Review Article

Measuring response to neoadjuvant therapy using biomarkers in pancreatic cancer: a narrative review

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Background and Objective: Pancreatic cancer is the 4th leading cause of cancer death in the US, with incidence increasing over the last 20 years. Recently neoadjuvant therapy (NAT) has emerged as an important tool in improving resectability and overall survival. The objective is to describe and discuss the current literature on the use of biomarkers in measuring response to NAT in pancreatic adenocarcinoma.

Methods: An electronic review of PubMed, Google Scholar and Cochrane was performed to obtain key literature on serum, imaging, clinical, and histologic biomarkers utilized to measure response to NAT in pancreatic cancer. This literature review included publications in English written between January 1, 2011 to March 31, 2022.

Key Content and Findings: An overview of four categories of biomarkers was evaluated for their utility in assessing both pathologic response and overall survival following NAT in pancreatic adenocarcinoma. Serum CA19-9 as well as CT radiomic features, FDG PET response and development of histologic grading system all show promise as markers of response to NAT.

Conclusions: While multiple promising modalities exist, all require some form of standardization in terms of predicting response to NAT. Further investigation and large-scale studies to evaluate the efficacy of various imaging modalities are necessary. Additionally, there needs to be standardization of histologic grading system post NAT, and consensus on CA19-9 cutoff values in determining NAT response.

Keywords: Neoadjuvant; pancreatic cancer; circulating tumor DNA (ctDNA); biomarker; radiomics

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Introduction

Pancreatic cancer is the 4th leading cause of cancer death in the US, with incidence increasing over the last 20 years (1). Historically, treatment of localized pancreatic cancer has centered upon curative-intent surgery for those who are eligible, followed by adjuvant chemotherapy. However, multiple studies have demonstrated that over half of all patients who undergo upfront resection are unable to complete adjuvant therapy (2). Recently, management of pancreatic ductal adenocarcinoma (PDAC) has shifted towards the use of neoadjuvant chemotherapy and chemo-radiation therapy especially in locally advanced and borderline resectable disease. The current preferred regimens in the neoadjuvant/adjuvant setting are FOLFIRINOX (or modified FOLFIRINOX) or gemcitabine + nab-paclitaxel with or without radiation. Neoadjuvant therapy (NAT) for pancreatic cancer has been

Table 1 PubMed search strategy performed on April 2022

Search #	Query	Results
1	Histologic response, neoadjuvant therapy, pancreatic cancer	27
2	Imaging, response to neoadjuvant, pancreatic cancer	537
3	Biomarkers, response to neoadjuvant therapy, PDAC	37
4	Clinical assessment, response to neoadjuvant therapy, pancreatic cancer	5
5	Biomarkers, chemotherapy, pancreas	1780
6	ctDNA, pancreas	67

PDAC, pancreatic ductal adenocarcinoma; ctDNA, circulating tumor DNA.

shown to increase margin-negative resection rate, reduce the rate of lymph node involvement as well as slow the development of micrometastasis (3-5). The use of NAT has the potential to improve resectability and survival in patients with PDAC, a concept which has been evaluated by a variety of recently reported clinical trials (5-7). However, evaluating treatment response to NAT remains a challenge. This review highlights the role of biomarkers in evaluating response to neoadjuvant treatment in pancreatic cancer. A biomarker is defined by the NIH Biomarker Working Group as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to therapeutic intervention" (8). To date, the most used biomarker in the detection and management of pancreatic cancer is Carbohydrate Antigen 19-9 (CA 19-9); however it is limited in its utility. Thus, multiple studies are ongoing to improve diagnosis and guide management PDAC (8-10). This review examines current available techniques which may be utilized to predict both treatment response as well as survival outcomes. For the purpose of this review, we did not delineate between specific regimens of chemotherapy or chemotherapy and radiation. We present the following article in accordance with the Narrative Review reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-22-49/rc).

Methods

An electronic review of PubMed, Cochrane and Google Scholar databases was conducted to obtain key literature related to NAT in pancreatic cancer. The following search terms were used: pancreatic cancer, neoadjuvant therapy, response to neoadjuvant therapy, serum biomarker, histologic grading, radiomics, ctDNA, CA 19-9 (*Table 1*). The results were narrowed to include studies published in English from 2011–2022 (*Table 2*). All prospective and retrospective cohort studies, as well as randomized controlled trials, systematic reviews, practice guidelines and metanalyses examining response to NAT were included. The selection was conducted by the authors. Both response to neoadjuvant chemotherapy and chemo-radiation were included.

