



The Role of Imaging in Current Treatment Strategies for Pancreatic Adenocarcinoma

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In pancreatic cancer, imaging plays an essential role in surveillance, diagnosis, resectability evaluation, and treatment response evaluation. Pancreatic cancer surveillance in high-risk individuals has been attempted using endoscopic ultrasound (EUS) or magnetic resonance imaging (MRI). Imaging diagnosis and resectability evaluation are the most important factors influencing treatment decisions, where computed tomography (CT) is the preferred modality. EUS, MRI, and positron emission tomography play a complementary role to CT. Treatment response evaluation is of increasing clinical importance, especially in patients undergoing neoadjuvant therapy. This review aimed to comprehensively review the role of imaging in relation to the current treatment strategy for pancreatic cancer, including surveillance, diagnosis, evaluation of resectability and treatment response, and prediction of prognosis.

Keywords: Pancreatic cancer; Imaging; Diagnosis; Resectability; Response evaluation; Prognosis

INTRODUCTION

Pancreatic cancer is the fifth most common cause of cancer-related deaths in South Korea, and the fourth leading cause of cancer-related deaths in the United States and Europe (1-4). Surgical resection is considered to be the only potentially curative treatment for pancreatic cancer. The majority of pancreatic cancer patients are diagnosed in locally advanced or metastatic status. Only 15% to 20% of pancreatic cancer patients are candidates for surgical resection (5).

The role of imaging has been evolving in line with the development of pancreatic cancer treatment, and imaging plays a crucial role in the screening, diagnosis, preoperative staging, postoperative surveillance, and treatment response

evaluation of pancreatic cancer. This review focused on the latest treatment strategies for pancreatic cancer, as well as the role, limitations, and the future direction of imaging.

Current Treatment Strategy for Pancreatic Cancer

Pancreatic cancer is divided into four categories according to the local tumor extent and the presence of disseminated disease (Fig. 1). Treatment options vary for each category as follows (5-7):

1) Resectable: tumors with a high probability of margin-negative resection

2) Borderline resectable: tumors that are involved with nearby structures and are neither resectable nor clearly unresectable with a high chance of a positive microscopic margin (R1) resection

3) Locally advanced: tumors that are involved with nearby structures to an extent that renders them unresectable despite the absence of evidence of metastatic disease

4) Metastatic: tumors that have disseminated.

Margin-negative (R0) resection of localized pancreatic cancer is considered as the only potentially curative treatment. The 5-year survival rate is approximately 18–24% when a R0 resection is achieved (8). R0 resection

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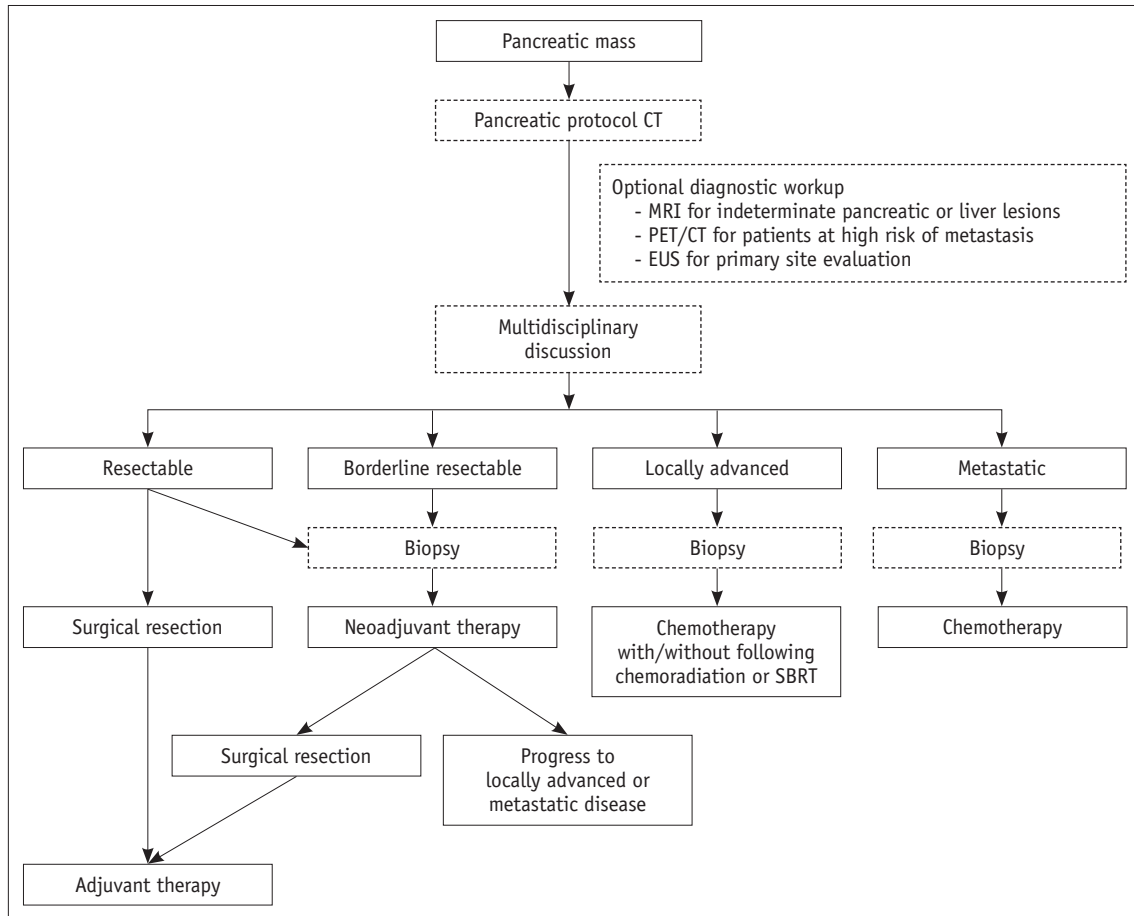


Fig. 1. Treatment strategy for pancreatic cancer. CT = computed tomography, EUS = endoscopic ultrasound, MRI = magnetic resonance imaging, PET = positron emission tomography, SBRT = stereotactic body radiation therapy

is defined by the absence of tumor cells within 1 mm of the surgical margin. Otherwise, the margin status is defined as a R1 or positive macroscopic margin (R2) (9, 10). Patients categorized with either R1 or R2 margins in surgical resection show poor 5-year survival rates of 8–11%, similar to locally advanced disease (9, 11–14). Patients who are considered to have high probability of R0 resection in radiologic evaluation are classified as “resectable,” and may be candidates for upfront surgery. To improve the survival of R0 resection patients, various adjuvant chemotherapeutic or chemoradiotherapeutic regimens have been attempted. According to two recent clinical trials, patients treated with combination chemotherapies, including modified 5-FU/leucovorin, oxaliplatin, and irinotecan (FOLFIRINOX) or gemcitabine + capecitabine, showed significantly better overall survival than those treated with gemcitabine monotherapy (15, 16). In all of the patients who underwent upfront surgical resection, adjuvant therapy is recommended, and the abovementioned

combination chemotherapies are preferred in patients with good performance status (17, 18).

