Comparison of Pancreatic Ductal Adenocarcinoma Imaging Modalities

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ABSTRACT
Pancreatic ductal adenocarcinoma is a fatal type of cancer with an increasing incidence rate in North America. The only curative procedure of this disease is the Whipple procedure, which is restricted only to those that received an early diagnosis. The remainder of the patients is informed of a dismal prognosis and undergo palliative care through systemic chemotherapy. Multiple modalities are involved in the staging and diagnosis of this disease. However, there seems to be a controversy regarding a gold standard or whether a gold standard exists. Additionally, various emerging techniques warrant heightened sensitivity and specificity in their designated modalities. Transabdominal ultrasound that is most commonly used as the first line of imaging for patients with epigastric pain is found to be virtually insensitive to neoplasms that have a size of 2 cm or less, limiting its application. However, sonographers could resort to contrasts and elastography to increase the conspicuity of the neoplasms. Moreover, endoscopic ultrasound has shown to be a promising imaging modality with an unprecedented degree of sensitivity to tumors with a diameter of less than 1.5 cm. The sensitivity and specificity values of MDCT, MRI, and PET were found to be comparable. The main conclusions consist of the fact that EUS is a highly sensitive test that should be accompanied by MRI, MDCT, PET, or TUS to increase its specificity. Lastly, empathetic communication is vital not only for patient comfort but also to improve the quality of the imaging assessment.

KEYWORDS: PDAC; US; MDCT; MRI; PET; Efficacy.

1. INTRODUCTION

Pancreatic cancer is a fatal type of cancer that is most common in the west, with a poor 5-year survival rate of only 4% [1]. Pancreatic Ductal Adenocarcinoma (PDAC) constitutes about 95% of pancreatic cancer cases [2]. PDAC is a type of exocrine cancer that develops from the ductal cells that line the Pancreatic Duct (PD) [3]. In most cases, the tumor develops at the head of the pancreas, eventually occluding the duct of Wirsung and the Common Bile Duct (CBD) [4]. Pancreatic cancer can also arise from Neuroendocrine Tumors (NETS) or cystic lesions; however, they are far less prevalent and not as lethal [1].

The underlying etiology of PDAC includes smoking, obesity, a personal medical history of chronic pancreatitis or diabetes, and a family history of PDAC [1]. The incidence of PDAC is rising by more than tenfold in the next decade, which is due to the obesity epidemic and the growing aging population [3]. The symptoms of PDAC are vague and include vomiting, weight loss, and changes to bowel habits [5]. More specific symptoms develop in the later stages of the disease, including new-onset diabetes, jaundice, epigastric pain, and asthenia [5]. Once specific symptoms arise and the diagnosis is established, PDAC has usually already been disseminated, and the patient is deemed ineligible to the Whipple surgery [4]. The patient would then undergo palliative care through systemic chemotherapy [5].

The discriminatory power of PDAC imaging modalities can be best evaluated by considering their respective specificity and sensitivity values [6]. Sensitivity is defined as the true positive rate, whereas specificity is the true negative rate [6]. The scope of this paper encompasses the subsequent imaging modalities: Transabdominal Ultrasound (TUS), Endoscopic Ultrasound (EUS), Multi-Detector Computed Tomography (MDCT), Magnetic Resonance Imaging (MRI), and Positron Emission Tomography (PET).

Patient satisfaction is commonly utilized as a measure of the quality of healthcare, as it affects clinical outcomes and patient retention [7, 8]. One of the most significant contributors to increased patient satisfaction levels is patient-centered communication that is predicated upon mutuality, egalitarianism, and respect. Patient satisfaction is also contingent upon the duration and safety of an imaging procedure [9, 10]. The goal of this paper is to compare the diagnostic performance and satisfaction rating of different PDAC imaging modalities to determine whether there is a gold standard for PDAC imaging. The results reveal that a multimodality approach best serves PDAC patients [9].

2. METHOD(S)

Peer-reviewed studies published in the past seven years that are contemporary with diagnostic technological advancements were utilized to address the objectives of this paper. Studies documented in English were considered, and studies, where the minimum population consisted of at least 50 subjects were noted. The minimum age of 19 was employed as a filter to ensure that the populations under consideration were composed of adults. Randomized Control Trials (RCTs), cohort, longitudinal studies, and meta-analyses were evaluated using the Cochrane Handbook for Systematic Reviews of Interventions. Databases used include PubMed, where the MeSh terms “Carcinoma, Pancreatic Ductal,” “Diagnostic Imaging,” and “Patient Care

Management" were utilized to investigate pancreatic cancer imaging. Boolean operators such as "AND" and "OR" were employed to refine the search, maximizing the relevance of the results. Additional databases used include Novanet, Cochrane, Google Scholar, Canadian Medical Association Journal (CMAJ), and Canadian Journal of Medical Sonography (CJMS).

