



Innovations in macroscopic evaluation of pancreatic specimens and radiologic correlation



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ARTICLE INFO

Article history:

Received 5 February 2016

Accepted 23 February 2016

Available online 11 March 2016

Keywords:

Pancreas

Neoplasms

MDCT

MRI

Histopathology

Specimen

ABSTRACT

The purpose of this study was to evaluate the feasibility of a novel dissection technique of surgical specimens in different cases of pancreatic tumors and provide a radiologic pathologic correlation. In our hospital, that is a referral center for pancreatic diseases, the macroscopic evaluation of the pancreatotomy specimens is performed by the pathologists using the axial slicing technique (instead of the traditional procedure with longitudinal opening of the main pancreatic and/or common bile duct and slicing along the plane defined by both ducts). The specimen is sliced in an axial plane that is perpendicular to the longitudinal axis of the descending duodenum. The procedure results in a large number of thin slices (3–4 mm). This plane is identical to that of CT or MRI and correlation between pathology and imaging is straightforward. We studied 70 cases of suspected different solid and cystic pancreatic tumors and we correlated the tumor size and location, the structure–consistency (areas of necrosis–hemorrhage–fibrosis–inflammation), the degree of vessels' infiltration, the size of pancreatic and common bile duct and the distance from resection margins. Missed findings by imaging or pitfalls were recorded and we tried to explain all discrepancies between radiology evaluation and the histopathological findings. Radiologic-pathologic correlation is extremely important, adding crucial information on imaging limitations and enabling quality assessment of surgical specimens. The deep knowledge of different pancreatic tumors' consistency and way of extension helps to improve radiologists' diagnostic accuracy and minimize the radiological-surgical mismatching, preventing patients from unnecessary surgery.

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1. Introduction

Pancreatic tumors represent a heterogeneous group of diseases presenting with different imaging characteristics. Malignant potential cannot always be decided on the basis of imaging findings and despite the advantages of multidetector computed tomography (MDCT) and magnetic resonance imaging (MRI), there is a well-known underestimation of pancreatic adenocarcinoma extent as well as a grey zone concerning mainly the treatment decision on cystic lesions.

In any case, imaging reflects the tumor characteristics on histopathology. Radiologic-pathologic correlation is a well estab-

lished way to understand and explain the imaging findings and realize the potential preoperative limitations. In our center, which is dedicated to hepatico-biliary and pancreatic surgery, we have recently adopted the axial slicing technique in pancreatic specimens. This technique permits the accurate correlation with axial MDCT and/or MRI images.

This is the first study to be performed on this novel technique of pancreatotomy specimen slicing, and there are not similar studies in the literature. The axial slicing technique offers many advantages in accurate estimation of tumors extend and in evaluation of possible discrepancies between the radiological and the histopathological findings. It can be applied as an important learning tool for the radiologists increasing their diagnostic capabilities in difficult or atypical cases of pancreatic tumors.

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2. Materials-methods

2.1. Patients group

This study is based on 70 cases of suspected pancreatic neoplasms evaluated by multi-detector computed tomography (MDCT) and/or Magnetic Resonance Imaging (MRI) who underwent surgery in our hospital. The patients' age ranged between 37 and 81 years old, 39 men and 31 women.

67 patients were considered as resectable while in three cases they met the criteria of borderline resectable disease and underwent surgery following chemotherapy as decided during the Multidisciplinary Team meeting. For resectability evaluation, the recent NCCN guidelines [1] as well as the consensus statement of the International Study Group of Pancreatic Surgery [2] were used.

2.2. Imaging evaluation

MDCT or MRI using a dedicated pancreatic protocol and state of the art techniques [3] was performed, no more than two weeks before surgery. The triple contrast phases taken on MDCT included a nonenhanced phase, a late arterial phase (10-s delay from the time of peak aortic enhancement), and a portal venous phase (35-s delay). Contrast-enhanced phases were performed craniocaudally, with thin collimation (0.5 or 0.625 mm), 120 kVp, and automatic modulation of the milliamperes. Three-millimeter axial images and 5 × 5-mm coronal and sagittal reformatted images were sent to the picture archiving and communication system and 0.5-mm-thick sections were sent to workstations for post processing (multiplanar reformations, maximum intensity projections, volume rendering and curved planar reformations) [4].

For the evaluation of resectability in locally advanced lesions Multi detector CT angiography was applied (MDCTA) using an additional early arterial phase. We routinely use bolus tracking with automatic power injectors and we set a region of interest on the abdominal aorta at the level of the celiac axis with a pre-defined enhancement threshold at 150HU. The maximum degree of circumferential contact (CC), the length of contact (LC) of the tumor with major vessels and the luminal narrowing of vessels (venous deformity, [VD]) were evaluated. For the reporting we used the standardized adenocarcinoma radiology reporting template as published in the consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association [5].

The sequences applied on MRI/MRCP were: T1-weighted gradient-echo; T2-weighted axial and coronal sequences, usually turbo spin echo; two dimensional (2D) and three dimensional (3D) MRCP; and T1-weighted 3D gradient-echo (GRE) before and after intravenous administration of gadolinium. Detection of pancreatic adenocarcinoma on MRI was based on unenhanced T1W (fat-suppressed) images and pancreatic-phase postgadolinium T1W spoiled GRE. Adenocarcinomas were expected to present as hypovascular lesions, while neuroendocrine tumors were expected to appear as hypervascular lesions. Magnetic Resonance Cholangiopancreatography (MRCP) was always done for tumors located in the pancreatic head and for periampullary lesions.

In equivocal cases Endoscopic Ultrasound (EUS) was performed and final decision for surgery was taken after the evaluation of EUS-FNA results.

