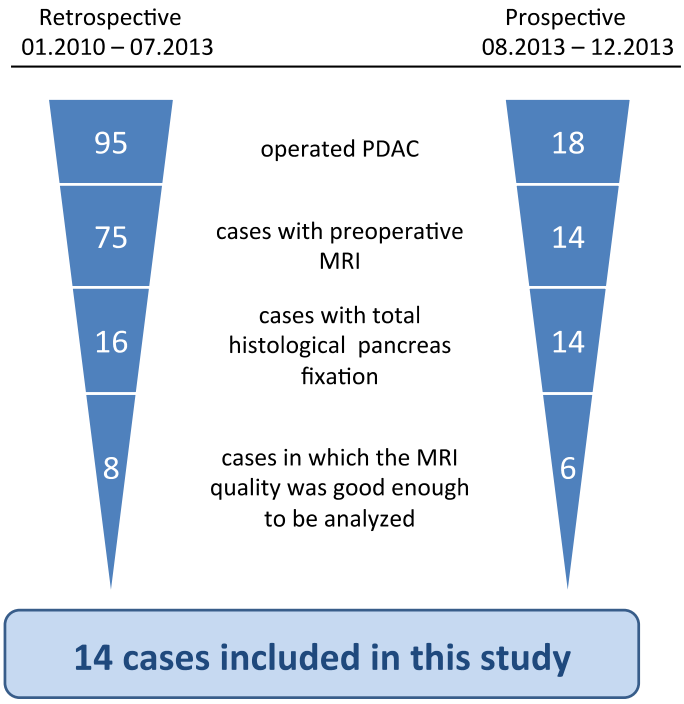
The local ethic committee has approved this study. All participating patients have signed an informed consent to participate in clinical research projects.

All patients who had a pancreaticoduodenectomy for PDAC from January 2010 to December 2013 were screened for possible inclusion into the study. The inclusion criteria were: patients with a

preoperative MRI of good quality and a histopathologically proven pancreatic head adenocarcinoma for which the tumor had been fixed in toto with the surrounding pancreatic parenchyma and had been well enough documented to reconstruct the tumor. The study was retrospective from January 2010 to July 2013 and prospective from August to December 2013.

For the retrospective part, the research has been started from January 2010 as a new protocol for the handling of the surgical specimen has been established (cutting the pancreas in a coronal plan rather than the earlier cutting of the pancreas in a perpendicular plan to the main pancreatic duct). This new protocol was based on the recommendations of the Verbeke et al. group(7) and permitted the much better comparison between histopathology and radiology.

For the retrospective part, 95 patients underwent a pancreaticoduodenectomy for pancreatic head ductal adenocarcinoma at the University Hospital CHUV in Lausanne (Switzerland) between January 2010 and July 2013. Of these 95 patients, 75 had a preoperative MRI. In 16 of 75 the tumor had been fixed in toto including the surrounding pancreas and the cases were well enough documented to enable the reconstruction of the initial slides arrangement. In 8 of these 16 cases the MRI quality was insufficient to be analyzed precisely. That gave 8 patients included in this study. In August 2013 the pathological processing protocol has been changed. The systematic in toto fixation of the tumor and the surrounding pancreas, with precise documentation of the samples arrangement and inking of the retroportal lamina have been added to it. That gave another 6 patients to be included in this study. Out of the 18 patients operated between August and December 2013, 14 had a preoperative MRI and in 6 cases, the MRI quality was good enough to be analyzed.



Analysis:

The size correlation between the MRI and the pathology has been verified with a two-tailed probability Student t-test. Though this didn't have any statistical relevance to prove the exactitude of the MRI, it was important to confirm the absence of statistical relevant differences between MRI and histopathological measurements.

As the study has been designed to look for tracks to tailor further studies, the main part of the analysis has been based on specificity, sensitivity, positive predictive value, negative predictive value and accuracy. Since the prognostic value of an R1 stage is critical for the survival, the aim was to avoid as much as possible not treating preoperatively a probable future R1 stage, even if that means sometimes treating patients, which would have had an R0 resection anyway. That means the highest possible sensitivity was sought, sometimes at the expenses of the specificity.

There are several ways correlate the measures taken on the MRI with the pathology. At first, measures taken on MRI were simply compared with the ones taken in pathology. Linear regression curves comparing the tumor size in both modalities were acquired. For the binary data the sensitivity, specificity, PPV (positive predictive value), NPV (negative predictive value) and accuracy were calculated. Regarding the comparison of the localization of the tumor (distance to the gland margins), the large amount of tumors coming to the pancreas margins in the data, didn't allow making a relevant linear regression curve. Instead the measurements were transformed into binary data (either tumor at the gland margin or not). That way, the precision of the MRI to predict the histopathological findings on each side of the pancreas could be assessed.

The second part of the analysis was based on trying to find MRI criteria to predict the R status. To find them, the different measurements were compared with the R status. For the distances measured on MRI (size and distance to edges) the cut off length, which predicted best weather a resection would be R1 or R0 were estimated. The sensitivity, specificity and accuracy of the invasion of the peri- and intrapancreatic structures to predict a future R1 status were calculated.