Localized pancreatic cancers with a low likelihood of R0 resection can be divided into borderline resectable and locally advanced disease. Borderline resectable pancreatic cancer indicates tumors that are potentially downstaged and resectable upon favorable response to neoadjuvant therapy. Neoadjuvant therapy can increase the R0 resection rate in subsequent surgical resection, treat micrometastasis at an earlier stage, and provide an observation period to exclude pancreatic cancer showing rapid progression and poor response to therapy. Chemotherapy or chemoradiation therapies are more likely to be tolerated in the preoperative stage than in the postoperative stage (14, 19). Two meta-analyses illustrated that approximately one-third of the borderline resectable pancreatic cancers could be completely resected, and the 5-year survival rate of those cases was promising (> 20%) (20, 21). Chemotherapy with or without subsequent chemoradiation is commonly used in

neoadjuvant therapy (22). However, no specific regimen is recommended due to limited evidence (5).

In unresectable pancreatic cancers, including locally advanced and metastatic disease, systemic chemotherapy is commonly employed. There are numerous options for a chemotherapeutic regimen. FOLFIRINOX/modified FOLFIRINOX, gemcitabine + nab-bound paclitaxel, and gemcitabine + cisplatin are the preferred regimens for patients with good performance status, while gemcitabine, capecitabine, and 5-FU monotherapy are the preferred regimens for patients with poor performance status. Chemoradiation or stereotactic body radiation therapy may be added for definitive treatment in locally advanced disease, and for palliative measures in metastatic disease.

Conventional Role of Imaging

Surveillance of Pancreatic Cancer

Surveillance is not recommended for asymptomatic general populations. In general populations, in which the incidence of pancreatic cancer is low (lifetime risk < 1.3%), the yield of surveillance is also low.

High-risk individuals (> 5% lifetime risk of pancreatic cancer) could be potential candidates for pancreatic cancer surveillance. High-risk individuals include 1) first-degree relatives (FDRs) of patients with pancreatic cancer from a familial pancreatic cancer kindred with at least two affected FDRs; 2) patients with Peutz-Jeghers syndrome; and 3) p16, BRCA2, and hereditary non-polyposis colorectal cancer mutation carriers with ≥ 1 affected FDRs (23). The detection of T1N0M0 pancreatic cancer that could be treated with R0 resection and high-grade dysplastic lesions should be the goal of surveillance. As screening modalities, endoscopic ultrasound (EUS) and magnetic resonance imaging (MRI) are preferred. These imaging modalities have excellent sensitivity for small pancreatic lesions and do not use ionizing radiation. A few studies compared the diagnostic accuracy of EUS and MRI in a surveillance setting (24, 25), and showed that EUS is more accurate in the detection of small solid lesions (24). However, MRI is more sensitive in the detection of cystic lesions and main pancreatic duct communication, allowing the diagnosis of intraductal papillary mucinous neoplasm, which is considered to be a precancerous lesion (24, 26).

Imaging Diagnosis of Pancreatic Cancer

For imaging diagnosis of pancreatic cancer, diverse

imaging modalities, including transabdominal ultrasound (US), computed tomography (CT), MRI and magnetic resonance cholangiopancreatography (MRCP), positron emission tomography (PET), and EUS are commonly used. The characteristics of these imaging modalities are summarized in Table 1.

Transabdominal Ultrasound

US is commonly used for initial imaging evaluation in asymptomatic or symptomatic patients. It is non-invasive, relatively inexpensive, and easily accessible. Pancreatic cancer often appears as a distinct or infiltrative hypoechoic focal pancreatic lesion, commonly accompanied by dilatation of the main pancreatic duct or bile duct. In conventional US, most focal pancreatic lesions exhibit hypoechogenicity; therefore, it is difficult to distinguish between pancreatic cancer and other focal pancreatic lesions. The diagnosis of pancreatic cancer in transabdominal US is highly dependent on the operator's technique, patient's body habitus, as well as the location and size of the tumor. The sensitivity and specificity of transabdominal US are considerably variable, ranging 68–95% and 50–100%, respectively (27–29). The limited diagnostic performance of US limits its role in the initial evaluation and lesion detection; therefore, US is rarely used for diagnosis, resectability evaluation, and response evaluation of pancreatic cancer.

Computed Tomography

CT shows excellent temporal and spatial resolution as well as wide anatomic coverage. It is recommended as the primary imaging modality for resectability evaluation according to the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines (5, 7). The use of CT for treatment decision-making should include a thin (preferably submillimeter) and continuous section and ≤ 3 mm reconstruction, multiplanar reformation including the coronal plane, and maximal intensity projection or three-dimensional (3D) volumetric thick section images for vascular evaluation. For a proper evaluation of pancreatic lesions and adjacent vascular structures, both the pancreatic phase (40–50 seconds from intravenous contrast injection) and venous phase (65–70 seconds) should be included (6, 7). If the CT images do not conform to the pancreatic protocol, re-examination using a high-quality pancreatic protocol CT is recommended for precise evaluation of tumor staging (30). Since pancreatic cancer can show rapid progression and dissemination,

Table 1. Characteristics of the Imaging Modalities Used for Diagnosis of Pancreatic Cancer

Imaging Modalities	Strengths	Weaknesses	Diagnostic Role in Imaging	Diagnostic Performance for Diagnosis of Pancreas Cancer
US	Accessibility	Sonographic window could be limited; operator dependent	Initial assessment of pancreatic lesion	Sensitivity 68–95% Specificity 50–100%
CT	High temporal and spatial resolution; wide anatomic coverage	Inappropriate for surveillance due to ionizing radiation; limited diagnostic performance in small pancreatic, hepatic, and peritoneal lesions	Primary imaging modality of pancreas cancer diagnosis, resectability evaluation, response evaluation	Sensitivity 89–91% Specificity 85–90%
MRI	Superior soft-tissue contrast; visualization of pancreatic and biliary duct abnormality	Lower spatial resolution; motion artifact	Adjunct diagnostic tool of equivocal pancreatic lesion and small hepatic lesion	Sensitivity 84–93% Specificity 82–89%
EUS	High spatial resolution; could be coupled with fine needle aspiration biopsy	Invasive; operator dependent	Adjunct diagnostic tool of equivocal pancreatic lesion Histologic diagnosis	Sensitivity 89–91% Specificity 81–86%
¹⁸ FDG PET/CT	Majority of pancreas cancer show increased ¹⁸ FDG uptake; useful in evaluation of lymph node and distant metastasis	Difficult to distinguish between pancreatic cancer and pancreatitis	Evaluation of lymph node and distant metastasis	Sensitivity 89–91% Specificity 70–72%

CT = computed tomography, EUS = endoscopic ultrasound, MRI = magnetic resonance imaging, PET = positron emission tomography, US = ultrasound, ¹⁸FDG = ¹⁸fluorine-2-fluoro-2-deoxy-D-glucose

imaging evaluation should be performed within a month of definitive treatment (31).