2.3. Surgical techniques

All cases were reviewed preoperatively in our Multidisciplinary team meeting, where the optimal treatment strategy for each patient is decided. Staging laparoscopy in assessing pancreatic cancer resectability is not routinely used [6]. Pancreatectomies were performed using a standard technique whereas in the majority

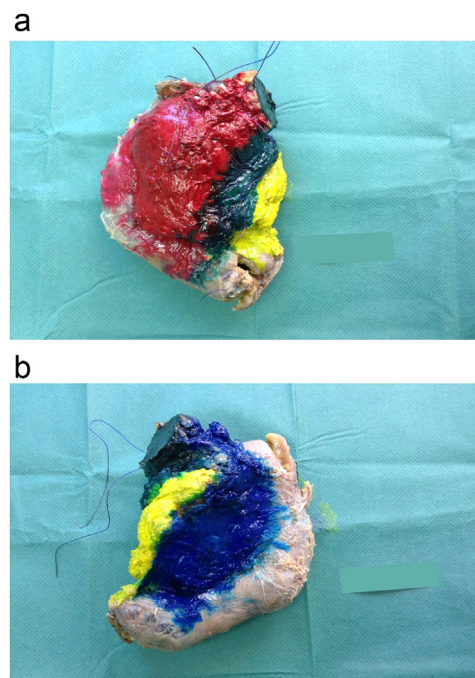


Fig. 1. Circumferential resection margins in a pancreatoduodenectomy specimen: anterior surface (red) (a), facing the SMV (green) (a), facing the SMA (yellow) (a,b) and posterior surface (blue) (b). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

of cases pylorus was preserved (pylorus-preserving pancreaticoduodenectomy: PPPD). Total pancreatectomy was carried out in cases of intraoperative repeated frozen section positive margins and in cases of multifocal intraductal papillary mucinous neoplasm (IPMN). Moreover total pancreatectomy was performed in patients where the pancreatic anastomosis could not be carried out with safety, mainly in those with soft and friable pancreatic texture.

Nowadays, despite the fact that clear and widely accepted definitions of resectability and borderline resectability exist, it seems that surgeons' capabilities can define resectability in many cases. The presence of distant metastases along with extensive, circumferential encasement of superior mesenteric artery or celiac abutment is considered as a non-resectable disease. Occurrences of inferior vena cava or aortic invasion and presence of unreconstructible portomesenteric occlusion are also included in the definition of unresectable disease [7].

However, as mentioned above, surgeons' capabilities and experience, especially in high volume centers, have lead to pancreatic surgery toward a new era regarding vascular reconstructions. There is clear evidence supporting straightforward exploration and resection in cases of reconstructible involvement of the mesentericoportal axis where complete tumor excision (R0) can be achieved [7–9]. On the other hand, arterial reconstruction cannot be regarded as a “gold standard”. Although there are reports in favor of SMA or celiac axis resection and reconstruction, there is lack of level I evidence regarding the benefits of arterial resection [7,8,10]. Another critical issue, often debated, is the extend of lymphadenectomy. We routinely perform standard lymphadenectomy as proposed by the ISGPS group [8,11].

2.4. Histopathology evaluation

In our hospital, the macroscopic evaluation of the PPPD specimens is performed by the pathologists using the axial slicing technique. After fixation and prior to slicing, inking of the margins and specimen surfaces is performed (Fig. 1a and b). Different col-

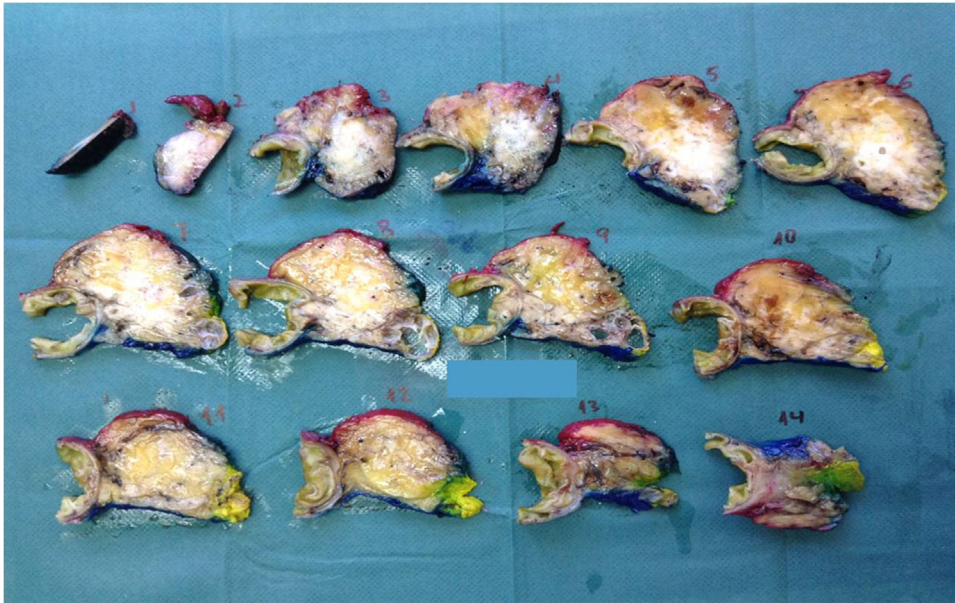


Fig. 2. After axial slicing of a pancreatoduodenectomy specimen, the slices are arranged in sequential order. To allow optimal correlation with preoperative imaging, they are arranged from cranial to caudal.

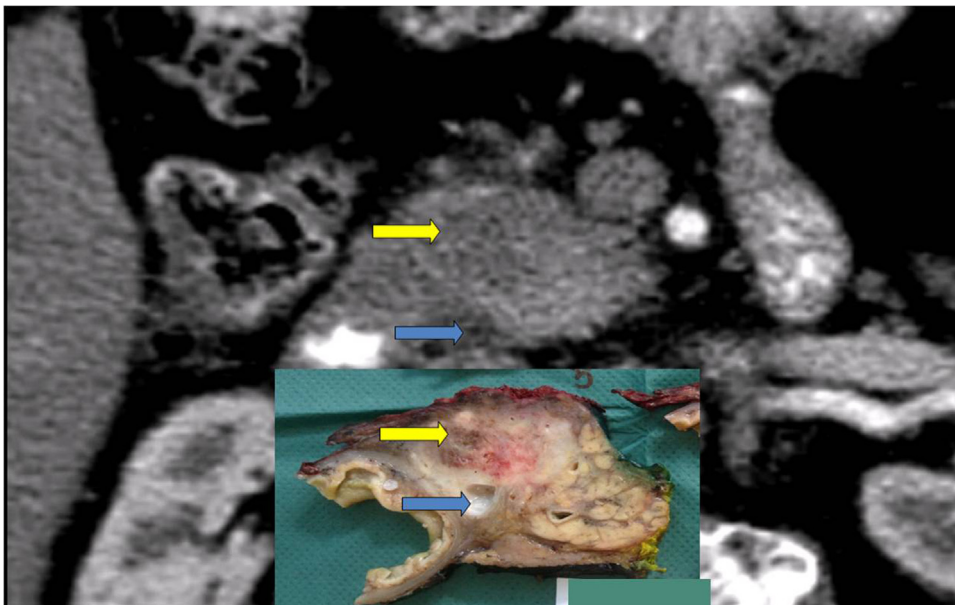


Fig. 3. Radiologic-pathologic correlation of a hypovascular mass in the anterior aspect of the pancreatic head on contrast enhanced CT (yellow arrow). Cystic part of a solid tumor is also evident (blue arrow). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

ors of ink are used, according to an agreed color code. This allows unequivocal identification of the surfaces during both macroscopic and microscopic examination.