When the specificity obtained was not good enough, two MRI measurements were put together to try to find a good correlation to the R status. Asking for two MRI conditions to be present to predict an R1 stage.

Results:

At the end of the selection process, 14 cases were identified, which were analyzed in the histopathology department and independently at the radiological department.

MRI to predict the histopathology:

Tumor size

In the 14 cases analyzed the mean tumor size on MRI was 32.9 ±16.5 mm for the left-right diameter compared to 28.0 ±11.5 mm on histopathology (p=0.02), 24.4 ± 9.1 mm for the antero-posterior diameter compared to 26.2 ± 8.9 mm (p=0.42), and 34.3 ± 16.4 mm for the greatest overall diameter compared to 32.1 ± 12.2 mm (p=0.64), respectively.

Local spreading of the tumor:

The accuracy of the MRI to assess the peripancreatic fat invasion for each pancreatic side (binary transformed measurements) lied in a range from 71 to 86% depending on the face analyzed (tables 2.2.1-4). The MRI could predict a T3 stage with an accuracy of 71% (table 2.3.3).

The accuracy of the MRI for the assessment of the invasion of the different surrounding and intrapancreatic structures was 71% for the invasion of the duodenum (table 2.3.4), 79% for the invasion of the retroportal lamina (table 2.3.1), 86% for the invasion of the CBD (common bile duct) (table 2.3.5), 93% for the invasion of the main pancreatic duct (table 2.3.6) and 56% for the invasion of the Vater ampulla (table 2.3.7). To assess the invasion of the retroportal lamina, the accuracy of the MRI was of 79% with a sensitivity of 0.82 and the specificity 0.67 (table 2.3.1).

For the assessment of the invasion of the PV/SMV there were only four cases. As the surgeon does not always excise it during the operation, the PV/SMV can only rarely been assessed in histopathology. Of these four cases, the MRI predicted an invasion on all four, but there were only three invasions at histopathology, in the fourth case, the tumor was lying 0.5 mm from the PV/SMV (table 2.3.2). Considering an absence of portal vein at histopathology as no histopathological invasion gave us an accuracy of 64% to predict the invasion (table 2.3.2bis).

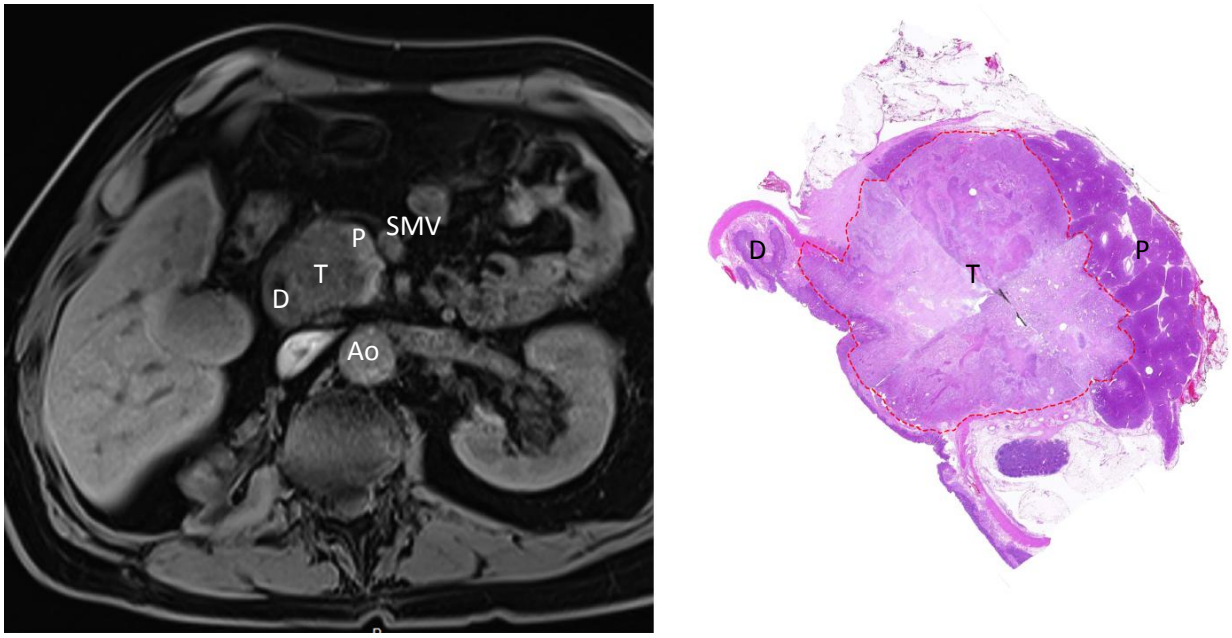


Image 3: Comparison between MRI and histopathology. Tumor (T), healthy pancreas (P), Duodenum (D), Aorta (Ao), superior mesenteric vein (SMV).