Pancreatic cancer is usually seen as a mass lesion that exhibits hypoenhancement compared to the adjacent parenchyma in the pancreatic phase. It may cause interruption and upstream dilatation of the pancreatic or bile duct, abutment or encasement of adjacent vascular structures, direct invasion of adjacent organs, and regional lymph node enlargement. In meta-analyses, CT has shown sensitivity of 89–91% and specificity of 85–90% for the diagnosis of pancreatic cancer (32-34). Liver, peritoneum, and distant lymph nodes are the most common metastatic sites. Approximately 5% of pancreatic cancer may exhibit isoattenuation in both the pancreatic parenchymal and venous phases (35, 36). In addition, CT shows low diagnostic accuracy for small liver, peritoneal, or lymph node metastasis (37-39).

Magnetic Resonance Imaging and Magnetic Resonance Cholangiopancreatography

MRI for pancreatic cancer evaluation is recommended to include the following sequences: T2-weighted fast spin-echo; T1-weighted in-and-out of phase gradient-echo; T2-weighted fat-suppressed fast spin-echo; diffusion weighted imaging (DWI); 3D T1-weighted fat-suppressed gradient-

echo dynamic images including precontrast, pancreatic, venous, and equilibrium phases; and T2-weighted MRCP sequences (7). The availability of various sequences and the superior soft-tissue contrast of MRI could assist in the detection and characterization of small, subtle, cystic, or isoattenuating pancreatic lesions and small liver lesions (Fig. 2). MRCP can non-invasively visualize abnormalities of the entire pancreatic and bile duct, including anatomic variations and obstructive dilatation. With these advantages, MRI is used as a problem-solving tool for indeterminate pancreatic lesions (especially small or isoattenuating tumors) or small liver lesions. MRI also shows some disadvantages, such as lower spatial resolution, vulnerability to motion artifacts, and limited multiplanar reformation capability. With its own advantages and disadvantages, MRI has shown similar diagnostic performance as CT. In meta-analyses, MRI has shown sensitivity of 84–93% and specificity of 82–89% for the diagnosis of pancreatic cancer (32-34, 40). In candidates for upfront surgery, MRI with DWI can detect hepatic metastasis in about 1.5–2.3% of patients with no hepatic lesions on CT, and about 10.5–13.6% of those with indeterminate liver lesions on CT (41). Particularly, MRI with hepatobiliary contrast using gadoxetic acid demonstrates higher sensitivity than CT (85% vs. 69%) and

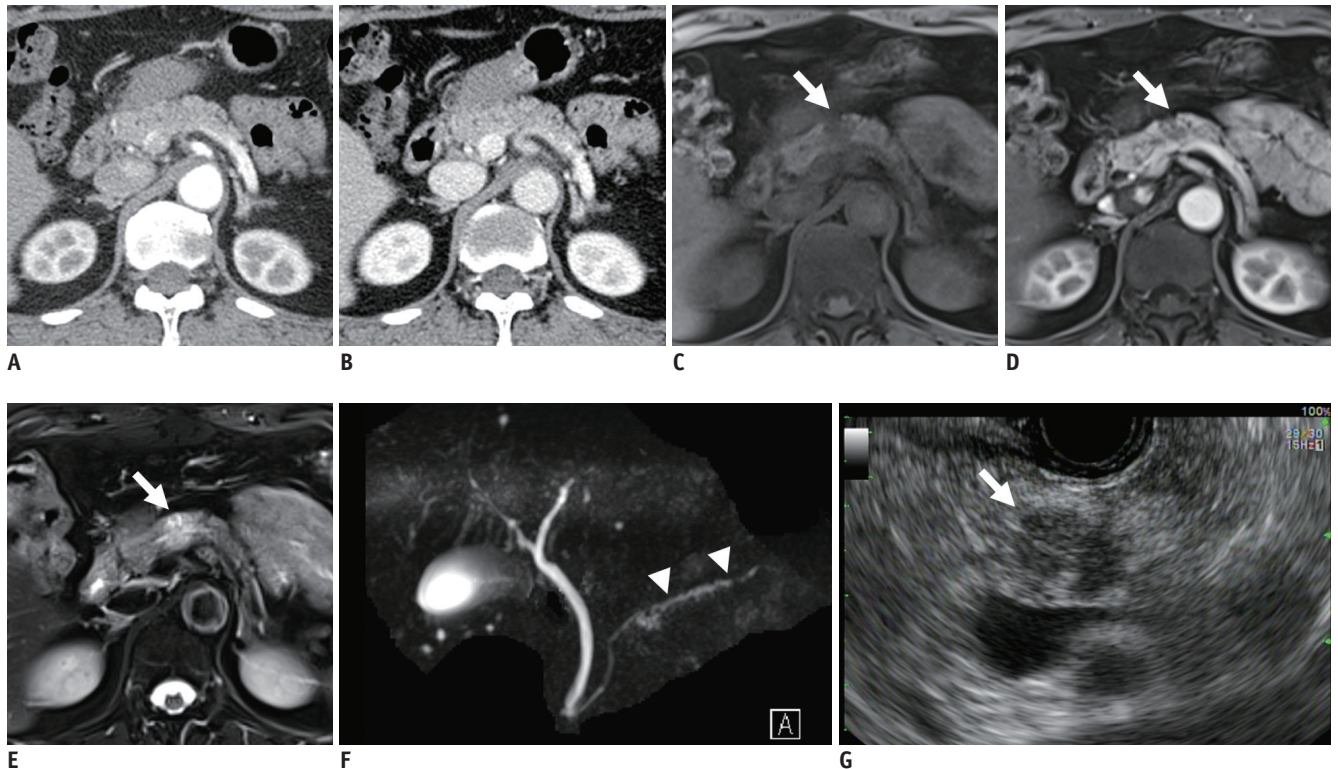


Fig. 2. Isoattenuating pancreatic cancer on CT. A 55-year-old female patient was referred for a small pancreatic lesion that was detected in transabdominal ultrasound (image was not available). Both pancreatic (A) and venous phases (B) in CT showed no demonstrable lesion in the pancreas or significant pancreatic duct dilatation. MRI showed an approximately 1.5-cm focal pancreatic lesion (white arrows) with hypointensity in the T1-weighted image (C), hypoenhancement in the pancreatic phase (D), and moderate hyperintensity in the T2-weighted image (E). Magnetic resonance cholangiopancreatography (F) showed minimal pancreatic duct dilatation distal to the pancreatic mass, suggesting duct involvement (white arrowheads). The mass was seen as a hypoechoic mass in EUS (G).

higher accuracy for differentiating between metastasis and hepatic microabscess (37, 42). With increased sensitivity for liver metastasis, an additional MRI may change the results of resectability assessments in a significant number of patients (14.4%) (Fig. 3) (43).