The specimen is sliced in an axial plane that is perpendicular to the longitudinal axis of the descending duodenum and it results in a large number of thin slices (3–4 mm), 12 on average or more (Fig. 2). This allows good view of all the key anatomical structures such as the ampulla, common bile duct and main pancreatic duct which are always found at the same position in the specimen slices and are therefore easily identified. Given this, any pathological lesion is identified easily and is located in relationship with the surrounding anatomical structures. As far as the assessment of the margin status is concerned, with this slicing technique, the entire surface of the pancreatic head can be inspected in detail in every specimen

slice. Taking in consideration all the above, this technique facilitates tissue sampling for microscopic examination.

This plane is identical to that of CT imaging or MRI leading to a straightforward radiological-pathological correlation. For tumors located in the body and tail we use the sagittal imaging plane for accurate correlation.

3. Results

The final results of the total 70 cases after histopathology evaluation were as follows: 33 pancreatic ductal adenocarcinomas and 2 acinar cell carcinomas, 4 ampullary adenocarcinomas, 6 neuroendocrine tumors (NETs), 4 common bile duct adenocarcinomas, 1 duodenal adenocarcinoma, 1 gastrointestinal stromal tumor (GIST),

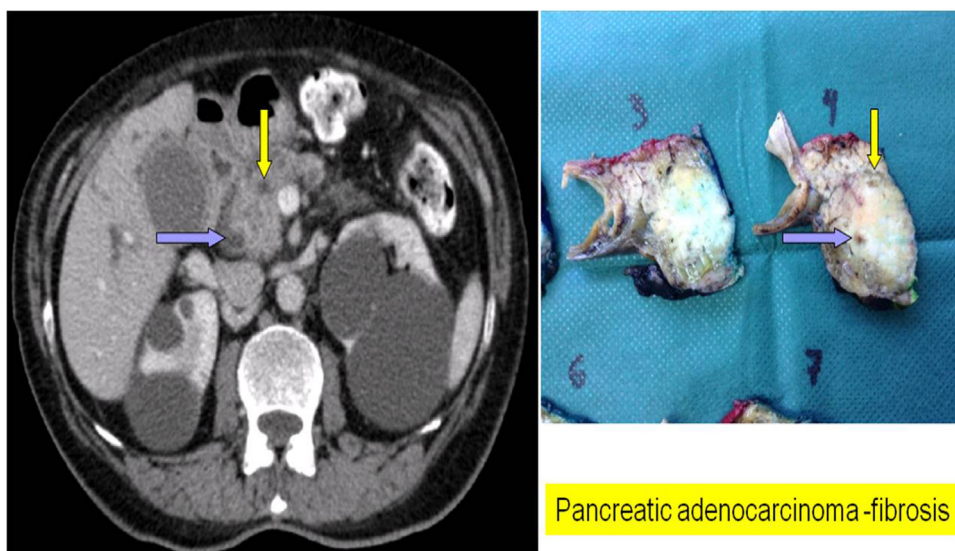


Fig. 4. Radiologic-pathologic correlation of an isoattenuating pancreatic adenocarcinoma on contrast enhanced CT due to fibrosis. Dilated pancreatic duct (blue arrow) and common bile duct (yellow arrow) are also evident. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

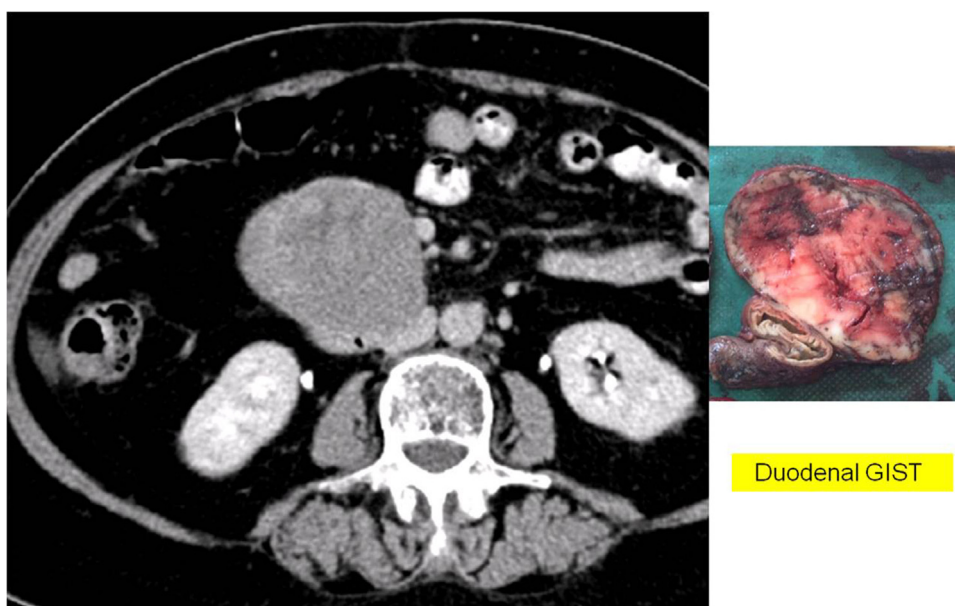


Fig. 5. Radiologic pathologic correlation of a large exophytic and partially necrotic duodenal GIST adjacent to the pancreatic head that was intact and displaced.

1 ampullary adenoma, 2 microcystic and 1 macrocystic serous adenomas, 4 mucinous cystic neoplasms (MCN), 5 intraductal papillary mucinous tumors (IPMN), 2 solid pseudopapillary tumors (SPT), 1 paraganglioma, 1 sclerosing cholangitis, 1 focal autoimmune pancreatitis, 1 ampulla fibrosis. Additionally four very small NETs and six IPMNs were incidentally revealed in 10 patients together with the primary tumor.