MRI to predict the R1 stage:

The best MRI size cut-off to predict a future R1 resection for either greatest overall dimension, left-right or antero-posterior size was 20 mm. This cut-off gave the following sensitivities and specificities: 100% and 80% for the left-right diameter and for the greatest overall diameter (table 3.1.1 and 3.1.3) and 89% and 80% for the antero-posterior size (table 3.1.2)

For the distance to the pancreas side, a cut-off was set at minimum 5 mm between the tumor and the peripancreatic fat to predict an R0 resection. This gave a sensitivity of 100% for all faces and specificity of 20 to 40 % (tables 3.2.3-6). Correlating a distance of less than 5mm from the tumor to both medial and posterior face with an R1 stage gave a sensibility of 100% and a specificity of 60% (accuracy of 86%) (table 3.2.7).

For the analysis of the distance from the tumor to the SMA and to the PV/SMV the cut-offs have been set at a minimum of 5 mm to be correlated with an R0 stage. That gave the following sensitivity and specificity values: 78% and 100% for the SMA (table 3.2.1) and 89% and 40% for the PV/SMV (table 3.2.2).

Correlating the invasion status of the different surrounding and intrapancreatic structures with an R1 stage gave the following interesting values of sensitivity and specificity: 89% and 60% for the invasion of the retroportal lamina (table 3.3.1), 67% and 100% for the invasion of the PV/SMV (table 3.3.2) and 100% and 40% for the T3 stage observed on MRI (table 3.3.3).

Discussion:

Summary of the results:

Looking at all these results, the overall accuracy of MRI to predict histopathological results has been good. The most promising features are the correlation of the size with the R status, the distance from the tumor to the medial and posterior side correlated with the R status, the distance to the SMA or to the PV/SMV correlated to the R status, the invasion status of the retroportal lamina and the predicted presence of T3 stage correlated with the R status. This study makes us glimpse at a whole new perspective for the MRI use in the preoperative staging of pancreatic cancer.

Limitations of the study:

Unfortunately, there is no similar literature to compare our findings with. Most studies assessing the accuracy of the MRI were done for the resectability criteria established by the NCCN and until now, no study has been done assessing the accuracy of the MRI to determine tumor's conspicuity.

The basis hypothesis we made, that the R stage is correlated with the survival, is yet not admitted throughout the scientific community(17). A meta-analysis was not able to prove its validity as an independent survival prognostic factor(6). We believe the poor uniform methodology between the histopathologists of different medical centers is the cause to that. Therefore, we outline the importance of a careful systematic histopathological processing of the tumor for the purpose of further studies, as showed by the Verbeke et al. group(3).

So far, MRI is not part of the standard preoperative procedure for pancreatic cancer. It is done from time to time for the patients for whom we could not get a precise image of the tumor on the CT. As we selected these patients, we might have selected more difficult cases and therefore we might not be very representative of the standard pancreatic head adenocarcinoma population.

For the future larger scale study we are launching, we will introduce systematic preoperative MRI. This MRI should be performed in dedicated gastro-intestinal imaging centers, as the quality of the MRIs we encountered when doing this study was very inconstant.

In pathology, it is of common knowledge that tissues shrink, when going through the procedure of conservation in paraffin. This shrinkage is estimated to be around 10% for lung tumors(18). We can reasonably assume a similar shrinkage for the pancreas, but as there is no precise documentation to assess this, we decided not to take it in consideration.

The time between the MRI and the operation varied from 1 day to 4 weeks. We assumed the tumor did not grow in between.

Implication for a larger study:

Some weak points of the study design have also been pointed out by this study.

This study showed, that between two physicians of different backgrounds, precise anatomical structures don't always have the same definition. As you may have noticed the radiologists definition of retroportal lamina differed slightly from the pathologists one. It seems therefore recommendable to precisely define every structure compared before the beginning of any study. A new histological staining of the retroportal lamina has also been introduced for the purpose of this study, as the histological localization wasn't always easy to delimitate precisely. It would be recommendable to keep this staining in future trials.

Finally, the interdisciplinarity of this type of study makes it a real challenge to coordinate, as it has to bring together people of various medical specialties. Regular meetings during the study period are needed to keep all focuses looking in the same direction.

Future perspectives:

The fundamental problem of the actual staging method is its aims. This method is based on the resectability of the tumor in terms of peroperative survival and not in terms of long-term survival. It only assesses if the operation mortality isn't too high for the patient, without predicting the chances of a complete resection. As an incomplete resection only has a very questionable benefit on the long-term survival, there is an urgent need for resectability criteria predicting the likelihood of a complete resection and so the long-term survival. We think these criteria will be to be found to found with MRI-based preoperative staging.

The retroportal lamina or mesopancreas has been of the biggest hopes in this study. This structure located on the lateral side of the SMA, between the SMA and the retroperitoneum posteromedially of the pancreas is mainly composed of fat tissue, nerves, and vascular elements(19). In this delicate place to operate, the invasion the nerve plexus passing through it is of bad prognosis(20). This site is a major site of R1(21) resection and therefore of local recurrence(22). In this study, we managed to predict an invasion with a sensitivity of 82% and an accuracy of 79% though the difference in the definition between the pathologists and the radiologists.