Serum biomarkers

Several serum biomarkers have been investigated in their utility in determining response to NAT. The most studied and only FDA approved serum biomarker is CA 19-9, however many other serum biomarkers are currently under investigation (10). Other serum biomarkers include carcinoembryonic antigen (CEA), circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs) (11).

Carbohydrate Antigen 19-9 (CA 19-9)

Carbohydrate Antigen 19-9, also known as sialylated Lewis a antigen, is normally synthesized by biliary and pancreatic ductal cells as well as the colon, endometrial and salivary epithelium (12). It is overexpressed in both benign inflammatory conditions such as pancreatitis and biliary obstructive processes but is also elevated in malignant processes (12). It has significant limitations and requires careful interpretation based on patient specific factors. About 5–10% of patients lack fucosyltransferase and may not secrete CA 19-9. As mentioned earlier, CA 19-9 is not specific to malignant processes and may be falsely elevated in patients with both intra and extrahepatic cholestatic disease (12). It is an important serum biomarker in pancreatic cancer and is clinically utilized as a standard method to assess serial response to therapy. It is the most validated and most used tumor marker for monitoring of therapy in patients with pancreatic adenocarcinoma (12).

Investigations into its use as a marker of response to NAT and predictor of resectability have demonstrated significant potential. Various groups have investigated CA19-9 both as a predictor of overall survival and tumor size reduction. In a retrospective analysis of serum CA 19-9 values pre and post NAT in patients undergoing NAT followed by

Table 2 Search strategy summary

Items	Specification
Date of search	April 21, 2022
Databases and other sources searched	Cochrane, Google Scholar, PubMed
Search terms used	Pancreatic cancer, neoadjuvant therapy, response to neoadjuvant therapy, neoadjuvant chemotherapy, radiomics, serum biomarker
Timeframe	January 2011–April 2022
Inclusion and exclusion criteria	Language: English; Studies: cohort studies, randomized controlled trials, systemic reviews, practice guidelines and meta-analyses
Selection process	Selection process was conducted by both authors

surgical resection, a reduction in serum CA 19-9 greater than 40% as well as an absolute cut off value of 91.8 U/mL post NAT were both independent predictors of a margin-negative resection for PDAC (13). In a systematic review of the prognostic value of CA 19-9 after NAT for PDAC, Ye *et al.* (14) found that a post-NAT serum CA 19-9 decrease of greater than 50% or normalization was associated with improved overall survival (13). Multiple studies have evaluated the magnitude of change in CA 19-9 as it relates to improvement in survival outcomes. Most reports evaluated in this review have utilized a CA 19-9 cutoff of >50% decrease or normalization of CA 19-9 values. Some studies including van Veldhuisen *et al.* (15) demonstrate that a decrease of 30% or more is also associated with an improved survival. However, Al Abbas *et al.* (16) found that a higher cutoff of >85% reduction was necessary to predict improvement in overall survival. All studies concurred that an increase in CA 19-9 during or after NAT was an overall poor predictor of survival and in general associated with a more aggressive tumor biology (13). Several studies recommended the extension NAT until either normalization of CA 19-9 or meeting of one of the cutoff values as a way to improve overall survival (13,15-17).

In addition to evaluating overall survival as an endpoint, Perri *et al.* (18) found that low post-treatment CA 19-9 correlated with "pathologic major response", translating to less than 5% of viable tumor cells on the final surgical specimen. While CA 19-9 shows promise in its utility as a response marker for NAT, it is likely not adequate as the sole indicator of response. Nearly 10% of patients are considered "non-secretors" and one-third of patients have normal baseline CA19-9 levels at presentation. Thus, utilization of CA 19-9 as a predictor of response to NAT would not be possible for this population (17). Truty *et al.* (17) conducted a retrospective analysis of all patients with borderline resectable and locally advanced PDAC who underwent NAT and found that use of multiple modalities including radiographic and histologic markers as well as CA 19-9 showed more utility than CA 19-9 alone in predicting both pathologic response to NAT and overall survival.