3.1. Typical findings in pancreatic adenocarcinoma

In 26 cases the imaging findings were typical and correlated perfectly with the histopathologic findings. As typical findings were considered: the presence of a mass showing attenuation difference, a hypovascular lesion (Fig. 3), pancreatic ductal dilatation and cut off, double duct sign, atrophy of the gland upstream of the tumor, signs of locally advanced disease, evidence of metastases or any combination of the above.

3.2. Atypical findings in pancreatic adenocarcinoma

As atypical-rare imaging findings were considered: the presence of an isoattenuating mass (3 cases) (Fig. 4), an exophytic tumor (finally proved to be a duodenal GIST) (Fig. 5), a diffusely infiltrating tumor (1 case) and the totally or partially cystic appearance (2 cases) (Fig. 6). Isoattenuation was in all cases attributed to the high grade of tumor fibrosis. Concerning the cystic parts of the solid tumors these were characterized by histopathology as cystic degeneration due to tumor necrosis, as cystic parts in variants of ductal adenocarcinoma or as small retention cysts (Fig. 3).

3.3. The heterogeneous group of cystic lesions

Despite the well known imaging difficulties in preoperative differential diagnosis of the exact type of a cystic tumor, the radiologic-pathologic correlation was excellent in all cases of

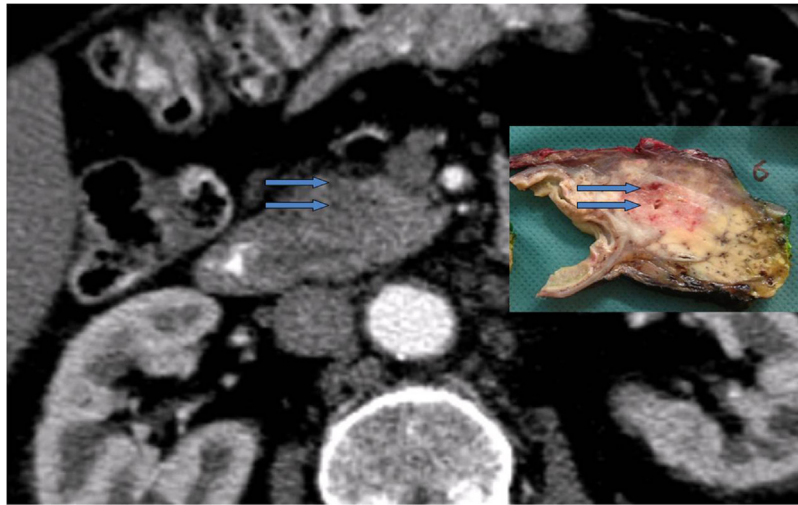


Fig. 6. Tiny cystic areas inside a ductal adenocarcinoma are recognized and correlated on CT images and histopathology (blue arrows). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

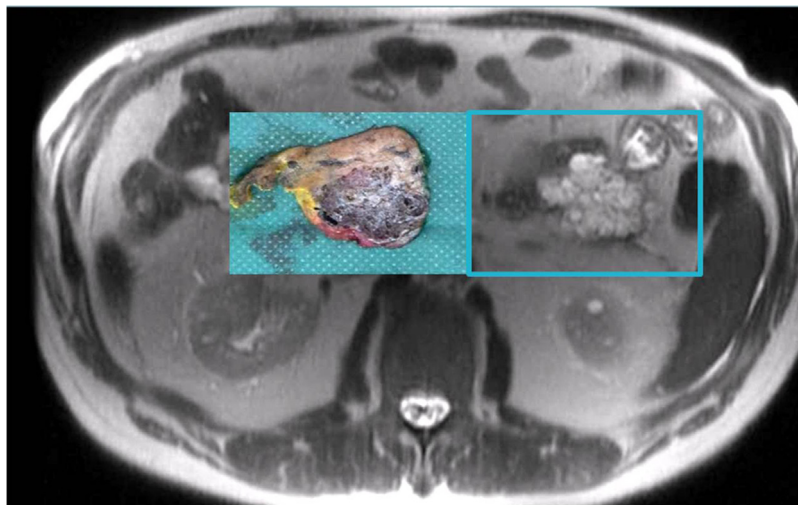


Fig. 7. Microcystic serous adenoma: typical sponge-like appearance of a large microcystic lesion perfectly correlated on T2-w MR image and macroscopic evaluation.

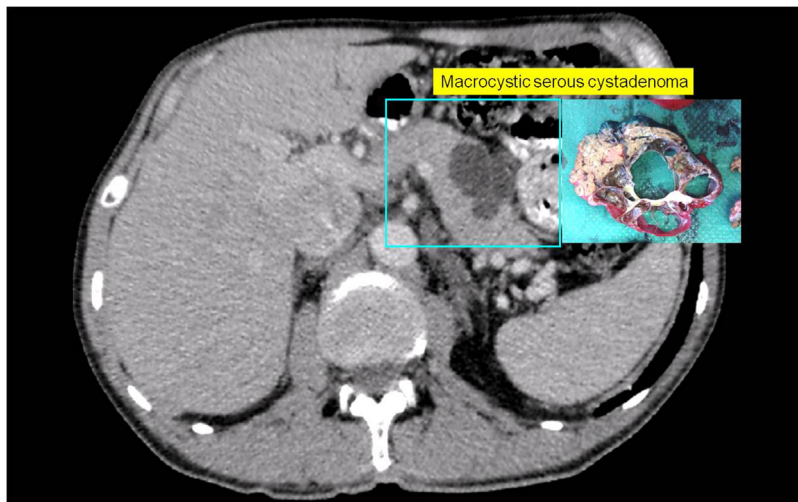


Fig. 8. Macrocystic serous adenoma: the large cystic spaces and the thin septa are evident in this well-defined benign cystic lesion on contract enhanced CT and macroscopy.