Having shown the relevance of an invasion of the retroportal lamina, we ought to talk about the total mesopancreatic excision. This technique published in some recent articles seems to show better results in term of residual tumor than the conventional Whipple procedure(23,24). As this operation decreases the rate of R1 stage tumors, it would be interesting to renew our comparison of the R stage with the invasion of the retroportal lamina on the MRI with such operated pancreas specimen.

If the good correlation of the greatest overall dimension was kept in a bigger sample, the prognosis could be easily predicted based on preoperative MRI. Referring to the studies made on postoperative greatest overall size measurements, its correlation with the prognosis seems very good(25).

Comment:

In this study, we did not consider the anterior face as a margin for the R status. However, we have to consider, that the presence of tumor cells at the anterior surface is not trivial for the prognosis(3). The role of this condition for the prognosis and treatment would have to be further investigated before being included it in the definition of the R stage.

Prospective study:

Drawing on this experiment and the conclusions we made, we have launched a prospective only study with systematic preoperative MRI for all pancreatic head adenocarcinoma. We are looking forward to draw conclusions on a statistically significant patient population and to improve the management and the survival of the pancreatic head ductal adenocarcinoma.

Conclusion:

MRI shows to be a promising tool for preoperative staging and for indications to neoadjuvant therapy, in a context of unsatisfying prognosis after R1 resection of pancreatic ductal head adenocarcinoma.

Annexes:

Tables:

1. Collected data:

Patient	CrCa[a] MRI	CrCa[a] path	LR[b] MRI	LR[b] path	AP[c] MRI	AP[c] path	Ov[d] MRI	Ov[d] path
1	28	12	32	30	34	26	34	32
2	33	16	38	27	24	25	38	29
3		16	51	38	22	35	51	48
4	33	20	33	24	26	35	33	35
5		12	19	20	14	21	19	26
6	35	12	30	25	26	19	35	29
7	38	12	30	33	32	26	38	40
8		28	77	60	32	31	77	60
9		20	16	22	18	19	18	26
10		12	17	13	14	18	17	18
11		12	12	15	10	10	12	15
12		28	38	34	41	30	41	37
13		20	37	26	32	46	37	47
14		39	31	25	17	26	31	26

Table 1.1: Tumor greatest dimensions in mm measured on the MRI (MRI) and on the histopathopathology (path) for one same patient. a) Cranio-caudal size b) left-right size c) anterio-posterior size, d) greatest overall tumor size.

Patient	Ant[a] MRI	Ant [a]path	Lat[b] MRI	Lat[b] path	Med[c] MRI	Med[c] path	Post[d] MRI	Post[d] path
1	0	0	0	0	0	0	0	0
2	0	0	0	1	0	0	2	5
3	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
5	8	3	7	0	0	0	0	0
6	4	5	3	10	0	0	0	0
7	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	10	0
10	2	4	0	0	12	12	0	0
11	19	>10	0	5	18	7	0	0
12	0	3	0	0	4	0	0	0
13	4	0	0	0	0	1	0	0
14	0	2	8	0	0	0	5	0

Table 1.2: Tumor minimal distance (mm) to the pancreas sides measured on the MRI (MRI) and on the histopathopathology (path) for one same patient. a) anterior side, b) lateral (duodenal) side, c) medial side, d) posterior side.

Patient	PV[a] MRI	PV[a] path	SMA[b] MRI	SMA[b] path
1	3		12	
2	0	0	0	
3	0	0	0	
4	4		10	
5	0		7	
6	0	0.5	3	
7	0	0	3	0
8	0		0	
9	2		>15	
10	15		>15	
11	>15		>15	
12	9		>15	
13	0		4	
14	0		0	

Table 1.3: Tumor minimal distance (mm) to the abdominal vessels measured on the MRI (MRI) and on the histopathopathology (path) for one same patient. a) portal vein/ superior mesenteric vein, b) superior mesenteric artery

Patient	T3[a] MRI	T3[a] path	Duo[b] MRI	Duo[b] path	PVinv[c] MRI	PVinv[c] path	CBD[d] MRI	CBD[d] path
1	1	1	1	1	0	(0)	1	0
2	1	1	0	0	1	1	1	0
3	1	1	1	0	1	1	1	1
4	1	1	1	1	0	(0)	1	1
5	1	1	0	0	0	(0)	1	1
6	1	0	0	0	1	0	1	1
7	1	1	1	1	0	1	1	1
8	1	1	0	1	1	(0)	1	1
9	0	1	0	1	0	(0)	1	1
10	1	0	1	1	0	(0)	1	1
11	0	1	0	0	0	(0)	1	1
12	1	1	1	1	0	(0)	1	1
13	1	1	1	1	1	(0)	1	1
14	1	1	0	1	1	(0)	1	1

Table 1.4: Invasion by the tumor of the intra- and extrapancreatic structures, 1 = yes, 2 = no, measured on the MRI (MRI) and on the histopathopathology (path) for one same patient. a) Presence of T3 stage, b) invasion of the duodenum wall (lamina muscularis propria).