Overall, CA 19-9 is a useful tool in assessing response to NAT in PDAC and could be used to guide overall length of neoadjuvant treatment, however further investigation and standardization of cutoff values is necessary. Furthermore, it should not be the only tool used for assessment given that a significant portion of patients with PDAC may either be non-secretors or present with normal CA 19-9 values.

ctDNA

Another potential serum biomarker for evaluating both pathologic response and overall survival is ctDNA. ctDNA is released into the bloodstream during cell death. There are two standard methods of ctDNA assessment: next generation sequencing (NGS) and droplet digital PCR (ddPCR). NGS is a platform that allows for sequencing of millions of small fragments of DNA, it can be used to sequence entire genomes or confined to specific areas of interest (19). Droplet digital PCR utilizes a small sample of material, performs a PCR and then analyzes that for specific target sequences such as a KRAS mutation (20). As it relates to ctDNA and detection or monitoring of cancer, these detection methods look for mutant allele fractions and tumor DNA in the bloodstream (21). Digital droplet PCR is highly sensitive and inexpensive, but it can only screen for specific known mutational variants or targets. By contrast,

NGS can evaluate an entire genome or a large panel of genes. However, this produces large quantities of data, of which the utility is less understood. In addition, NGS can be more expensive (20).

Data on the use of ctDNA as a potential prognostic indicator in patients undergoing NAT for PDAC is limited. Yin *et al.* (22) evaluated the presence of ctDNA in patients with PDAC with pathologic complete response after NAT. They found that ctDNA may have some utility in detecting recurrence of PDAC after NAT and surgery. The study however only consisted of 34 patients and only 16 were evaluated in follow up with ctDNA testing. Kitahata *et al.* (23) reported on the amount of ctDNA in plasma of patients with borderline resectable disease who underwent NAT followed by surgery. This prospective study consisted of 55 total patients, and they found that positive postoperative ctDNA was significant predictor of poor survival in patients with borderline resectable pancreas cancer. In addition, they demonstrated that when combined with CA19-9 measurements, it became an even stronger prognostic marker for relapse free survival and overall survival (23). While the use of ctDNA is promising as a potential marker for disease recurrence and overall survival in PDAC, larger scale prospective studies are needed to fully assess the utility of this biomarker.

Other serum biomarkers

Other serum biomarkers have been studied for their use in evaluating pathologic response to NAT for PDAC. CEA is commonly used in colorectal cancer and has been noted to be elevated in more than 60% of patients with PDAC, however it has low diagnostic sensitivity for the disease and thus is not commonly used (24). Recently, in a retrospective review of 319 patients with localized PDAC, Kato *et al.* (25) found that high CEA level pre-neoadjuvant chemoradiation was the most significant independent predictor of poor post-surgical disease free and overall survival. While CEA may not be useful as a diagnostic biomarker in PDAC, it could prove more useful as a prognostic or predictive biomarker in patients undergoing NAT.

Cancer antigen 125 (CA-125) has also been evaluated as diagnostic and prognostic biomarker in PDAC. It has a lower sensitivity than CA 19-9 and while it can be followed if high at baseline diagnosis, it has not proven to be as useful as other biomarkers (8).

CTCs are tumor cells that enter the peripheral circulation and are thought to ultimately play a role in metastatic disease (11). In a meta-analysis of 19 studies, with over 1300 patients with pancreatic cancer, Wang *et al.* (26) found that patients with detectable CTC (CTC positive) had worse overall and disease-free survival than those without detectable CTC. Additionally, they found that patients of Asian and Western ethnicity who were CTC positive had significantly shorter overall survival (26). Martini *et al.* (27) similarly found worse overall survival for patients with detectable CTC at diagnosis. While CTC appears to be a useful prognostic biomarker, larger scale studies are needed to improve CTC isolation techniques and to further assess utility as a therapeutic predictive biomarker (27).

Imaging biomarkers

In addition to serum biomarkers, assessment of tumor response to NAT has been examined in multiple imaging modalities. The term "radiomics" has been increasingly utilized to describe the analysis of imaging features and their use in prognostic modeling and outcome analysis (28). Triple phase computed tomography (CT) is the most common clinically utilized modality in the evaluation of pancreatic cancer, followed by MRI. PET scan is not commonly used in assessing disease burden in pancreatic cancer; however, several studies have evaluated its utility in assessing response to NAT (29-31).