3. DIAGNOSTIC ACCURACY AND SATISFACTION RATING OF TUS

The first line of imaging to investigate the symptoms of jaundice and epigastric pain is usually TUS [11]. While TUS is inexpensive, non-invasive, and is readily available, it is not the ideal imaging modality for the detection of pancreatic masses [11]. TUS is highly capable of capturing contour irregularities that allude to an underlying mass; however, visualization of pancreatic morphology is often challenging in obese or flatulent patients, obscuring pathological nuances [11]. Multiple studies reported a TUS sensitivity percentage within the range of 91%-93% and a specificity value in the range of 59%-67% [11, 12]. The low specificity is due to the identification of many false positives, indicating that TUS fails to adequately distinguish PDAC from other focal lesions [13].

Contrast-Enhanced Ultrasonography (CE-US) has been shown to increase the sensitivity and specificity for depicting occult pancreatic lesions [13]. CE-US encompasses the use of microbubbles that are encased by a lipid monolayer and are intravenously administered to the patient prior to commencing imaging [14]. The increased prospect of detecting tumors stems from the enhanced backscatter that the acoustic impedance differential generates [13]. As a result, blood vessels are accentuated to an unprecedented degree, permitting the detection of micro-vascularization of PDAC lesions [15]. CE-US also utilizes blood pool agents that remain in the intravascular space for prolonged periods, making them suitable for evaluating malignancies with highly permeable capillary networks [15]. In this case, the disorganized vascular networks of the poorly perfused neoplasms can be screened, and staging is made possible.

Doppler artifacts such as blooming flow and reduced temporal resolution are avoided, making CE-US a more sensitive alternative to power Doppler [15]. Since the grade of anaplasia positively correlates with the extent of vasculature disorganization, the stage of the neoplasms can be inferred [13]. Important considerations accompanying the use of contrast include needle specifications and the injection site [16].

Contrast injection through a 23-gauge needle is generally recommended as the destruction of the microbubbles is minimized at a variety of flow rates [16]. Higher gauge needles should be avoided as high hydrostatic pressures are poorly tolerated by the microbubbles [16]. Peripheral intravenous administration is more commonly practiced, but if body habitus poses an issue, then administering the contrast through a Central Venous Catheter (CVC) can be performed [17]. Contrast arrival time would be drastically reduced, facilitating the accommodation of medical emergencies [17].

Secondary signs of PDAC should also be utilized to substantiate the diagnosis. These include the seemingly idiopathic dilatation of the PD ($> 3\ \mathrm{mm}$) and the CBD ($> 8\ \mathrm{mm}$) [17]. Signs of pancreatitis, including the development of an abscess, fibrosis, or cystic structures, could also be seen if the tumor occludes the duct of Wirsung [3]. Upstream atrophy of the pancreas, abrupt disruption of the PD, and desmoplasia may be suggestive of a neoplasm [18]. It is also vital to examine adjacent blood vessels to inspect for encasement [3].

Visualization of the body and the tail of the pancreas may be compromised due to the presence of the stomach anteriorly that generates posterior shadowing [19]. Oral administration of water would serve as a better window for delineating the entirety of the pancreas and allow the sonographer to confidently survey the body and tail of the pancreas [20]. The presence of PDAC tumors in the tail or body is quite a lethal occurrence, as symptomatic presentation is delayed, which would lead to an unacceptably late diagnosis. Methodical sweeping of the head, uncinate process, neck, body, and tail of the pancreas, in all planes, will reduce the prospect of missing a subtle adenocarcinoma [20].

Tissue elasticity can be evaluated as a complementary parameter to validate the diagnosis [18]. Shear Wave Elastography (SWE) is a contemporary technique utilized to evaluate the mechanical properties of soft tissue [21]. Early PDAC neoplasms usually display increased stiffness relative to normal pancreatic parenchyma, and thereby the characterization of a homogenous tumor is made feasible [18]. Tumors undergo multiple developments in the course of their viability, often leading them to possess a heterogenous presentation [21]. Calcifications and fibrosis may increase the stiffness in one region of the tumor, while cystic degeneration and hemorrhage may decrease the degree of stiffness in the same area [21]. In these instances, the isotropic assumption of SWE is violated, and incorrect speed estimates are generated. SWE's failure to fully account for the viscous and mechanical properties of the neoplasm limits its applicability, rendering it insensitive in the detection of late-stage adenocarcinomas. Furthermore, passive strain from the pancreas due to aortic pulsation could also interfere with the SWE's function.