Patient	Wirs[a] MRI	Wirs[a] path	Vater[b] MRI	Vater[b] path	RetPo[c] MRI	RetPo[c] path
1	1	1	0	0	1	1
2	1	1	0	0	1	1
3	1	1	0	0	1	1
4	1	1	0	1	0	1
5	1	1	0	0	1	1
6	1	0	0	0	1	1
7	1	1	0	1	1	1
8	1	1	0	1	1	1
9	1	1	0	1	0	0
10	1	1	1	1	1	0
11	1	1	0	0	0	0
12	1	1	1	1	1	1
13	1	1	0	1	1	1
14	1	1	0	1	0	1

Table 1.5: Invasion by the tumor of the intra- and extrapancreatic structures, 1 = yes, 2 = no, measured on the MRI (MRI) and on the histopathopathology (path) for one same patient. a) invasion of the Wirsung Duct, b) invasion of the Vater ampulla, c) invasion of the retroportal lamina

Patient	Vasc[a]	Lymph[b]	Perineur[c]	R0 (royal)[d]	R0* AJCC[e]	R1(Royal)[d]	Local R1*[e]
1	1	1	1	0	0	med	med
2	1	1	1	0	0	post	post
3	1	1	1	0	0	med	med
4	1	1	1	1	1	0	0
5	1	1	1	1	1	0	0
6	1	1	1	0	1	med + post	0
7	1	1	1	0	1	med	0
8	0	1	1	0	0	post + med	post + med
9	1	1	1	1	1	0	0
10	1	1	1	1	1	0	0
11	0	0	1	1	1	0	0
12	1	1	1	0	1	med	0
13	1	1	1	0	1	med+post	0
14	1	1	1	0	1	med+post	0

Table 1.6: Histopathological only measured features. a) tumor invading capillaries at histopathology, b) tumor invading lymphatic vessels at histopathology, c) tumor invading the nerves at histopathology, d) according to the definition of the royal college of pathologists, e) according to the definition of the AJCC.

2. Correlations MRI - Histopathology:

2.1 Tumor size :

Left-Right diameter (mm)		MRI	Histo
		32	30
		38	27
		51	38
Mean MRI	32.93	33	24
Median MRI	31.50	19	20
		30	25
Mean Histo	28.00	30	33
Median Histo	25.50	16	22
		17	13
p value	0.02	12	15
		38	34
		37	26
		31	25
		77	60

Table 2.1.1: Correlation of the greatest left-right diameter measured on MRI and at Histopathology.

Antero-posterior diameter (mm)		MRI	Histo
		34	26
		24	25
		22	35
Mean MRI	24.43	26	35
Median MRI	25.00	14	21
		26	19
Mean Histo	26.21	32	26
Median Histo	26.00	18	19
		14	18
p value	0.42	10	10
		41	30
		32	46
		17	26
		32	31

Table 2.1.2: Correlation of the greatest antero-posterior diameter measured on MRI and at Histopathology.

Greatest overall diameter (mm)		MRI	Histo
		34	32
		38	29
		51	48
Mean MRI	34.36	33	35
Median MRI	34.50	19	26
		35	29
Mean Histo	33.43	38	40
Median Histo	30.50	18	26
		17	18
p value	0.64	12	15
		41	37
		37	47
		31	26
		77	60

Table 2.1.3: Correlation of the greatest overall diameter measured on MRI and at Histopathology.

2.2 Tumor localization

Medial invasion		
	Histo +	Histo −
MRI +	10	1
MRI −	1	2

Sensitivity	0.91
Specificity	0.67
PPV	0.91
PNV	0.67
Accuracy	0.86

Table 2.2.1: Correlation of the assessment of the overpassing of the pancreas boundary on the medial side between MRI and Histopathology.

Posterior invasion

	Histo +	Histo −
MRI +	11	2
MRI −	1	0

Sensitivity	0.92
Specificity	0.00
PPV	0.85
PNV	0.00
Accuracy	0.79

Table 2.2.2: Correlation of the assessment of the overpassing of the pancreas boundary on the posterior side between MRI and Histopathology.

Duodenal invasion

	Histo +	Histo −
MRI +	9	2
MRI −	2	1

Sensitivity	0.82
Specificity	0.33
PPV	0.82
PNV	0.33
Accuracy	0.71

Table 2.2.3: Correlation of the assessment of the overpassing of the pancreas boundary on the lateral side between MRI and Histopathology.

Anterior invasion

	Histo +	Histo −
MRI +	7	1
MRI −	2	4

Sensitivity	0.78
Specificity	0.80
PPV	0.88
PNV	0.67
Accuracy	0.79

Table 2.2.4: Correlation of the assessment of the overpassing of the pancreas boundary on the lateral side between MRI and Histopathology.

2.3 local tumor invasion

Retroportal lamina invasion

	Histo +	Histo −
MRI +	9	1
MRI −	2	2

Sensitivity	0.82
Specificity	0.67
PPV	0.90
PNV	0.50
Accuracy	0.79

Table 2.3.1: Correlation of the assessment of the retroportal lamina invasion between MRI and Histopathology.

PV/SMV invasion

	Histo +	Histo −
MRI +	3	1
MRI −	0	0

Sensitivity	1
Specificity	0
PPV	0.75
PNV	-
Accuracy	0.75

Table 2.3.2: Correlation of the assessment of the PV/SMV invasion between MRI and Histopathology.