Pancreatic cancer shows hypointensity in precontrast T1-weighted images. In T2-weighted images with or without fat suppression, the signal intensity of pancreatic cancer is variable (44). After contrast enhancement, the tumor usually shows hypoenhancement in the pancreatic phase, and occasionally delayed enhancement in the equilibrium phase. Since the majority of pancreatic cancers show restricted diffusion, DWI could help detect pancreatic cancer (45, 46). However, pancreatitis could appear as restricted diffusion, which is often indistinguishable from pancreatic cancer on DWI. In addition, DWI has poor spatial resolution and is vulnerable to artifacts caused by motion or bowel gas (47). Pancreatic cancer also often exhibits upstream pancreatic duct dilatation or cutoff on MRCP or T2-weighted imaging.

Positron Emission Tomography

¹⁸Fluorine-2-fluoro-2-deoxy-D-glucose (¹⁸FDG) is the most widely used radiotracer in PET scans. As a glucose analogue, ¹⁸FDG allows *in vivo* imaging of glycolytic activity, which is usually elevated in solid tumors, including pancreatic cancer. Both *KRAS* mutation, which is observed in most (> 90%) pancreatic cancers, and a hypoxic microenvironment increase ¹⁸FDG uptake by upregulating *HK2* and *GLUT1* expression. Since focal pancreatitis can also exhibit increased ¹⁸FDG uptake, it is difficult to distinguish between pancreatic cancer and focal pancreatitis (48). The potential additional benefits of ¹⁸FDG-PET or ¹⁸FDG-PET/CT over pancreatic CT in the diagnosis of pancreatic cancer remain debatable (34, 49-51). ¹⁸FDG-PET/CT shows a sensitivity of 89-91% and specificity of 70-72% for diagnosis of pancreatic cancer (33, 34). PET/CT covers the entire body and is beneficial for finding distant metastases. It may also be useful in lymph node staging (51, 52). The NCCN guidelines recommend that PET/CT should not be a substitute for pancreatic CT or MRI; however, it

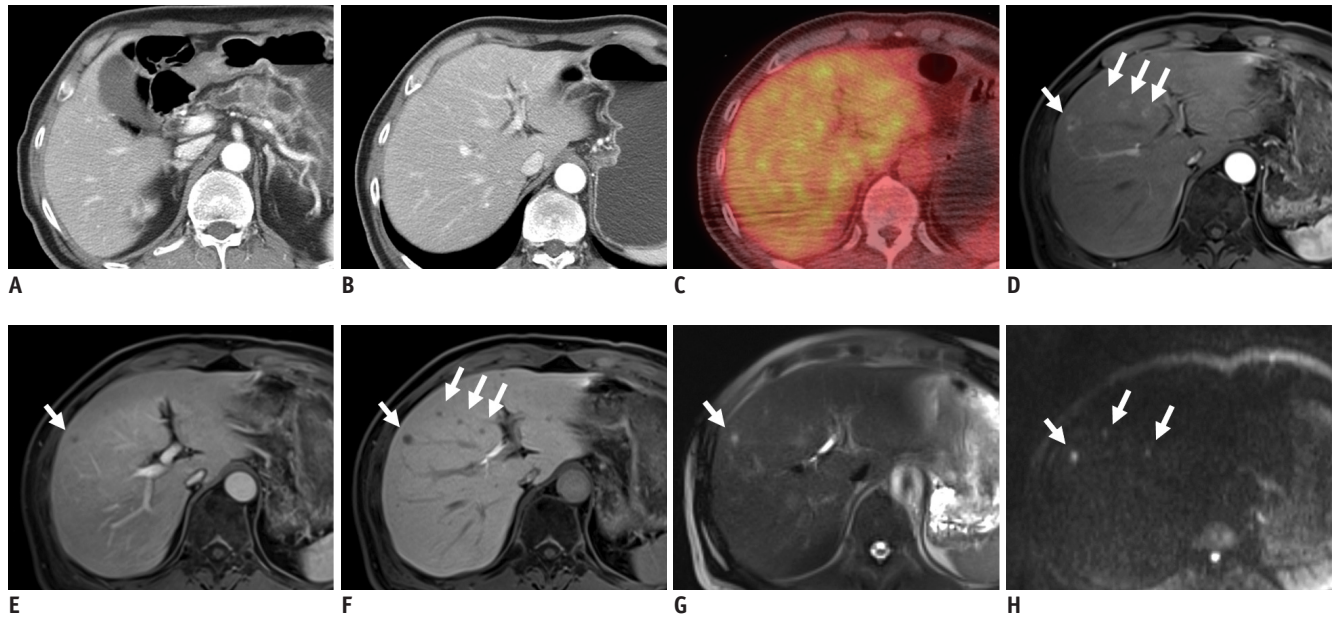


Fig. 3. Detection of small liver metastasis in MRI. A 65-year-old male patient was admitted for chronic pancreatitis and pancreatic body cancer. Since there was no apparent vascular invasion in CT (A) and no demonstrable metastatic lesion in CT (B) and PET/CT (C), the pancreatic lesion was considered to be resectable. However, MRI showed multiple small hepatic lesions (white arrows) with peripheral enhancement in the pancreatic phase (D), hypointensity in the venous phase (E), decreased uptake in the hepatobiliary phase (F), hyperintensity in the T2-weighted image (G), and high signal intensity in the diffusion weighted image (b = 800) (H), suggesting liver metastases.

could be combined with CT or MRI as an adjunct modality in patients at high risk of metastatic disease, such as those with borderline resectable disease, markedly elevated CA19-9 levels, large primary tumors, large regional lymph nodes, and a very symptomatic presentation (7).

Endoscopic Ultrasound

Because of its high spatial resolution, EUS can be used to obtain additional information for pancreatic cancers when the pancreatic lesion is equivocal in CT or when there is questionable blood vessel or lymph node involvement (53-55). However, the operator dependence of EUS and anatomic variations of the celiac and superior mesenteric arteries can limit the diagnostic capability of EUS. EUS shows sensitivity of 89-91% and specificity of 81-86% for the diagnosis of pancreatic cancer (33, 34). However, the inclusion of EUS as a routine imaging tool for a resectability evaluations remains controversial. EUS is included as a routine imaging tool in the ESMO guidelines, but not in the NCCN guidelines. The primary goal of EUS is to perform pathologic diagnosis using fine-needle aspiration (FNA).