Studies imaging homogenous neoplasms found great success with the use of elastography, claiming that the results of SWE closely aligned with the Fine Needle Aspiration (FNA) findings. Giovannini *et al*. also found that elastography can assist in distinguishing benign from malignant focal lesions, which would increase the specificity of sonographic examinations [22]. Yeoh *et al*. also reported an improvement in the differential diagnosis by comparing the median shear moduli of a variety of masses [21]. Both studies hesitate to assert that elastography would replace FNA, as PDAC lesions tend to vary dramatically in their mechanical properties and as such elastography should be reserved as a secondary assessment that complements the biopsy findings [3].

Beyond the diagnostic capacity of TUS, patient satisfaction with the nature of TUS imaging is an important consideration [23]. Patients tend to favor TUS over other imaging modalities as there are no safety concerns, and abdominal exams usually take less than 20 minutes [23-25]. Intimate patient interaction is a major asset of sonography, permitting the sonographer to practice a variety of communication techniques that can alleviate the patient's distress or fears [23]. PDAC patients undergoing epigastric pain, turmoil, and depression require a communication technique like "RESPECT" that can help provide temporary relief [24]. This type of communication method is progressive, consisting of rapport formation and patient-centered communication styles [24, 26].

Multiple studies stressed the importance of establishing a rapport to ascertain a positive experience for the patient [23-25]. Rapport is predicated upon mutuality and is best characterized as being in the center of a continuum, that consists of autonomy on one end, and paternalism on the other [27]. By establishing a rapport, a mutual sense of control and responsibility is achieved, and an interpersonal connection develops [27].

Adopting a patient-centered communication style entails the technologist adapting to the patient's preferred disposition, pace, and tone of speech [24]. This method facilitates the recognition of the patient's emotions and is the first step towards empathetic communication [23]. By implementing such techniques patient compliance is improved, and undesirable physiological responses to imaging are circumvented [27].

4. DIAGNOSTIC ACCURACY AND SATISFACTION RATING OF EUS

Endoscopic Ultrasound (EUS) is an invasive procedure where a high-frequency transducer is inserted through the esophagus and into the descending part of the duodenum to image the pancreas [12]. EUS imaging of the pancreas has proven to be highly sensitive, capable of capturing lesions with a size of ≤ 1.5 cm [4]. Kamata *et al*. found a specificity value of 98% and a sensitivity value of 90%, attributing it to the absence of intervening bowel gas and the proximity of the transducer to the lesions [28]. EUS could also be coupled with novel techniques such as elastography, contrast enhancement, or FNA to increase its diagnostic power, making EUS the dominant imaging modality [28, 4].

EUS cannot explore the full extent of metastasis, as it is limited to viewing only the pancreas and surrounding lymph nodes, and consequently, EUS is most effective when coupled with TUS, CT, or MRI, allowing for an overarching survey [4, 28]. EUS-FNA procedure usually takes 30 minutes and involves minor risks of excessive bleeding and perforation [29]. Patients are placed under conscious sedation to make the procedure tolerable and patients receive a concise description of the procedure before commencing to address any concerns they may have [30].

5. DIAGNOSTIC ACCURACY AND SATISFACTION RATING OF MDCT

MDCT is commonly used to image patients with suspected pancreatic tumors. On MDCT, PDAC lesions often appear hypo-enhancing with ill-defined margins [4]. However, in 10% of cases, pancreatic tumors are iso-enhancing, in which secondary signs such as dilation of the PD or BD, an abrupt cutoff of the PD, or pancreatic contour irregularities should be noted [4]. MDCT has a reported sensitivity in the range of 87%-96% and a specificity of 86% [4, 31]. The high sensitivity and specificity are attributed to the viewing phases utilized to increase the conspicuity of the tumor [31]. These include the portal venous phase, which allows for the screening of venous encasement, and the pancreatic parenchymal phase, which maximizes the enhancement between the adenocarcinomas and the surrounding pancreatic parenchyma [4]. The arterial phase also permits the inspection of arterial invasion [4].

Although MDCT presents as a promising modality, its sensitivity declines when delineating iso-enhancing lesions with a size of ≤ 1.5 cm, warranting the use of EUS for a more accurate assessment [31]. Additionally, radiation exposure and contrast nephrotoxicity are undesirable features of MDCT [3]. MDCT scan takes only 15 minutes to complete and staying completely still during the scan is not imperative [32]. The primary concern with MDCT is the high dose of radiation [32].

