Undetected Pancreatic Adenocarcinoma on Computed Tomography: Frequency According to Scan Protocol

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ABSTRACT **Background:** Computed tomography (CT) is the main diagnostic modality for detecting pancreatic adenocarcinoma.

Objectives: To assess the frequency of missed pancreatic adenocarcinoma on CT scans according to different CT protocols.

Methods: The medical records of consecutive pancreatic adenocarcinoma patients were retrospectively collected (12/2011–12/2015). Patients with abdominal CT scans performed up to a year prior to cancer diagnosis were included. Two radiologists registered the presence of radiological signs of missed cancers. The frequency of missed cancers was compared between portal and pancreatic/triphasic CT protocols.

Results: Overall, 180 CT scans of pancreatic adenocarcinoma patients performed prior to cancer diagnosis were retrieved; 126/180 (70.0%) were conducted using pancreatic/triphasic protocols and 54/180 (30.0%) used portal protocols. The overall frequency of missed cancers was 6/180 (3.3%) in our study population. The frequency of missed cancers was higher with the portal CT protocols compared to the pancreatic/triphasic protocols: 5/54 (9.3%) vs. 1/126 (0.8%), $P = 0.01$. CT signs of missed cancers included small hypodense lesions, peri-pancreatic fat stranding, and dilated pancreatic duct with a cut-off sign.

Conclusions: The frequency of missed pancreatic adenocarcinoma is higher on portal CT protocols. Physicians should consider the cancer miss rate on different CT protocols.

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KEY WORDS: computed tomography (CT), education, imaging protocols, pancreatic adenocarcinoma (PDAC) diagnosis

Pancreatic cancer is a highly lethal malignancy. It is the third leading cause of cancer-related death in the Western world [1-3]. Initial symptoms are often nonspecific, including abdominal pain, weight loss, asthenia, anorexia, and jaundice [4-6].

Abdominal computed tomography (CT) is the main diagnostic tool for various gastrointestinal complaints, with millions of scans performed worldwide every year. CT commonly serves as a primary imaging modality for the detection of pancreatic malignancy and is considered the gold standard for determining staging.

Pancreatic adenocarcinoma (PDAC) diagnosis is determined using a dedicated biphasic CT protocol comprised of a pancreatic phase scan (starting 35–45 seconds after intravenous contrast iodine-based injection) or a portal phase (performing another scan 65–70 seconds from contrast material injection) [7-9].

A pancreatic phase scan is optimal for PDAC detection, making this desmoplastic tumor conspicuous compared to the normally enhancing pancreatic parenchyma. Portal phase is superior for assessing regional and distant spreading to peritoneum and liver.

Survival of PDAC depends on early detection, with surgical resection being the only potentially curative therapy [4,6]. Therefore, clinicians must be aware of the reliability and potential pitfalls of different CT protocols when diagnosing pancreatic malignancy.

Despite the importance of avoiding delayed diagnosis, there are few publications regarding the rate of missed pancreatic adenocarcinoma. In this study, we assessed the frequency of missed pancreatic adenocarcinoma on CT scans according to different CT protocols.

PATIENTS AND METHODS

STUDY DESIGN

The medical records of consecutive patients with histopathological diagnosis of pancreatic adenocarcinoma were retrospectively retrieved using a computerized search in our department's radiological information system (12/2011–12/2015). Search parameters included the terms *pancreatic adenocarcinoma*, *pancreatic tumor*, *pancreatic mass*, *pancreatic malignancy*, or *pancreatic cancer*. Demographics, clinical data, and CT referral indications were retrieved from the electronic medical records.

Only patients with a new diagnosis of PDAC were included. Other pathologies, such as pancreatic neuroendocrine tumors, were excluded.

For each patient, we obtained the initial CT scan in which PDAC was first identified. These scans were considered as the ref-

erence scans for our study. In addition, we collected all CT scans performed within one year prior to the reference scan for each patient. Although we did not set a specific minimum time interval between the reference scan and the prior scans, the minimum interval between CT scans in our study cohort was one month.