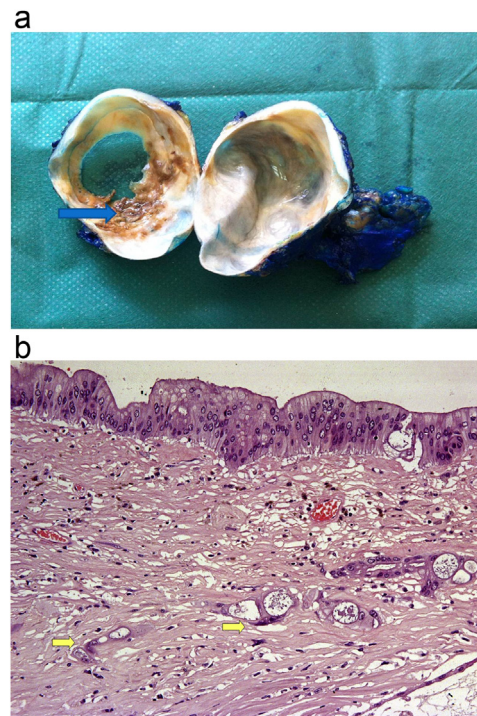


Fig. 9. A mucinous cystic neoplasm is shown, presenting a fibrotic area (blue arrow) and no evidence of adenocarcinoma (a) in the macroscopic evaluation. Microscopically (b: H/EX200) an associated invasive carcinoma of less than 0.5 cm in size behind the fibrotic area was revealed (yellow arrow). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

microcystic (Fig. 7) and macrocystic serous adenomas (Fig. 8), mucinous cystic neoplasms (MCN), different types of IPMNs and SPTs. The solid and cystic parts were well correlated as well as the thickness of the cyst wall and the component. In one case of mucinous cystic neoplasm, microscopic evaluation revealed an associated invasive carcinoma, which was missed both on macroscopic evaluation and on imaging, even retrospectively (Fig. 9a and b).

3.4. The hypervascular lesions

All lesions that were proven to be NETs were hypervascular on imaging (Fig. 10). Although early arterial phase is not routinely used except for MDCTA, missed NETs are in most of the cases related to the very small size and not the contrast phase. The rare

paraganglioma was also hypervascular thus preoperative differential diagnosis from a NET was not achieved. Macroscopically, these tumors share similar features (they are well-circumscribed mostly solid tumors with pale or red-tan color) and even in microscopy the differential diagnosis can be challenging (Fig. 11). Acinar cell tumors were also hypervascular both on imaging and histopathology.

3.5. The very small tumors

In one case of ampullary tumor only secondary imaging findings were evident (dilatation of pancreatic duct, common bile duct or both) while the tumor was not revealed because of its very small size. Macroscopically, dilatation of both pancreatic and common

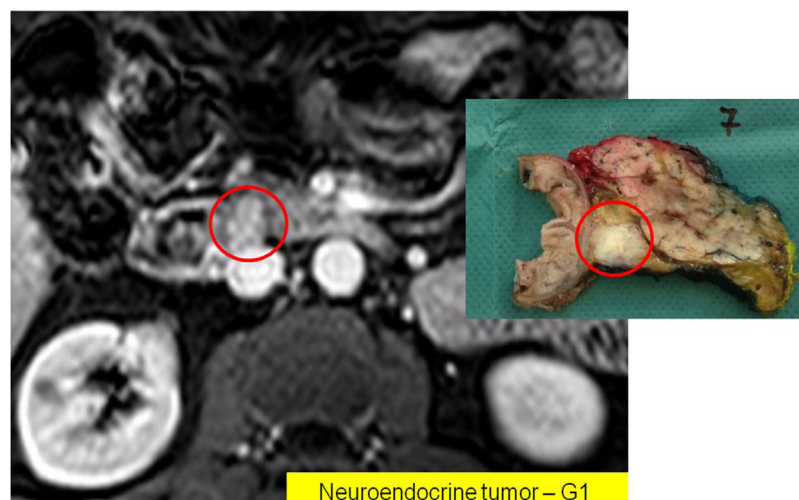


Fig. 10. MRI-pathologic correlation of a small hypervascular neuroendocrine tumor in the periampullary area.

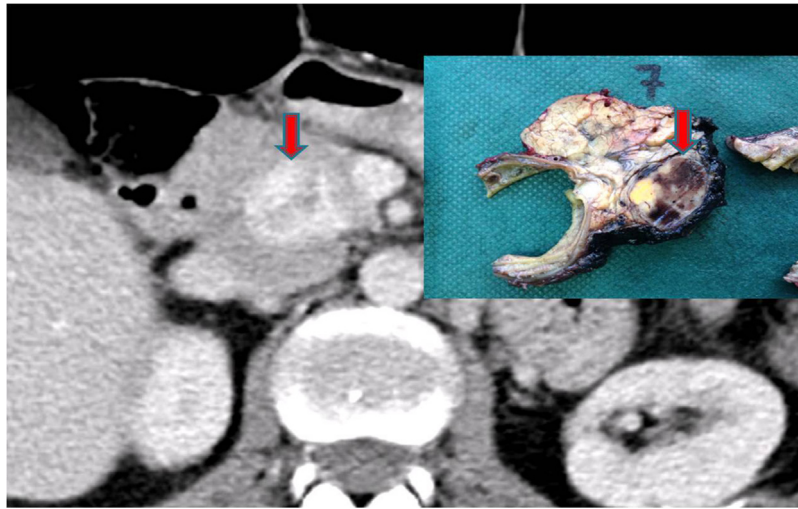


Fig. 11. A rare pancreatic head hypervascular paraganglioma showing marked heterogeneity was revealed in a patient suffering from Hirschsprung's disease.