Histologic Diagnosis of Pancreatic Cancer

For patients with resectable disease, preoperative histologic confirmation is not mandatory, and resection

should not be delayed when clinical suspicion of pancreatic cancer is high (7). However, biopsy should be performed for patients with unresectable disease before initiating neoadjuvant or systemic chemotherapy with or without radiation. FNA using EUS is commonly performed for pathologic diagnosis. According to a recent meta-analysis, EUS-guided FNA has a sensitivity of 91% and specificity of 97% (56). Owing to the shorter penetration depth of EUS-guided FNA, in comparison with percutaneous CT or US-guided FNA, the diagnostic yield is similar, and the probability of postprocedural complications and peritoneal seeding is low (57, 58). Even in patients with resectable disease, FNA was not significantly associated with increased mortality, suggesting that FNA can be safely performed without having a significant impact on the patient's clinical course (59). If EUS-guided FNA for a tumor is not possible, other methods such as brushing cytology with cholangiography, CT- or US-guided percutaneous biopsy, and laparoscopic biopsy could be performed as alternatives. Percutaneous biopsy is contraindicated in potentially resectable pancreatic cancer, due to the risk of tumor seeding (5).

Recently, the importance of genetic profiling of tumors has been gradually emphasized. In the recently updated NCCN guidelines, genetic profiling of tumor tissue was

strongly recommended (17). Genetic profiling may require additional tissue sampling; however, it could provide clinically relevant information. Targeted DNA sequencing and analysis using biopsied tissue could be performed without delaying routine diagnostic workup for pancreatic cancer, which could identify potentially actionable targets in 17–26% of patients (60, 61).

Staging of Pancreatic Cancer

For pathologic staging, tumor-node-metastasis (TNM) staging developed by the American Joint Committee on Cancer is commonly used. Recently, TNM staging was updated to the 8th edition (62). In the 8th edition, T stage was changed to be based on the tumor size, and the extrapancreatic extension and resectable status were removed from the definition of T stage (Table 2). Regional lymph node metastasis was subdivided into N1 and N2, according to the number of metastatic lymph nodes. With the changed definitions of T and N stages, the 8th edition provides better reproducibility and improved prognostic accuracy compared to the 7th edition (63–66). Particularly, the newly introduced N2 stage is highly prognostic, emphasizing the importance of nodal staging (63, 64).

The treatment strategy for pancreatic cancer is determined by the resectability status, and pathologic staging is only possible in resected pancreatic cancers; therefore, the clinical utility of pathologic TNM stage is limited.

Resectability Evaluation

The resectability of pancreatic cancer plays a pivotal role in deciding the treatment strategy. Localized pancreatic cancers can be categorized as resectable pancreatic cancers that are candidates for upfront surgical resection, borderline resectable pancreatic cancers that could be candidates for surgical resection upon favorable response to neoadjuvant therapy, and locally advanced pancreas cancers in which surgical resection is difficult to attempt and chemotherapy and/or radiation therapy are preferred. Several resectability criteria have been proposed (Table 3), and they share key anatomic structures for determining resectability, including the celiac artery, common hepatic artery (CHA), superior mesenteric artery (SMA), superior mesenteric vein (SMV), and portal vein (PV) (6, 7, 14, 67). Detailed assessment of vascular contact or involvement should be performed, including abutment (tumor involvement of $\leq 180^\circ$ of the vascular circumference), encasement (tumor involvement of

$> 180^\circ$ of the vascular circumference), deformity, occlusion, and thrombosis (bland or tumor) (Fig. 4).

The main difference between guidelines is related to the inclusion of surgical reconstructability of artery and vein in the determination of borderline resectability. For SMV/PV, in all guidelines, surgically reconstructable involvement of pancreatic cancer was used as a criterion for borderline resectability. For CHA, the MD Anderson and Alliance for Clinical Trials in Oncology group criteria use surgically reconstructable involvement as a criterion for borderline resectability; however, the NCCN criteria use celiac axis or CHA-celiac bifurcation involvement as a criterion. For the celiac axis, surgically reconstructable involvement is a criterion for borderline resectability in MD Anderson criteria. In contrast, NCCN criteria describe the cases of borderline resectability in detail, according to tumor location. For SMA, all guidelines use the criteria for tumor abutment rather than surgical reconstructability in determining borderline resectability.

Although the definition of resectability is debatable, both the NCCN and ESMO guidelines currently recommend the use of NCCN resectability criteria, which is adapted from a consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association (8, 68). When resectability was evaluated by NCCN guidelines, the R0 resection rate in upfront surgery was reported to be 73%, 55%, and 16% in resectable, borderline resectable, and locally advanced status, respectively (69).

The resectability of pancreatic cancer should be determined through a multidisciplinary consultation, ideally including diagnostic imaging, interventional endoscopy, medical oncology, radiation oncology, surgery, pathology, geriatric medicine, and palliative care (7). For proper communication among experts in various fields, the use of a structured reporting form is recommended for radiologic reporting (68).

In a meta-analysis performed in 2005, sensitivity and specificity of helical CT for resectability were 81% and 82%, respectively, while those of MRI were 82% and 78%, respectively (32). A prospective study published in 2004 also showed that helical CT has a superior diagnostic performance (sensitivity and specificity of 76% and 97%, respectively) compared to MRI (57% and 90%) and EUS (23% and 100%) (70). In these reports, most of the CTs were helical CT, not multidetector CT, with limited 3D reformatting capability, and MRI showed low spatial resolution with two-dimensional T1 sequences (≥ 5 mm

Table 2. Pathologic Tumor-Node-Metastasis Staging System of the AJCC

T Category	AJCC 7th Edition		AJCC 8th Edition	
	T Criteria		T Criteria	Changes in 8th Edition
TX	Primary tumor cannot be assessed		Primary tumor cannot be assessed	
T0	No evidence of primary tumor		No evidence of primary tumor	
Tis	Carcinoma <i>in situ</i> , including PanIN with high-grade dysplasia		Carcinoma <i>in situ</i> , including PanIN, IPMN, ITPN, and MCN with high-grade dysplasia IPMN, ITPN, and MCN with high grade dysplasia were added to this category	
T1	Tumor limited to the pancreas, 2 cm or less in greatest dimension		Tumor ≤ 2 cm in greatest dimension T1a: tumor ≤ 0.5 cm in greatest dimension T1b: tumor > 0.5 cm and < 1 cm in greatest dimension T1c: tumor 1–2 cm in greatest dimension T1 were subcategorized into T1a, T1b, and T1c based on size	
T2	Tumor limited to the pancreas, more than 2 cm in greatest dimension		Tumor > 2 cm and ≤ 4 cm in greatest dimension Definitions of T2, T3 were based on size	
T3	Tumor extends beyond the pancreas, but without involvement of the celiac axis or the SMA		Tumor > 4 cm in greatest dimension Extrapancreatic extension was removed from the criteria	
T4	Tumor involves the celiac axis or the SMA (unresectable primary tumor)		Tumor involves celiac axis, SMA, and/or CHA, regardless of size Resectability was removed from the definition	
N Category	N Criteria		N Criteria	
NX	Regional lymph nodes cannot be assessed		Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis		No regional lymph node metastasis	
N1	Regional lymph node metastasis		Metastasis in one to three regional lymph nodes Regional lymph node positivity was divided to N1 and N2 based on the number of metastatic lymph nodes	
N2			Metastasis in four or more regional lymph nodes	
M Category	M Criteria		M Criteria	
M0	No distant metastasis		No distant metastasis	
M1	Distant metastasis		Distant metastasis	
Prognostic Stage Groups	Criteria		Criteria	
0	Tis N0 M0		Tis N0 M0	
IA	T1 N0 M0		T1 N0 M0	
IB	T2 N0 M0		T2 N0 M0	
IIA	T3 N0 M0		T3 N0 M0	
IIB	T1 N1 M0		T1 N1 M0	
	T2 N1 M0		T2 N1 M0	
	T3 N1 M0		T3 N1 M0	
III	T4 (any N) M0		T1 N2 M0	
			T2 N2 M0	
			T3 N2 M0	
			T4 (any N) M0	
		T1–3 N2 M0 pancreatic cancers were added to stage III		
IV	(Any T) (any N) M1		(Any T) (any N) M1	