PV/SMV invasion*

	Histo +	Histo −
MRI +	3	1
MRI −	4	6

Sensitivity	0.43
Specificity	0.86
PPV	0.75
PNV	0.60
Accuracy	0.64

Table 2.3.2bis: Correlation of the assessment of the PV/SMV invasion between MRI and Histopathology.

* Considering, an absence of PV/SMV on the pathological specimen meaning no microscopical invasion.

T3 Stage

	Histo +	Histo −
MRI +	10	2
MRI −	2	0

Sensitivity	0.83
Specificity	0.00
PPV	0.83
PNV	0.00
Accuracy	0.71

Table 2.3.3: Correlation of the assessment of the presence of a T3 stage between MRI and Histopathology.

Duodenum wall invasion

	Histo +	Histo −
MRI +	6	1
MRI −	3	4

Sensitivity	0.67
Specificity	0.80
PPV	0.86
PNV	0.57
Accuracy	0.71

Table 2.3.4: Correlation of the assessment of the duodenal wall invasion between MRI and Histopathology.

Common bile duct invasion

	Histo +	Histo −
MRI +	12	2
MRI −	0	0

Sensitivity	1.00
Specificity	0.00
PPV	0.86
PNV	0.00
Accuracy	0.86

Table 2.3.5: Correlation of the assessment of the common bile duct invasion between MRI and Histopathology.

Main pancreatic duct invasion

	Histo +	Histo −
MRI +	13	1
MRI −	0	0

Sensitivity	1.00
Specificity	0.00
PPV	0.93
PNV	0.00
Accuracy	0.93

Table 2.3.6: Correlation of the assessment of the wirsung duct invasion between MRI and Histopathology.

Vater ampulla invasion

	Histo +	Histo −
MRI +	2	0
MRI −	6	6

Sensitivity	0.25
Specificity	1.00
PPV	1.00
PNV	0.50
Accuracy	0.57

Table 2.3.7: Correlation of the assessment of the Vater ampulla invasion between MRI and Histopathology.

3. Correlations MRI findings - R1 stage:

3.1 Correlations MRI measured size – R1:

Left-right diameter >20mm and R1		
	Histo +	Histo −
MRI +	9	1
MRI −	0	4

Sensitivity	1.00
Specificity	0.80
PPV	0.90
PNV	1.00
Accuracy	0.93

Table 3.1.1: Correlation of a greatest left-right diameter greater than 20mm on MRI with the presence of R1 stage.

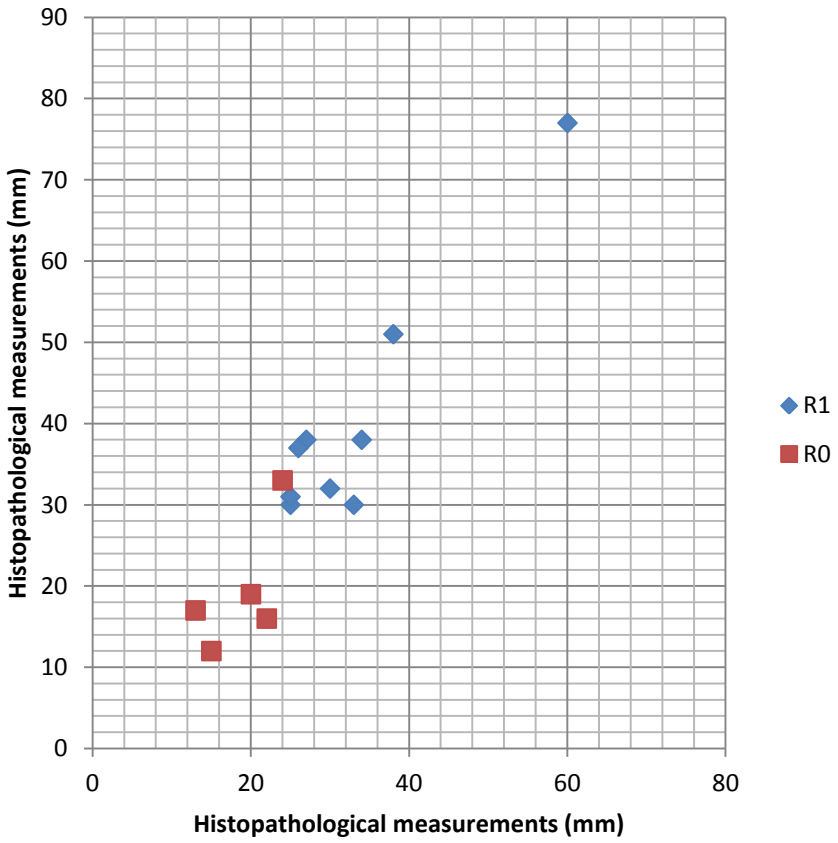


Table 3.1.1bis: Correlation between the greatest left-right diameter measured on MRI and at Histopathology with R stage.