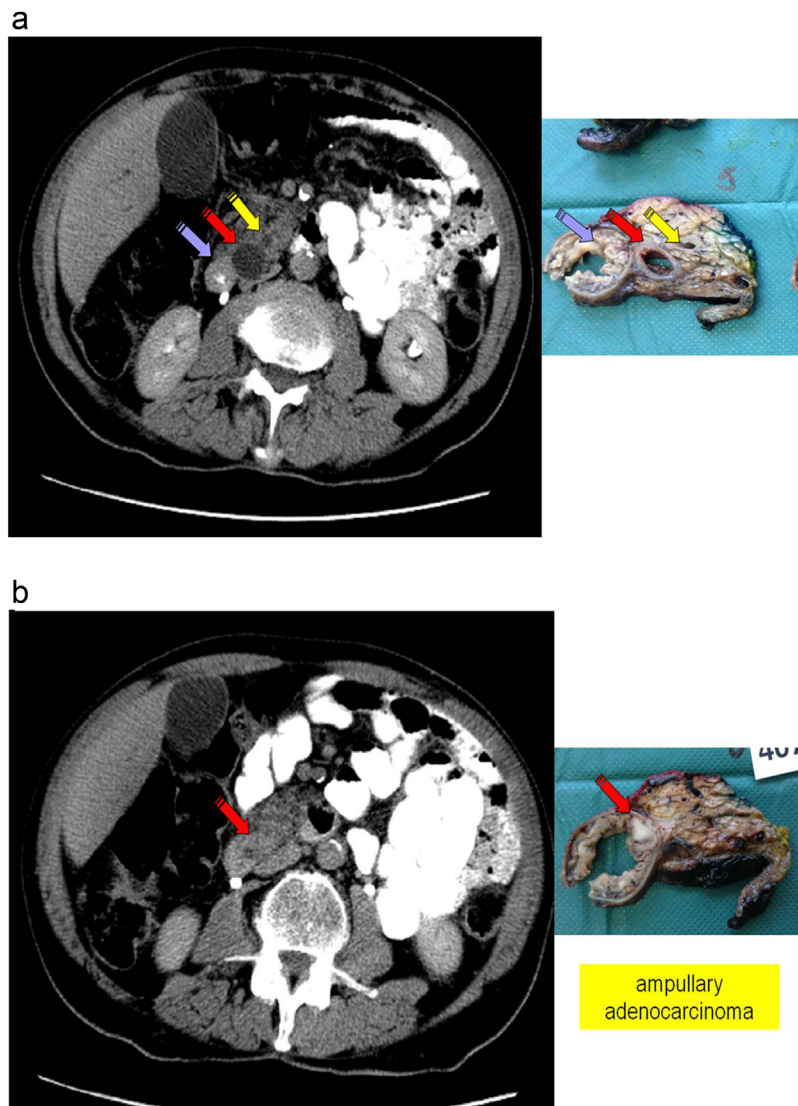


Fig. 12. Nice depiction and correlation of the duodenum (blue arrow), the markedly dilated CBD (red arrow) and the less dilated MPD (yellow arrow) (a). A very small ampullary adenocarcinoma was found that was missed by imaging (red arrow in b). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

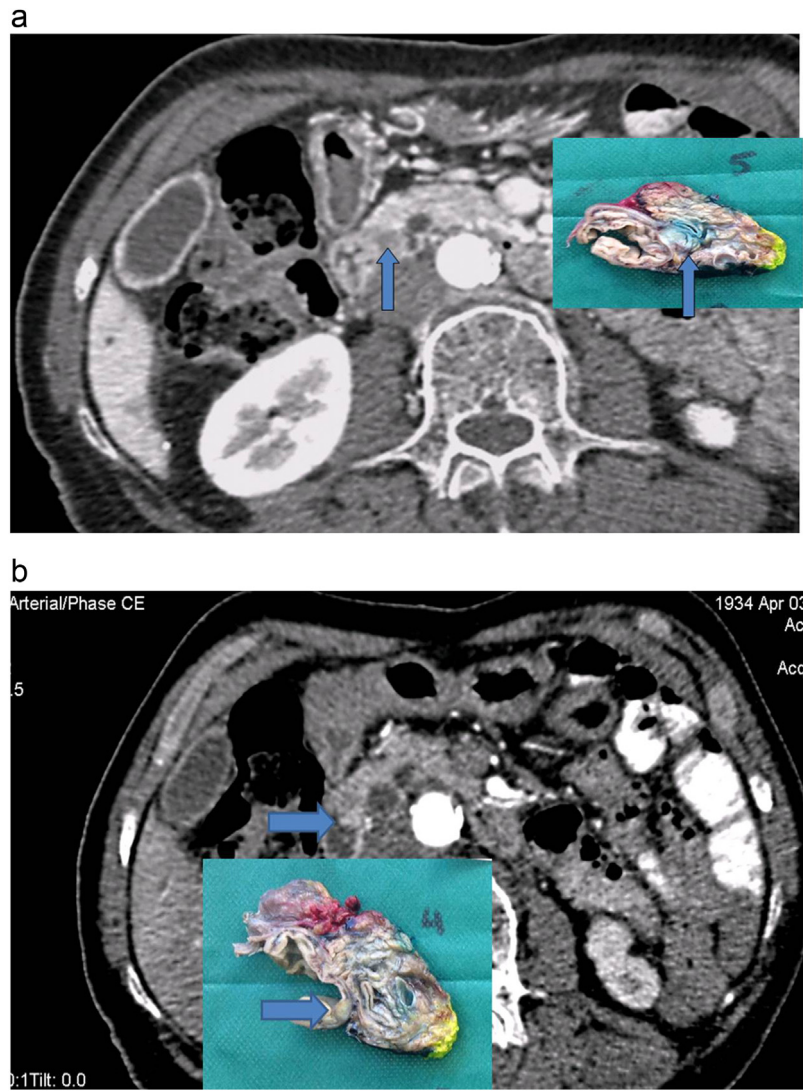


Fig. 13. The fibrotic and hyperplastic ampulla was misinterpreted as a tumor on imaging (blue arrow in a). A small duodenal NETG1, just above the fibrotic ampulla, was revealed on histopathology (blue arrow in b). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

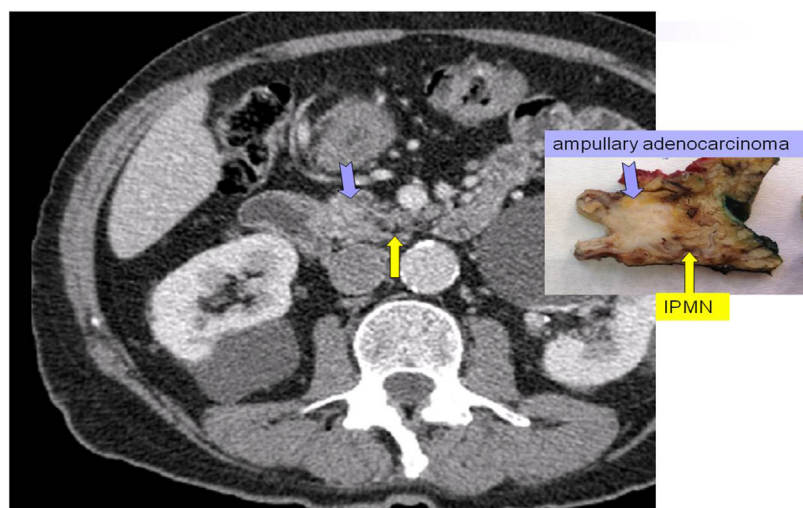


Fig. 14. A large periampullary tumor (blue arrow) together with an intraductal papillary mucinous neoplasm (IPMN) in the uncinete process (yellow arrow) is evident. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