AJCC = American Joint Committee on Cancer, CHA = common hepatic artery, IPMN = intraductal papillary mucinous neoplasm, ITPN = intraductal tubulopapillary neoplasm, MCN = mucinous cystic neoplasm, PanIN = pancreatic intraepithelial neoplasia, SMA = superior mesenteric artery

section thickness). More recently, several studies compared the diagnostic performance for resectability between multidetector CT and MRI with a 3D T1 sequence for dynamic phases. They showed similar diagnostic performance of multidetector CT (sensitivity and specificity of 87–88% and 63–86%, respectively) and MRI (sensitivity and specificity of 83–93% and 50–75%, respectively). Although MRI shows similar diagnostic performance as that of CT, CT is preferred

over MRI due to the limited availability and high cost of MRI.

A problem with resectability evaluations using the current imaging modalities is the debate in interobserver agreements. One study reported a very high interobserver agreement on NCCN criteria (71), while another study demonstrated low interobserver agreement even with experienced radiologists, particularly for borderline

Table 3. Comparison of Resectability Criteria for Pancreatic Cancer without Distant Metastasis

Resectability Status	Resectability Criteria			
	MD Anderson (14)	AHPBA/SSAT/SSO (6)	Alliance (60)	NCCN (7)
Celiac artery				
Resectable	No involvement	No involvement	No involvement	No involvement
Borderline	Short-segment abutment or encasement		Abutment ($\leq 180^\circ$)	Abutment ($\leq 180^\circ$) (Body/tail only) encasement ($> 180^\circ$) without aorta nor gastroduodenal artery, reconstructable with modified Appleby procedure
Locally advanced	Encasement and no technical option for reconstruction	Any involvement	Encasement ($> 180^\circ$)	(Head/uncinate only) encasement ($> 180^\circ$) (Body/tail only) encasement ($> 180^\circ$), surgically unreconstructable
CHA				
Resectable	No involvement	No involvement	No involvement	No involvement
Borderline	Short-segment abutment or encasement	Abutment ($\leq 180^\circ$) or gastroduodenal artery encasement up to hepatic artery	Any surgically reconstructable involvement	Any involvement without celiac axis or CHA bifurcation
Locally advanced	Encasement and no technical option for reconstruction	Encasement ($> 180^\circ$)	Surgically unreconstructable involvement	Any involvement with celiac axis or CHA bifurcation
SMA				
Resectable	No involvement	No involvement	No involvement	No involvement
Borderline	Abutment ($\leq 180^\circ$)	Abutment ($\leq 180^\circ$)	Abutment ($\leq 180^\circ$)	Abutment ($\leq 180^\circ$)
Locally advanced	Encasement ($> 180^\circ$)	Encasement ($> 180^\circ$)	Encasement ($> 180^\circ$)	Encasement ($> 180^\circ$)
SMV/PV				
Resectable	Patent	No abutment, distortion, tumor thrombus, or encasement	No involvement or abutment ($\leq 180^\circ$)	No involvement or abutment ($\leq 180^\circ$), without vein contour irregularity
Borderline	Short-segmental occlusion and surgically reconstructable	Any surgically reconstructable involvement	Any surgically reconstructable involvement	Encasement ($> 180^\circ$), or abutment ($\leq 180^\circ$) with venous contour irregularity or thrombosis, but surgically reconstructable
Locally advanced	Occluded and no technical option for reconstruction	Surgically unreconstructable involvement	Surgically unreconstructable involvement	Surgically unreconstructable involvement or occlusion

AHPBA = American Hepato-Pancreato-Biliary Association, NCCN = National Comprehensive Cancer Network, PV = portal vein, SMV = superior mesenteric vein, SSAT = Society for Surgery of the Alimentary Tract, SSO = Society of Surgical Oncology

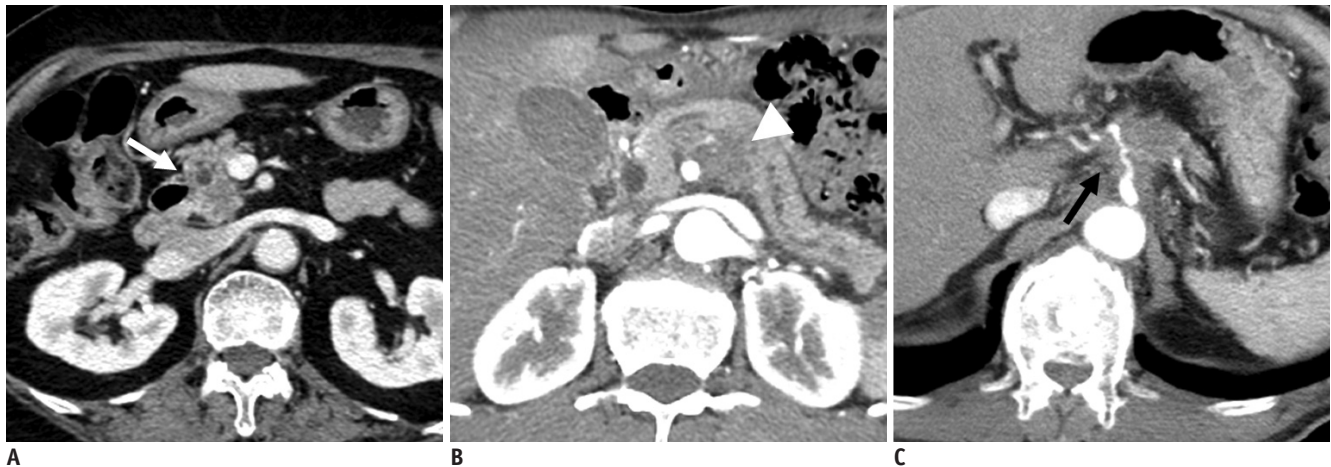


Fig. 4. Resectability of pancreatic cancer determined by the National Comprehensive Cancer Network criteria.

A. Approximately 2-cm resectable pancreatic cancer (white arrow) confined to the pancreas showing no vascular involvement.