To evaluate any potential cases of pancreatic cancer that might have been missed by the original imaging report, a primary reader (a senior diagnostic radiologist with 5 years of experience [MDI]) thoroughly examined each CT scan. Any suspected missed cases were then re-evaluated by two senior radiologists (both with over 10 years of experience [SA, EK]), who reviewed the scans and were aware of the original CT report.

Missed PDAC was defined as either a pancreatic mass that was not reported, or as ancillary features of malignancy (e.g., peripancreatic fat stranding, dilatation of pancreatic duct with or without a cut-off sign, and peripancreatic lymphadenopathy) that were not reported. Small tumors were defined as having a diameter of less than 20 mm, as defined by Yoon et al. [10].

All research methods were performed in accordance with relevant guidelines and regulations of the Declaration of Helsinki. The institutional review board at Sheba Medical Center approved this retrospective study. Informed consent was waved.

Table 1. Study cohort data including clinical indications for CT referral according to CT protocols

Data type	Entire cohort	Portal	Pancreatic/ triphasic
Number of patients	180	54 (30%)	126 (70%)
Male-to-female ratio	108:72	39:15	69:57
Age in years, mean	66.4 ± 10.8	66.4 ± 10.0	66.5 ± 11.2
Performing institutes: University hospitals/ outpatient clinics	94/180 (52%)	28/54 (52%)	66/126 (52.4%)
Number of undetected cancers	6 (3.3%)	5 (9.3%)	1 (0.8%)
Clinical indication for CT			
Obstructive jaundice	36 (20%)	8	28
Abdominal pain	96 (53.3%)	34	62
Lethargy	15 (8.3%)	3	12
Weight loss	63 (35%)	20	43
Anorexia	27 (15%)	9	18
New onset diabetes	8 (4.4%)	1	7
Pancreatitis	5 (2.7%)	3	2
Back pain	23 (12.8%)	8	15
Nausea/vomiting	24 (13.3%)	7	17
Change in bowel habits	16 (8.9%)	8	8
Night sweat	5 (2.7%)	1	4
Elevated CA19-9 marker	3 (1.7%)	0	3
Other	17 (9.4%)	6	11
Incidental finding	8 (4.4%)	2	6

CT = computed tomography

IMAGING TECHNIQUE

CT scans were performed at several institutes. The scans were categorized according to the CT protocol that was used.

A dual phase *pancreatic-protocol* CT included a pancreatic phase performed with a scan delay of 40–45 seconds following a bolus of intravenous contrast agent and a portal venous phase performed with a scan delay of 65–70 seconds.

A *triphasic CT protocol* with late arterial (scan delay 35–45 seconds) and portal phases (scan delay 65–70 seconds) was followed by an additional delayed scan 3–5 minutes following intravenous (IV) contrast bolus.

All protocols included in the study were conducted with non-contrast scan prior to injection of intravenous contrast.

STATISTICAL ANALYSIS

Descriptive statistics were used to summarize the study's characteristics. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 20 (SPSS, IBM Corp, Armonk, NY, USA). A P-value < 0.05 was considered statistically significant.

Differences in miss rates were compared between the portal CT protocol group and the pancreatic/triphasic CT protocols (Fisher's exact test). We also compared differences in miss rates between university hospitals and outpatient clinics and between portal CT scans and pancreatic/triphasic CT scans (Fisher's exact test).

RESULTS

We retrieved 193 PDAC records with CT scans performed prior to PDAC diagnosis; 126/193 (65.3%) of the scans were pancreatic or tri-phasic CT protocols and 54/193 (28.0%) were portal CT protocols. We excluded 13/193 scans (6.7%) that used non-contrast only CTs. In total, 180 patients were included in the study. Table 1 summarizes the study cohort according to CT protocol. The age range was 43–90 years.