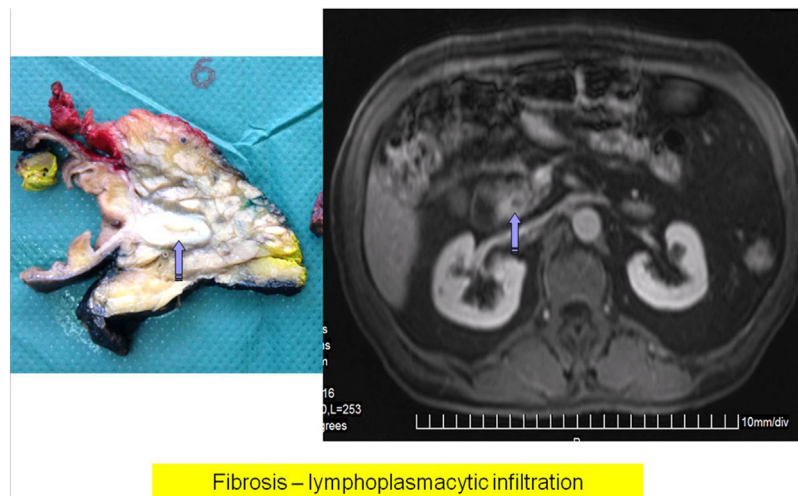


Fig. 15. A misleading case of post inflammatory fibrosis presenting as markedly thickened wall of the distal common bile duct.

bile duct was observed, caused by a small whitish tumor at the ampulla (Fig. 12a and b). It should be noted that in one case it was possible to locate retrospectively a very small NET in the duodenal wall just above a fibrotic ampulla of Vater, on arterial phase and thin section axial MDCT. Macroscopically, it was a small tanned solid tumor, 0.6 cm in greatest the diameter, located in the duodenal wall (Fig. 13a and b).

3.6. The missed co-existed tumors

As mentioned before, in 10 patients histopathology revealed more than one lesion (4 NETs and 6 branch duct IPMNs). Two small IPMNs were located in retrospective evaluation of the images on the workstation after the histopathology assessment. They were branch-duct IPMNs that macroscopically appeared as grapelike dilations of the branch ducts (Fig. 14). The additional findings were considered as incidental rather benign lesions and their presence did not change the therapeutic plan.

3.7. Imaging pitfalls

We encountered three cases of wrong interpretation of a mass-like lesion as a tumor. The first case presented with atypical imaging finding of segmental autoimmune pancreatitis. In the second case there was a “malignant” type stenosis of the distal common bile duct in a patient with painless obstructive jaundice that was finally proved to be fibrosis (probably a chronic stage of sclerosing cholangitis) (Fig. 15). Macroscopic evaluation was also misleading, revealing thickening of the common bile duct wall was observed, raising suspicion of carcinoma. Finally in the third case presenting with a double duct sign and an enlarged ampulla, evident also in macroscopy, microscopic evaluation revealed hyperplasia and fibrosis of the ampulla and an incidental finding of a small NET just above the ampulla (evident also in the retrospective review of thin slices on MDCT images) (Fig. 13).

3.8. The accuracy in resectability evaluation

67 patients were considered as resectable and 3 as borderline resectable and were operated after preoperative chemotherapy according to current guidelines. No surgery was aborted due to metastases or locally advanced tumors, but finally there were three R1 resections (distance of the tumor from the resection margin less than 1 mm). Vascular reconstructions were performed in five cases after careful preoperative evaluation of MDCTA. Vascular anatomic

variations were also noticed in ten cases (common hepatic artery originating from the superior mesenteric artery, replaced or accessory left or right hepatic artery, right hepatic artery originating from the aorta and left hepatic artery originating from the common hepatic artery) and were also studied properly on 3D images before surgery planning. All patients were finally reviewed during the postoperative oncology meeting and chemotherapy was proposed according to the final disease stage.

The accuracy in resectability evaluation after chemotherapy was 100% and all our patients underwent curative R0 resections. Fibrosis was found after treatment and no vessels infiltration was revealed by histopathology, even in the cases where there wasn't an evident clear plan on imaging between the main peripancreatic vessels and the tumor (Fig. 16).

4. Discussion

The axial slicing technique is a dissection technique introduced by C. Verbeke and is based on serial specimen slicing in the axial plane [12], instead of the traditional procedure with longitudinal opening of the main pancreatic and/or common bile duct and slicing along the plane defined by both ducts. Serial slicing along a single fixed plane (identical to the axial plane of computed tomography) without disruption of the tumor and native structures allows careful evaluation of the cancer and its relationship to both the various specimen surfaces and the key anatomical structures like the surrounding vessels, as well as the entire circumferential margin (CRM) [13]. These advantages are of great importance for accurate staging and reliable identification of tumor origin.

Axial slicing is easy to perform, regardless of the location and nature of the pathology encountered, allowing extensive views of the lesion as the entire surface (or CRM) of the pancreatic head remains intact. The numerous specimen slices generated by the axial dissection technique provide also excellent views of the local anatomy and pathological changes. The application of this technique furthermore enhances the ability of accurate radiologic-pathologic correlation as the orientation of slices is similar with axial CT and/or MRI.

Contrast enhanced images seem to better correlate with macroscopic findings as detailed evaluation of the structure and tumor consistency is possible [14–18]. Concerning the cystic pancreatic tumors, T2 w images correlated better with histopathology in all tumor types. It should be noticed that in the microcystic adenomas contrast enhanced images were misleading, mainly because of intense enhancement and the pseudo-solid appearance which