B. Approximately 2.5-cm borderline resectable pancreatic cancer (white arrowhead) exhibiting superior mesenteric artery contact of less

than 180°. **C.** Approximately 3.7-cm locally advanced pancreatic cancer (black arrow) showing encasement of the celiac artery and proximal common hepatic artery.

resectable cases (72).

Surveillance after Surgical Resection

The value of postoperative surveillance in pancreatic cancer is controversial. Although routine surveillance imaging studies would increase medical costs, there is no firm evidence of routine surveillance increasing survival rates (73-75). Although carbohydrate antigen 19-9 (CA19-9) is the most widely used serum biomarker for postoperative surveillance, CA19-9 surveillance lacks evidence for survival benefits (76). The ESMO guideline does not recommend routine imaging studies for postoperative surveillance. In contrast, the NCCN guideline recommends chest CT, abdominal and pelvic CT or MRI, and serum CA19-9 examination every 3–6 months for 2 years after surgery and then every 6–12 months.

Unsolved or Debated Issues Related to Imaging in Pancreatic Cancer

Resectability Evaluation in Patients Receiving Neoadjuvant Treatment

When evaluating images of patients undergoing chemotherapy or chemoradiation with the aim of neoadjuvant therapy, the radiologist should evaluate both the progression and regression of the disease. Assessment of an increasing tumor extent or newly occurring metastatic lesions is important, as the lesion in such cases often

becomes unresectable and the treatment strategy must be changed.

Radiologic evaluation of tumor regression is known to be more difficult than tumor progression in pancreatic cancer, especially after neoadjuvant therapy. Radiologic response does not accurately reflect pathological tumor regression (77). Neoadjuvant therapy induces necrosis, edema, inflammation, and fibrosis of the tumor, interfering with the radiologic evaluation of tumor regression (77, 78). Therefore, neoadjuvant therapy decreases the accuracy of CT scans in determining resectability. Overestimation of the remaining tumor size and vascular invasion is commonly known to occur (79). Thus, changes in tumor size are not well-associated with resectability after neoadjuvant therapy (80).

In a retrospective study, among 122 borderline resectable patients who underwent neoadjuvant therapy, only a small proportion demonstrated a radiologic complete response (0%) or partial response (12%), while the majority showed stable disease (69%). Radiologic downstaging from borderline resectable to resectable status was only observed in one (0.8%) patient. Despite the limited radiologic response, 66% (85/129) of the patients underwent surgical resection, and R0 resection was achieved in 95% (81/85) of patients who underwent surgery. Tumor response evaluated by the Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 was not associated with overall survival (81). Another study showed that the majority of patients who underwent neoadjuvant therapy and surgical resection continued to exhibit a locally advanced or borderline resectable stage

(70%) on CT. However, R0 resection was possible in 92% of cases (82).

To overcome the limitations of radiologic response evaluation, several alternative assessment methods have been investigated (83-85). A recent prospective study suggested that partial regression of tumor contact with vascular structures on pancreatic CT indicates a high likelihood of R0 resection and suitability for surgical exploration (86). A perivascular halo in post-neoadjuvant therapy CT could also be a sign of regression of tumor-vascular contact and the possibility of R0 resection (87). Increased tumor attenuation in the pancreatic and venous phases of post-neoadjuvant CT, compared to pre-neoadjuvant CT, was most likely attributed to increased fibrosis and was associated with R0 resection (88). However, changes in tumor attenuation require prospective validation, as other studies have shown contradictory results (86, 89).

Recent studies have indicated that quantitative radiomic analysis is promising for predicting histologic tumor response. In patients with appropriate histologic response to chemoradiation, a decreased mean CT number, skewness, and increased kurtosis have been observed in posttreatment unenhanced CT (90).

Perfusion or diffusion parameters could also be used to predict resectability after neoadjuvant treatment. A high value of the volume transfer constant in pretreatment CT or MRI was significantly correlated with radiologic tumor response (91, 92). Preoperative or postoperative apparent diffusion coefficient (ADC) values were significantly associated with R0 resection (93, 94). An increased ADC in post-chemoradiation MRI compared to that in pre-chemoradiation MRI was associated with a histopathological response of pancreatic cancer, suggesting that ADC is a potential biomarker for pathological response (94). A small prospective study showed an association between the metabolic response in PET/CT ($\geq 30\%$ decreased ^{18}F FDG uptake after neoadjuvant therapy) and histologic tumor regression (95). Another study also showed that better pathologic response is expected in a metabolic responder (pretreatment standardized uptake value [SUV] ≥ 4.7 and $\geq 46\%$ decreased ^{18}F FDG uptake after neoadjuvant therapy) (96).

These novel imaging parameters, including radiomics, perfusion, diffusion, and metabolic imaging, demonstrate promising results; however, there is limited evidence for predicting R0 resection before surgical resection.

Response Evaluation in Locally Advanced Pancreatic Cancer

In patients with unresectable disease, the World Health Organization (WHO) guidelines or RECIST version 1.0 or 1.1 are widely used for evaluation of response to chemotherapy and/or chemoradiation. In recent phase III clinical trials comparing combined chemotherapy regimens (FOLFIRINOX or gemcitabine + nab-paclitaxel) and gemcitabine monotherapy, RECIST 1.0 was used for response assessment (97, 98). In these studies, progression-free survival increased along with the overall survival in the combined chemotherapy group, suggesting that progression defined by RECIST 1.0 has clinical relevance. However, evaluation of imaging response in unresectable disease is associated with the same problems as those encountered in cases undergoing neoadjuvant therapy, including difficulties in size measurement in infiltrative or irregular tumors as well as inaccuracies in the assessment of tumor regression (Fig. 5). In a consensus statement from the National Cancer Institute clinical trials planning meeting on pancreatic cancer treatment, tumor shrinkage assessed by either WHO or RECIST was not recommended as a primary endpoint of clinical trials, as they are poor surrogates for overall survival (99).

In the nab-paclitaxel + gemcitabine phase III trial, metabolic response defined by decreased SUV on ^{18}F FDG-PET/CT was more frequently observed than radiologic response, and metabolic response was associated with longer overall survival (100).