6. DIAGNOSTIC ACCURACY AND SATISFACTION RATING OF MRI

Contrast-enhanced MRI has similar sensitivity and specificity values to MDCT; however, with MRI's heightened contrast resolution, the prospect of detecting minute adenocarcinomas increases [4]. Most PDAC tumors that are occult in MDCT are sufficiently conspicuous in MRI, making MRI the better alternative [11]. The major limitation of MRI is the breathing artifact that reduces the resolution, especially for abdominal examinations [11]. PDAC tumors appear hypointense in T1 and T2 with poorly defined margins and generally display restricted diffusion on diffusion-weighted imaging [4].

Patient interaction during MRI scans is highly limited due to the isolated nature of the scans [10]. Formation of a rapport is highly unlikely in the short time spent preparing the patient for imaging [9, 10]. Multiple studies found that isolation, regardless of duration, has a negative impact on the patient's psyche [24, 33, 34]. Patients find the presence of the technologist nearby reassuring, permitting them to have a sense of control [10, 35]. Other factors to consider include space constriction, which can induce a claustrophobic attack, high levels of noise that may exacerbate anxiety levels, and soft tissue heating generated by prolonged radiofrequency irradiation [24].

7. DIAGNOSTIC ACCURACY AND SATISFACTION RATING OF FDG PET

PET has a sensitivity value of 92%, compared to CT (87%) and MRI (69%). Additionally, PET has a specificity value of 65% in contrast to higher rates of CT (96%) and MRI (93%) [36, 37]. PET has the advantage of implementing glycolytic rates for detecting cancerous lesions. The Warburg effect, a hallmark of cancer, explains how proliferating tumor cells produce energy via glycolysis at faster rates. In PDAC, over 90% of the tumors carry a mutation that allows glucose uptake via different mechanisms. However, a caveat in PDAC is that glucose intolerance is a frequent complication. Elevated serum glucose levels can decrease the glucose uptake in the pancreatic tumor, which is responsible for most false-negative results on the PET scan [9, 20, 31]. On a more positive note, earlier studies have shown how PET can be used to differentiate between other pancreatic conditions such as chronic pancreatitis and autoimmune pancreatitis, demonstrating better diagnostic performance compared to CT [37, 39]. One of the main limitations of PET is the lack of anatomical information provided when used independently.

PET scans adopt all the technical challenges of a whole-body MRI assessment, including claustrophobia, physical discomfort, acoustic noise, scan duration, coping with emotions elicited during the scan like uneasiness and isolation. Subjects also need to perform PET imaging preparations, including fasting, administration of FDG, and water consumption [20, 21]. This may further increase the stress and discomfort of the subjects during the examination. It is vital for patients to be calm and relaxed during PET studies as emerging literature indicated that false positives may be present in overly anxious patients [36, 37, 39].

8. CONCLUSION

All the imaging modalities have their advantages and disadvantages, and the selection of one imaging modality over another will ultimately be contingent upon the stage of PDAC development, body habitus, and inter-related medical conditions. The stage of PDAC development is intrinsically linked to symptomatic presentation. If the patient presented non-specific symptoms, such as epigastric pain, then the imaging modality of choice is likely TUS. Despite high patient satisfaction levels during a TUS scan, the establishment of a diagnosis of PDAC by exclusively relying on TUS is seldom the case. This is the result of the low specificity of TUS, and the intervening bowel gas that degrades images of the body and the tail of the pancreas [36]. Other TUS constraints, such as operator-dependence, necessitate further imaging through MDCT, PET, or MRI

If venous or arterial encasement is sought, then MDCT serves as the superior contender [36]. For instance, the presence of venous tumor thrombus, which is a pivotal marker that helps distinguish neuroendocrine tumors from PDAC, is best delineated through MDCT [37]. If high soft-tissue contrast resolution is needed to detect minute adenocarcinomas, then MRI would be the appropriate imaging modality [11]. MRI accommodates patients with impaired renal function since iodine-based contrasts needed for MDCT are avoided [10]. MDCT, on the other hand, better accommodates patients with severe claustrophobia as spatial constriction is not a concern, and increased respiration does not influence the quality of the images [4]. PET permits for full-body surveying for the metastatic spread that may have occurred through hematogenous or lymphatic routes.

EUS has the highest sensitivity but is incapable of identifying distant metastases, and as such, it should be accompanied by TUS, MDCT, PET, or MRI [12]. EUS has the major advantage of being seamlessly coupled with FNA, which is not possible with MRI or CT. A multimodality approach that accounts for the severity of the symptoms, patient's medical conditions, and body habitus ensures the patient is diagnosed promptly and also maximizes patient satisfaction.

CONFLICT OF INTEREST

There is no conflict of interest to disclose.

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