The referral indications for performing CT scans were retrieved and were grouped into 14 categories [Table 1]. Patients could have more than one referral indication. The most frequent indication was abdominal pain (96/180 patients [53.3%]) followed by weight loss (63/180 [35.0%]). The *Other* category included lower limb thrombosis, ischemia or edema, heartburn, splenomegaly, elevated liver enzymes, shoulder, flank, or chest pain. Most incidental masses were detected on CT surveillance for previous malignancy (breast, prostate, and lymphoma) or pancreatic/liver cyst follow-up. Two incidental masses were found during a workup for bleeding ulcer and trauma.

The overall frequency of missed tumors and ancillary find was 6/180 (3.3%). The miss rate was significantly higher in portal CT protocols. Five cancers were missed on portal scans, and a single tumor was missed in a pancreatic protocol: portal protocol: 5/54 (9.3%) vs. pancreatic/triphasic protocol: 1/126 (0.8%), P = 0.01, odds ratio 12.8. There was a similar distribution of

Figure 1. CT surveillance of a 62 years-old male with a history of prostate cancer

CT = computed tomography

[A] Portal CT scan, undetected small hypodense mass in the head of the pancreas

[B] CT scan 6 months later with pancreatic protocol, showing enlargement of the hypodense mass and detected new liver metastases

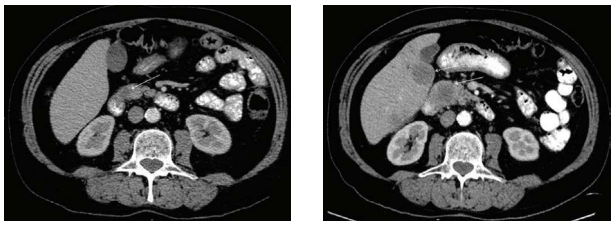


Figure 2. Chest–abdomen CT scan of 57-year-old male, investigation of dyspnea

CT = computed tomography

[A] Portal CT scan, undetected peripancreatic fat stranding

[B] CT follow-up with pancreatic protocol 2 months later due to increased abdominal pain, showing increased peripancreatic fat stranding and new liver metastasis

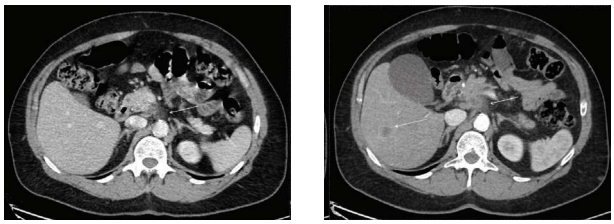
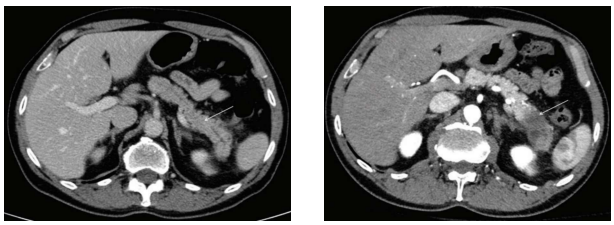


Figure 3. CT scan of 67-year-old male, ischemic limb

CT = computed tomography

[A] Portal CT scan showing slightly dilated distal pancreatic duct with cutoff sign

[B] Triphasic CT 6 months later due to recurrent limb ischemia, showing a large hypodense mass in the tail of pancreas.



missed tumors and ancillary findings between university hospitals and outpatient centers: university hospitals: 3/96 (3.1%) vs. outpatient centers 3/77 (3.9%), $P = 1$.

The following CT malignancy ancillary findings were retrospectively identified in missed cancers. Three patients demonstrated small (diameter ≤ 20 mm) hypodense lesions [Figure 1]. Three additional patients did not reveal a detectable pancreatic mass but exhibited peri-pancreatic fat stranding (2 cases) [Figure 2] and dilated pancreatic duct with a cut-off sign (1 case) [Figure 3]. Focal atrophy, a known early sign of PDAC [11,12] was not detected among missed tumors in our study population.