Predicting Prognosis in Patients with Upfront Surgery

According to the current guidelines, resectable pancreatic cancers are recommended for upfront surgery (5, 7, 18). However, resectable pancreatic cancers with high-risk features, such as high serum CA19-9 levels, large primary tumors, large regional lymph nodes, as well as excessive weight loss and extreme pain, could also be candidates for neoadjuvant therapy (7). Recently, the role of neoadjuvant strategy has been gradually increasing. In a recent meta-analysis, surgery after neoadjuvant therapy was reported to improve overall survival compared to adjuvant chemotherapy after upfront surgery (101). To date, no large-scale phase III trial has been published; however, small prospective trials showed better survival using neoadjuvant strategies (102). If we could perform preoperative survival stratification of the candidates for upfront surgery, patients with predicted poor prognosis may be good candidates for

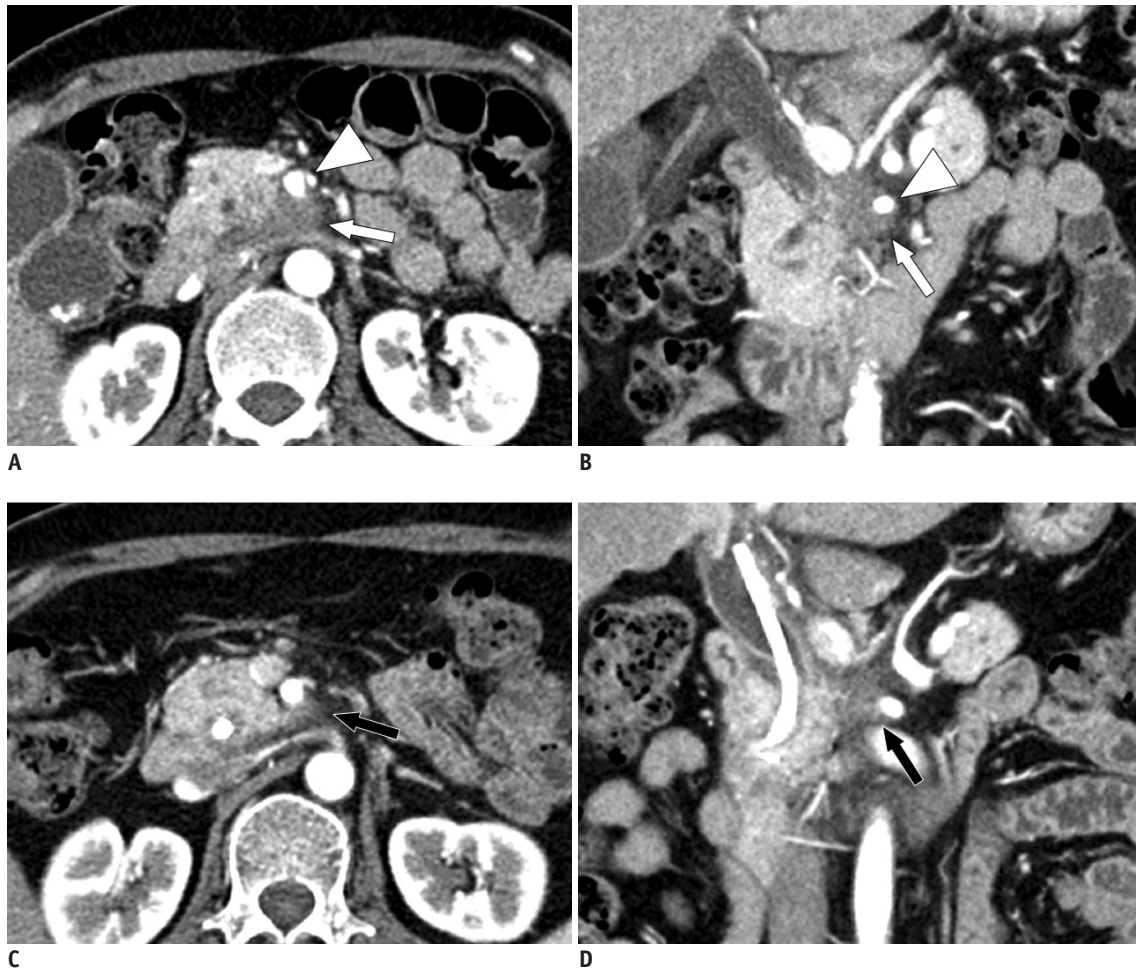


Fig. 5. Pancreatic cancer showing partial response after a long period of chemotherapy. A 55-year-old female was diagnosed with pancreatic cancer in the uncinate process.
A, B. The pancreatic phase of initial CT showed an infiltrative hypoenhancing mass lesion (white arrows) involving the uncinate process and retroperitoneal margin, as well as encasing superior mesenteric artery (white arrowheads) and its jejunal branches, suggesting locally advanced tumor. **C, D.** After approximately 2 years of FOLFIRINOX chemotherapy, the lesion (black arrows) showed a reduction in size and extent of vascular involvement. It was apparent that the tumor became smaller with chemotherapy, but it was difficult to determine exactly how much of the viable tumor remained. The patient underwent pancreaticoduodenectomy, and margin negative (R0) resection was achieved without resection of vessels.

neoadjuvant strategies. Imaging studies are expected to play an important role in the survival stratification and assessment of resectability. However, only a limited number of studies are being performed on the imaging prognostic biomarker.

Pancreatic cancers with irregular rim-like enhancement and a relatively hypovascular central area on dynamic MRI showed poor differentiation and frequent tumor necrosis, as well as poorer disease-free survival and overall survival (103). Similarly, several studies demonstrated that lower enhancement of pancreatic cancer in the venous phase of CT was associated with poor overall survival (104-106). A CT texture analysis revealed that low average attenuation and standard deviation in the pancreatic phase image was associated with poor disease-free survival (107). Poorly

enhancing areas of pancreatic cancer correspond to necrotic or fibrotic areas, which contribute to the aggressive nature of the disease (108).

DWI is another imaging method that reflects the fibrotic stromal component of pancreatic cancer (109, 110). However, the prognostic significance of ADC is variable; some studies showed strong association between low ADC values and poor overall survival, while others demonstrated no significant association (103, 111-113). Recently, the low ADC value of the upstream pancreas was reported to be significantly associated with overall survival after curative resection, suggesting an association between inflammation and pancreatic cancer progression (111).

¹⁸F-FDG-PET/CT can also be used to predict the postsurgical outcome of pancreatic cancer. Several studies have reported

that the metabolic tumor volume, total lesion glycolysis, or maximum SUV (SUVmax) were associated with disease-free survival or overall survival. In particular, pancreatic cancers with high SUVmax values showed consistently poor overall survival, although the cutoff point was different among studies (114-117).

Summary

In pancreatic cancer, imaging plays an essential role in the surveillance, diagnosis, resectability evaluation, and response evaluation. With the development of therapeutic strategies for pancreatic cancer, the role of imaging has been gradually changing. Surveillance of pancreatic cancer should be performed only in high-risk individuals, and MRI and EUS are the preferred imaging modalities. CT is primarily used for imaging diagnosis and resectability evaluation of pancreatic cancers, and MRI, PET-CT, and EUS could be optionally used at the radiologist's discretion. It is not accurate to evaluate the regression of pancreatic cancer in imaging after chemotherapy or chemoradiation therapy, and tumor shrinkage in imaging is a poor surrogate for overall survival of pancreatic cancer. Although innovative evaluation methods using new radiologic criteria (i.e., perfusion imaging, radiomics, DWI, PET/CT, etc.) have been proposed, there is insufficient evidence for their clinical usefulness. Post-surgical outcome prediction in resectable pancreatic cancers, treatment response evaluation, and prognosis prediction of unresectable pancreatic cancers are problems that remain unsolved.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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