CT

The use of CT and more specifically CT radiomics as a prognostic indicator has been used in other cancers such as non-small cell lung cancer, renal cell carcinoma and colorectal cancer (28,32). In a retrospective study, Khalvati *et al.* (28) assess the prognostic value of CT-derived radiomic features for resectable PDAC and identified several radiomic features which were statistically significant for prognostication of overall survival. Two features common across several studies included entropy which measures randomness or non-uniformity of a selected area, and cluster tendency, which is a measure of groupings of pixels with similar gray values (28). A combination of several of these features is used to create a radiomic signature which can then be reproduced and validated (28). Elsherif *et al.* (33) found that CT radiomic features, most specifically, the integral total Hounsfield units, from

baseline, pre-NAT and post-NAT imaging studies could potentially serve as markers when used concurrently with serum and pathologic biomarkers for assessment of LN status after NAT. Utilization of multi-phasic CT alone, independent of the study of radiomics, has not been shown to be reliable in evaluating tumor response to NAT (29). Post treatment changes, specifically following radiation, are difficult to differentiate on CT from tumor progression, regression, or stability (29,34,35). However, significant size changes, tumor-vessel involvement and lymph nodes are still generally well assessed on CT and thus developing a set of CT specific radiomic features with higher sensitivity and specificity than CT alone would be useful in determining NAT response (36).

MRI

MRI and the use of diffusion weighted (DW) imaging has also been evaluated in its role for assessing potential fibrotic changes following NAT in PDAC (29). DW imaging depicts the diffusion of water molecules between extra and intracellular space and as such could be used to differentiate between tumor, which has a high cellular density and inflammatory change which will not (37). More specifically, the fibrotic changes seen in PDAC can be quantified using the apparent diffusion coefficient (ADC) on DWI, which measures the magnitude of diffusion of water molecules within tissue (37). In a prospective analysis of DW-MRI metrics obtained at baseline, week 2 and week 8 of chemotherapy initiation, DW-MRI showed more accuracy compared with RECIST 1.1 criteria in categorizing responding versus non-responding patients to NAT (36). Several other studies found similar results in using DWI to investigate tumor response to NAT. Erstad *et al.* (38) compared the use of a type I collagen targeted MRI probe (CM-101) to the standard Gd-DOTA contrast agent in their abilities to identify chemotherapy induced fibrosis in mice model PDAC. CM 101 is a 17 amino acid peptide with a binding affinity for human type 1 collagen (38). The authors found that CM 101 selectively bound to fibrotic tissue with high amounts of type 1 collagen, which led to its delayed clearance and reduced MR signal loss over time. This led to a specific enhancement of PDAC tumor fibrosis relative to the surrounding pancreatic parenchyma. Additionally, the probe was able to detect changes in the tissue post chemotherapy (38). Thus, CM 101 probe on MRI could become useful in monitoring tumor changes during chemotherapy as well as in the initial evaluation of PDAC.

Fluorodeoxyglucose positron emission tomography (FDG PET)

FDG PET is not commonly used in clinical staging of PDAC. However, a recent study examined the use of maximum standardized uptake value (SUVmax) as a marker for response to NAT in PDAC (29). SUVmax reflects glucose metabolism of tumors and is a ratio of tracer uptake in the area of interest compared to the tracer uptake in the whole body (29). Choi *et al.* (30) found that greater than 50% decrease in SUVmax after one cycle of chemotherapy was associated with R0 resection. Panda *et al.* (31) assessed utility of FDG-PET in predicting pathologic response and overall survival after NAT and found that complete metabolic response, as well as a decrease in SUVmax of 70% or greater were both predictors of both pathologic response to NAT and improved overall survival.

Endoscopic ultrasound (EUS)

Other imaging modalities have been evaluated for their usefulness in evaluation of PDAC post NAT. EUS is the standard staging modality which is utilized for fine needle and core-needle biopsy of newly diagnosed pancreatic tumors (34). In a systematic review aimed at determining the accuracy of imaging in predicting margin-negative resection for borderline resectable PDAC, Barreto *et al.* (34) found that decreased tumor stiffness on EUS elastography may be a potential marker of NAT response and resectability. Stiffness on EUS elastography is defined as the distortion of tissue after application of pressure usually via manual compression, where larger tissue distortion equates with decreased stiffness or softer tissue (39). Additionally, change in tumor size on EUS can also provide valuable pre-operative planning information (29).