DISCUSSION

In this study, we examined the failure to diagnose PDAC in different CT protocols. Our cohort consisted of 180 patients. We found a 9.3% miss rate of PDAC in portal CT scans. To the best of our knowledge, this is the largest cohort to investigate missed PDAC in abdominal CT scans regarding different CT protocols.

Previous studies have investigated the missed detection of pancreatic tumors in imaging. Kielar and co-authors [13] reported 13 pancreas-related errors out of 222 imaging errors, one of which involved a missed pancreatic mass. Donald and colleagues [14] identified 558 diagnostic imaging errors, with CT scans accounting for 43%, and 4 cases of missed pancreatic tumors. Kang et al. [11] analyzed 257 PDAC patients and found 107 studies with missed and misinterpreted imaging findings in 66 patients (62% missed and 46% misinterpreted). Hoogenboom et al. [12] described 60 PDAC patients with various pre-diagnostic CT protocols, where a pancreatic mass was retrospectively suspected in approximately 50% of cases by two independent reviewers. These studies did not specifically address the missed rate of pancreatic tumors in relation to CT protocol.

We found a significantly higher miss rate (9.3%) of PDAC in portal CT scans, which corresponds with current literature highlighting the superiority of the pancreatic phase in demonstrating pancreatic adenocarcinoma due to better tumor-to-pancreas contrast [7-9]. Moreover, the lower rate of missed pancreatic tumors on pancreatic and triphasic CT scans may be attributable to increased awareness of subtle imaging findings when interpreting these scans, which are typically more relevant to a clinical question of tumor detection [15,16]. Because pancreatic adenocarcinoma is a lethal malignancy and early detection is essential for improving survival rates, knowledge of CT techniques is essential.

Previous studies have investigated the secondary imaging findings of undetected pancreatic tumors. Yoon et al. [10] found that approximately one-fourth of small (< 2 cm) pancreatic masses were isoattenuating and showed pancreatic duct abnormalities, including cut-off or dilatation. Ahn et al. [17] described focal hypoattenuation and pancreatic duct dilation with or without interruption as the most useful findings for avoiding delayed diagnosis of pancreatic cancer. Other studies [11,12,18,19] have found that pancreatic duct dilation, duct interruption, focal atrophy, perivascular soft tissue, and imaging features of acute pancreatitis are strongly associated with PDAC.

In our study, undetected tumors exhibited focal hypodense lesions only retrospectively identified, peripancreatic fat stranding, and dilated pancreatic duct with a cut-off sign. Focal atrophy was not detected among missed tumors in our study population. We recommend that radiologists pay attention to these signs.

Our study has several limitations. First, it is a retrospective study, which was necessary to obtain an accurate estimation of the miss rate of PDAC. Second, CT scans were performed at several different institutions, reflecting real-life variability. Third, there is a possibility of selection bias, as the patients included in our study predominantly exhibited symptoms and were referred for imaging prior to receiving a diagnosis. This aspect reflects the natural course of patient evaluation in real-life scenarios. Last, the number of missed cases in our study is relatively small, although statistical significance was observed.

CONCLUSIONS

We revealed a higher miss rate of PDAC in portal CT scans, underscoring the significance of familiarity with diverse CT protocols. Radiologists' attentiveness to subtle secondary imaging findings may facilitate early detection of this fatal cancer. Further research is necessary to assess the impact of missed PDAC on patient outcomes and to develop strategies to minimize the risk of missed diagnoses.

All references must be cited in numerical order in the body of the text. Please fix.