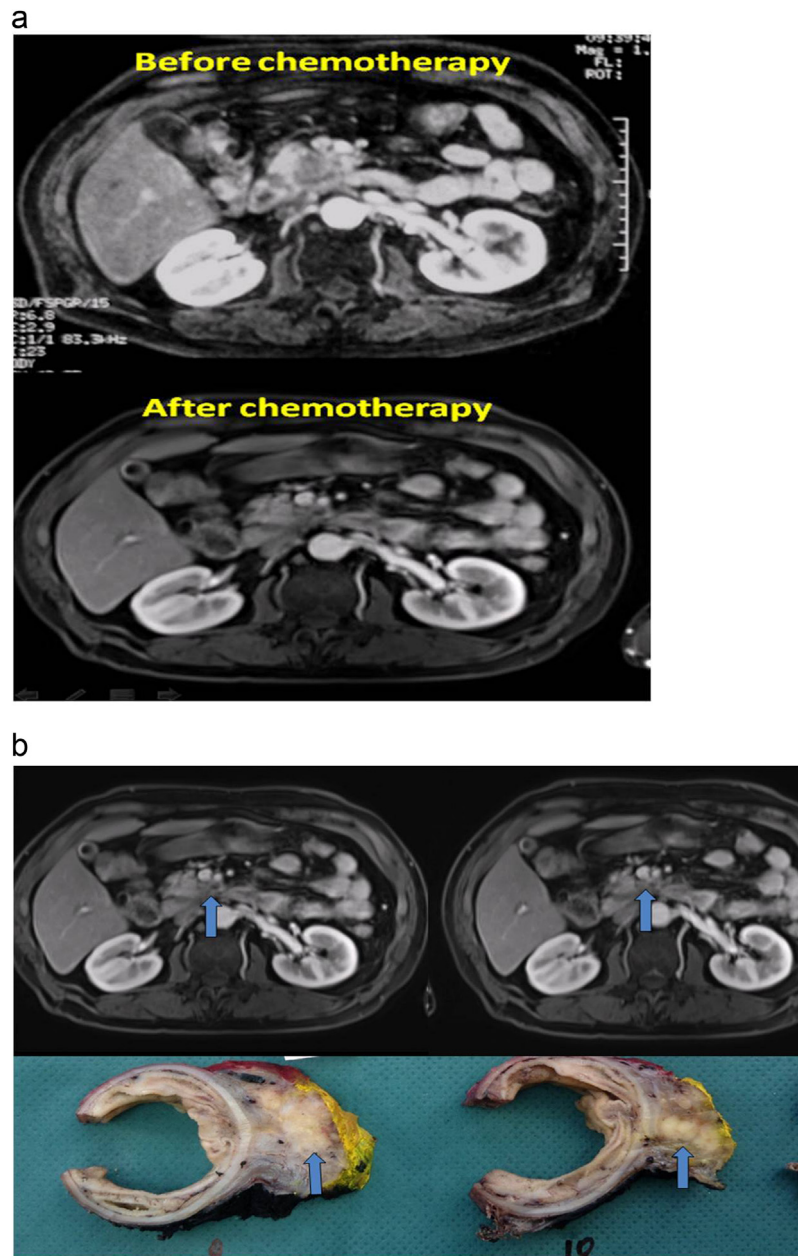


Fig. 16. A borderline resectable tumor on contrast enhanced CT before and after treatment (a). The radiologic-pathologic correlation of the specimen with evident post treatment changes adjacent to superior mesenteric artery (blue arrows in b). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

should be kept in mind for this type of sponge-like tumors [19]. MRI was also able to depict hemorrhagic content in SPT. On the other hand, differential diagnosis between infiltrative IPMN of the main duct and pancreatic adenocarcinoma was not possible by imaging in our cases. The size of the dilated pancreatic duct seems not to correlate directly with the possibility of the presence of an IPMN, although it has been described in the literature as a worrisome feature [20].

DWI technique was not applied in all cases, but on the other hand the evaluation of this sequence was beyond the scope of this article. Nevertheless, it should be noted that even with the use of this technique it was not possible to evaluate early development of adenocarcinoma in the walls of a mucinous cyst in one case, while there was strong restriction in diffusion in a case of a SPT mimicking pancreatic adenocarcinoma. The well known overlap in ADC values of pancreatic cancer and mass-forming focal

pancreatitis [21,22] was also noticed in our study in the three cases of wrong interpretation of sclerosing cholangitis with fibrosis, ampulla hyperplasia with fibrosis and focal autoimmune pancreatitis as cholangiocarcinoma, periampullary tumor and pancreatic adenocarcinoma respectively.

As far as accuracy in resectability status is concerned, it is known that MDCT and MDCTA are the most effective tools used for the therapeutic planning specifically in locally advanced and borderline marginally resectable tumors [4]. This new category recognized as “borderline resectable tumors” has lead to conflicting statements on the accurate definition [23,24]. It seems that these patients are not good candidates for immediate surgery, while the use of preoperative chemotherapy may increase the possibility of an R0 resection [25,26].

While histological diagnosis is not required for patients with presumed pancreatic cancer who are going to be treated with

surgery, biopsy is required prior to initiation of neoadjuvant therapy in patients with borderline resectable pancreatic cancer. Fine needle aspiration (FNA) is the preferred method for obtaining a tissue diagnosis and it is also applied in our center in patients with borderline or unresectable pancreatic tumors. Percutaneous CT or EUS guided FNA can be used alternatively, depending on the site and the size of the tumor [27].

In all but three cases in our study, preoperative imaging evaluation was correct and R0 resections were achieved. In three cases the tumor was finally more extended than predicted ending up to R1 resections. This was mainly attributed to underestimation of the degree of vessels infiltration, something also described in other studies. What is important to emphasize it that although in the literature the accuracy of MDCT and MDCTA vary according to the type of the scanner used, all authors agree that sensitivity and positive predictive value reach 100% while negative predictive value and specificity are lower (75–85% in different series).

Until now accurate specific criteria for the estimation of resectability following chemotherapy are lacking, thus the evaluation has to be done using the established resectability guidelines before treatment. Nevertheless it should be noted that fibrosis as a result of the treatment could be misinterpreted as residual tumor adjacent to the vessels. So, accurate evaluation specifically in fibrotic tumors is not always possible and may lead to overestimation of tumors extent, preventing a possible curative operation. In a recent study it is suggested that response of borderline resectable pancreatic cancer to neoadjuvant therapy is not definitely reflected by radiographic indicators [28] thus in the absence of metastases, patients with borderline tumors may undergo a surgical attempt even if they do not fully fulfill the criteria of resectability as estimated by imaging.

5. Conclusions

Radiologic–pathologic correlation of pancreatic tumors with the axial slicing technique offers many advantages by adding important information. First of all it permits a detailed quality assessment of the surgical specimen and in the same time a retrospective evaluation of the possible missed additional findings or mismatches between imaging and histopathology findings. Through the recognition of the histopathology basis of atypical findings, a better understanding of the facts leading to incorrect radiologic interpretation is achieved while in the same time the reasons of under- or overstaging are more clearly depicted. This may also serve as an excellent educational tool enhancing radiologists' ability toward more accurate diagnoses and surgeons toward a better understanding of imaging limitations.

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