Antero-posterior diameter >20mm and R1		
	Histo +	Histo −
MRI +	8	1
MRI −	1	4

Sensitivity	0.89
Specificity	0.80
PPV	0.89
PNV	0.80
Accuracy	0.86

Table 3.1.2: Correlation of a greatest antero-posterior diameter greater than 20mm on MRI with the presence of R1 stage.

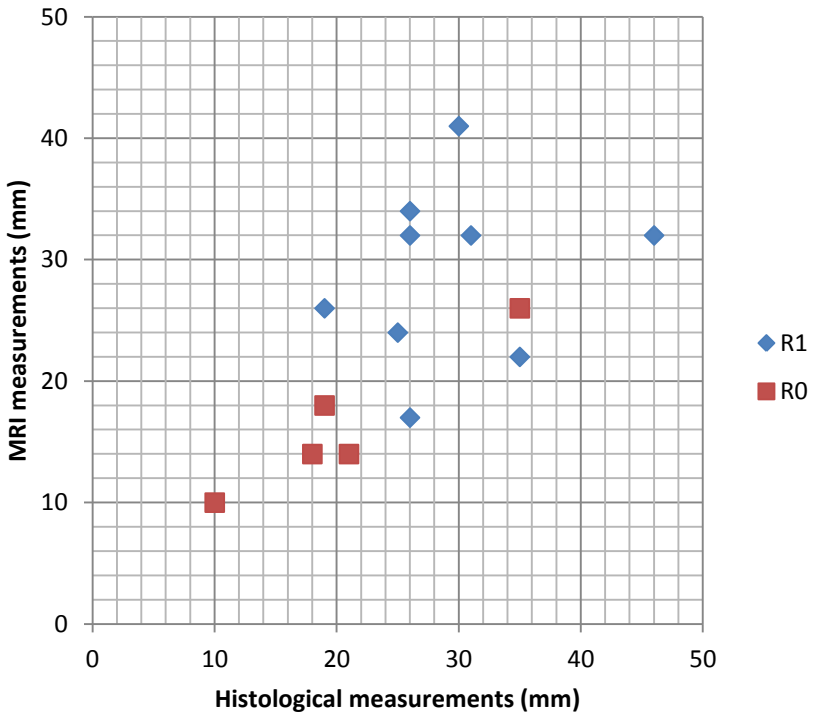


Table 3.1.2bis: Correlation between the greatest antero-posterior diameter measured on MRI and at Histopathology with R stage.

Overall diameter >20mm and R1		
	Histo +	Histo −
MRI +	9	1
MRI −	0	4

Sensitivity	1.00
Specificity	0.80
PPV	0.90
PNV	1.00
Accuracy	0.93

Table 3.1.3: Correlation of a greatest overall diameter greater than 20mm on MRI with the presence of R1 stage.

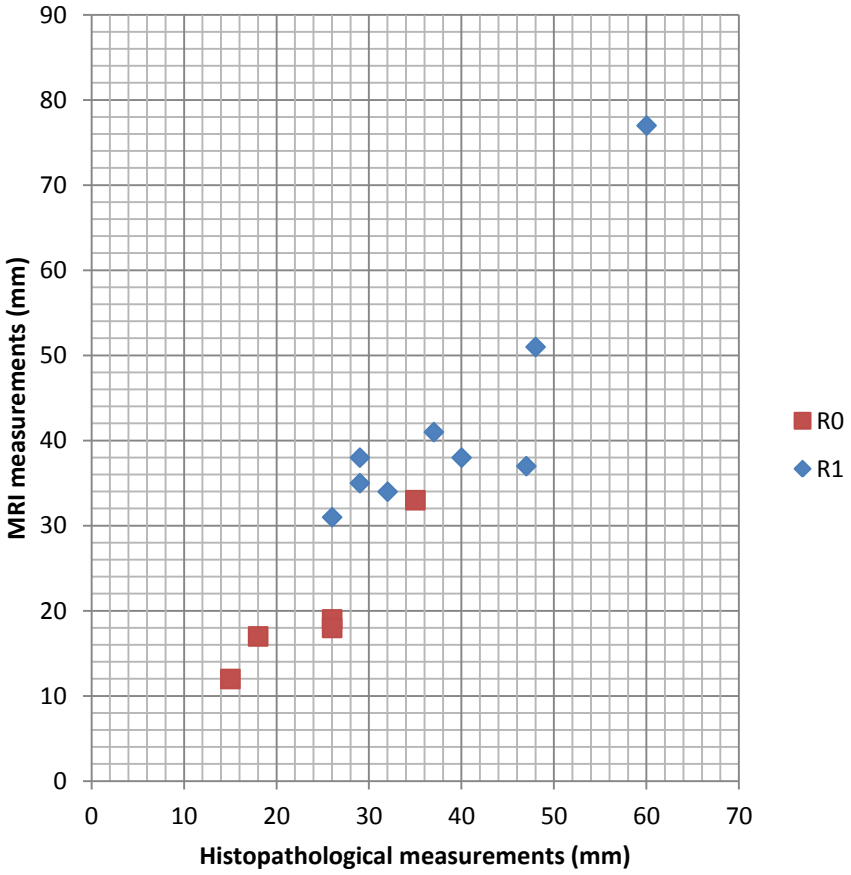


Table 3.1.2bis: Correlation between the greatest overall diameter measured on MRI and at Histopathology with R stage.