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References

1. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin* 2023; 73 (1): 17-48.
2. Hu JX, Zhao CF, Chen WB, et al. Pancreatic cancer: a review of epidemiology, trend, and risk factors. *World J Gastroenterol* 2021; 27 (27): 4298-321.
3. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021; 71 (3): 209-49.
4. Mizrahi JD, Surana R, Valle JW, Shroff RT. Pancreatic cancer. *Lancet* 2020; 395 (10242): 2008-20.
5. Park W, Chawla A, O'Reilly EM. Pancreatic cancer: a review. *JAMA* 2021; 326 (9): 851-62.
6. McGuigan A, Kelly P, Turkington RC, Jones C, Coleman HG, McCain RS. Pancreatic cancer: a review of clinical diagnosis, epidemiology, treatment and outcomes. *World J Gastroenterol* 2018; 24 (43): 4846-61.
7. Kobi M, Veillette G, Narurkar R, et al. Imaging and management of pancreatic cancer. *Semin Ultrasound CT MR* 2020; 41 (2): 139-51.
8. Zhang L, Sanagapalli S, Stoita A. Challenges in diagnosis of pancreatic cancer. *World J Gastroenterol* 2018; 24 (19): 2047-60.
9. McKinney M, Griffin MO, Tolat PP. Multimodality imaging for the staging of pancreatic cancer. *Surg Oncol Clin N Am* 2021; 30 (4): 621-37.
10. Yoon SH, Lee JM, Cho JY, et al. Small (≤ 20 mm) pancreatic adenocarcinomas: analysis of enhancement patterns and secondary signs with multiphasic multidetector CT. *Radiology* 2011; 259 (2): 442-52.
11. Kang JD, Clarke SE, Costa AF. Factors associated with missed and misinterpreted cases of pancreatic ductal adenocarcinoma. *Eur Radiol* 2021; 31 (4): 2422-32.
12. Hoogenboom SA, Engels MML, Chuprin AV, et al. Prevalence, features, and explanations of missed and misinterpreted pancreatic cancer on imaging: a matched case-control study. *Abdom Radiol (NY)* 2022; 47 (12): 4160-72.
13. Kielar AZ, McInnes M, Quan M, O'Sullivan J. Introduction of QUIP (quality information program) as a semi-automated quality assessment endeavor allowing retrospective review of errors in cross-sectional abdominal imaging. *Acad Radiol* 2011; 18 (11): 1358-64.
14. Donald JJ, Barnard SA. Common patterns in 558 diagnostic radiology errors. *J Med Imaging Radiat Oncol* 2012; 56 (2): 173-8.
15. Klang E, Eifer M, Kopylov U, et al. Pitfalls in diagnosing colon cancer on abdominal CT. *Clin Radiol* 2017; 72 (10): 858-63.
16. Singh H, Sethi S, Raber M, Petersen LA. Errors in cancer diagnosis: current understanding and future directions. *J Clin Oncol* 2007; 25 (31): 5009-18.
17. Ahn SS, Kim MJ, Choi JY, Hong HS, Chung YE, Lim JS. Indicative findings of pancreatic cancer in prediagnostic CT. *Eur Radiol* 2009; 19 (10): 2448-55.
18. Gangi S, Fletcher JG, Nathan MA, et al. Time interval between abnormalities seen on CT and the clinical diagnosis of pancreatic cancer: retrospective review of CT scans obtained before diagnosis. *AJR Am J Roentgenol* 2004; 182 (4): 897-903.
19. Elbanna KY, Jang HJ, Kim TK. Imaging diagnosis and staging of pancreatic ductal adenocarcinoma: a comprehensive review. *Insights Imaging* 2020; 11 (1): 58.

Capsule

Scars after a heart attack

After a cardiac injury such as a heart attack, the damaged heart tissue is replaced with scar tissue consisting of fibroblasts, which have been considered electrically inert. Recent studies, however, have demonstrated that fibroblasts can electrically couple with cardiomyocytes. Using optogenetics, **Wang** et al. confirmed that scar fibroblasts indeed couple with cardiomyocytes and identified two mechanisms by which this occurs. One of these mechanisms involves gap junctions, as previously suggested, but the other is an ephaptic mechanism involving cell depolarization across a junctional cleft, and these are functionally redundant. Current treatment of scar-associated arrhythmias creates additional scarring and may need to be reevaluated given the risk of worsening arrhythmias.

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