Correlations MRI localisation – R1:

Distance to SMA <5mm and R1		
	Histo +	Histo −
MRI +	9	1
MRI −	0	4

Sensitivity	0.78
Specificity	1.00
PPV	1.00
PNV	0.71
Accuracy	0.86

Table 3.2.1: Correlation of a minimal distance to the SMA smaller than 5mm on MRI with the presence of R1 stage.

Distance to PV/SMV <5mm and R1		
	Histo +	Histo −
MRI +	8	3
MRI −	1	2

Sensitivity	0.89
Specificity	0.40
PPV	0.73
PNV	0.67
Accuracy	0.71

Table 3.2.2: Correlation of a minimal distance to the PV/SMV smaller than 5mm on MRI with the presence of R1 stage.

Distance to anterior side <5mm and R1		
	Histo +	Histo −
MRI +	9	3
MRI −	0	2

Sensitivity	1.00
Specificity	0.40
PPV	0.75
PNV	1.00
Accuracy	0.79

Table 3.2.3: Correlation of a minimal distance to the anterior pancreas boundary smaller than 5mm on MRI with the presence of R1 stage.

Distance to medial side <5mm and R1		
	Histo +	Histo −
MRI +	9	3
MRI −	0	2

Sensitivity	1.00
Specificity	0.40
PPV	0.75
PNV	1.00
Accuracy	0.79

Table 3.2.4: Correlation of a minimal distance to the medial pancreas boundary smaller than 5mm on MRI with the presence of R1 stage.

Distance to posterior side <5mm and R1		
	Histo +	Histo −
MRI +	9	4
MRI −	0	1

Sensitivity	1.00
Specificity	0.20
PPV	0.69
PNV	1.00
Accuracy	0.71

Table 3.2.5: Correlation of a minimal distance to the posterior pancreas boundary smaller than 5mm on MRI with the presence of R1 stage.

Distance to lateral side <5mm and R1		
	Histo +	Histo −
MRI +	9	4
MRI −	0	1

Sensitivity	1.00
Specificity	0.20
PPV	0.69
PNV	1.00
Accuracy	0.71

Table 3.2.6: Correlation of a minimal distance to the lateral pancreas boundary smaller than 5mm on MRI with the presence of R1 stage.

Distance to both posterior and medial side <5mm and R1		
	Histo +	Histo −
MRI +	9	2
MRI −	0	3

Sensitivity	1.00
Specificity	0.60
PPV	0.82
PNV	1.00
Accuracy	0.86

Table 3.2.7: Correlation of a minimal distance to both posterior and medial pancreas boundary smaller than 5mm on MRI with the presence of R1 stage.

3.3 Correlation local tumoral invasion – R1 stage:

Invasion of the retroportal lamina and R1		
	Histo +	Histo −
MRI +	8	2
MRI −	1	3

Sensitivity	0.89
Specificity	0.60
PPV	0.80
PNV	0.75
Accuracy	0.79

Table 3.3.1: Correlation of an invasion of the retroportal lamina on MRI with the presence of R1 stage.

Invasion of the PV/SMV and R1		
	Histo +	Histo −
MRI +	6	0
MRI −	3	5

Sensitivity	0.67
Specificity	1.00
PPV	1.00
PNV	0.63
Accuracy	0.79

Table 3.3.2: Correlation of an invasion of the PV/SMV on MRI with the presence of R1 stage.

T3 stage predicted and R1

	Histo +	Histo −
MRI +	9	3
MRI −	0	2

Sensitivity	1.00
Specificity	0.40
PPV	0.75
PNV	1.00
Accuracy	0.79

Table 3.3.3: Correlation of predicted T3 stage on MRI with the presence of R1 stage.

Invasion of the duodenum and R1

	Histo +	Histo −
MRI +	5	2
MRI −	4	3

Sensitivity	0.89
Specificity	0.40
PPV	0.73
PNV	0.67
Accuracy	0.71

Table 3.3.4: Correlation of an invasion of the duodenum on MRI with the presence of R1 stage.

Invasion of the common bile duct and R1

	Histo +	Histo −
MRI +	9	5
MRI −	0	0

Sensitivity	1.00
Specificity	0.00
PPV	0.64
PNV	0.00
Accuracy	0.64

Table 3.3.5: Correlation of an invasion of the common bile duct on MRI with the presence of R1 stage.

Invasion of the main pancreatic duct and R1		
	Histo +	Histo −
MRI +	9	5
MRI −	0	0

Sensitivity	1.00
Specificity	0.00
PPV	0.64
PNV	0.00
Accuracy	0.64

Table 3.3.6: Correlation of an invasion of the common bile duct on MRI with the presence of R1 stage.

Invasion of the Vater ampulla and R1		
	Histo +	Histo −
MRI +	1	1
MRI −	8	4

Sensitivity	0.11
Specificity	0.80
PPV	0.50
PNV	0.50
Accuracy	0.36

Table 3.3.7: Correlation of an invasion of the retroportal lamina on MRI with the presence of R1 stage.

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