Imaging characteristics across a multitude of modalities are potential useful tools in predicting response to NAT. The use of standardized radiomic features and agreement on specific imaging modality is the next necessary step in creating a method for quantifying and prognosticating response to NAT. In addition, the availability of expertise to evaluate key radiomic biomarkers may become a limiting feature in terms of generalizability and incorporation into standard of care testing.

Histopathologic biomarkers

While imaging and serum biomarkers may allow for

better understanding of tumor regression and response to NAT during therapy, prior to surgery, use of pathologic grading and evaluation for tumor regression in the surgical specimen is also an important tool in understanding response to NAT and overall prognosis. Three grading systems that have been most popularized are the College of American Pathologists (CAP), Evans', and MD Anderson Tumor Regression Grading Systems (40). CAP Grading System uses a score of 0 (no viable cancer cells present, complete response), 1 (near complete, single or rare groups of cancer cells), 2 (residual cancer with obvious tumor regression) and 3 (extensive residual cancer with no regression) (41). The Evans' Grading System grades I-IV based on the percent of tumor cells present. A score of I refers to less than 10% tumor cell destruction, or no tumor cell destruction, IIa refers to 10–50% destruction, IIb equates to 51–90% destruction, III means <10% of viable tumor cells are visualized and IV means no viable tumor cells are seen (40). The MD Anderson grading system uses scores 0–2. Zero refers to no residual tumor present, while 2 refers to greater than 5% residual tumor present (40,42). Ahn *et al.* (40) compared each of these grading systems and demonstrated that the four tier CAP grading system was the most prognostic indicator of overall survival (P=0.043). Additionally, the CAP system correlated with radiologic response (P=0.007) to NAT, but did not correlate with CA 19-9 levels (40). These findings were similar to those of Kim *et al.* (43) who compared Evans and CAP grading systems and found they were both prognostic in patients who underwent neoadjuvant chemotherapy. Kim *et al.* (43) noted that both CAP and Evans grading systems overall correlated significantly with both disease-free and overall survival. They did note however that among individual Evans grades, a grade IIa score, which refers to less than 50% destruction of tumor cells, was associated with better overall survival than a grade IIb score, which refers to greater than 50% destruction of tumor cells. This discrepancy between individual grades was thought to be secondary to the Evans system's dependency on accurate measurement of tumor dimension, which has high variability between different evaluating pathologists (43).

Redegalli *et al.* (44) and Lee *et al.* (45) proposed two separate histologic grading systems. Redegalli *et al.* proposed a system which evaluated 20 morphologic features via comprehensive histologic analysis including tumor grade, nodes, stroma to neoplasia ratio, vascular invasion and wall alteration, presence of granulocytes, macrophages, fibrosis as well as several other features. They compared this system with the three aforementioned grading systems in predicting disease free and overall survival. While their study population was small (69 patients), the authors found that multiple aspects of their scoring system correlated with overall survival and disease-free survival. They are currently enrolling a large cohort for further validation (44). Lee *et al.* (45) proposed a modified version of the CAP grading system, using a three-tier histologic tumor regression grading scheme (HTRG 0: no viable tumor; 1: <5% viable tumor cells; 2: >5% viable tumor cells). They found that patients with HTRG 0 or 1 had lower lymph node metastases (P=0.004), recurrence (P=0.01), longer disease-free survival (P=0.004) and overall survival (P=0.02) when compared to those with HTRG 2 (45).

Chatterjee *et al.* (42) specifically examined the prognostic significance of the current aforementioned grading systems on patients treated with chemoradiation. The authors graded specimens using CAP and Evans systems and correlated those with survival. Patients with pathologic complete response and minimal residual tumor were found to have better overall survival than those with moderate or poor response. However, with respect to stratification within each grading system, they did not find a significant difference in disease free or overall survival between Evans histologic grade I and grade IIa or IIb. Similarly, when evaluating the CAP system, no difference in survival was found between CAP grades 2 or 3 (42). In contrast with patients treated chemotherapy alone, this study demonstrates that in patients treated with neoadjuvant chemoradiation, current histologic grading systems may not correlate as well with pathologic response and survival and thus a modified grading system may be necessary (42).

Clinical assessment

The use of patient reported information, nutritional status and functional status has not been well studied as it relates to response and prognosis following NAT for PDAC. Murthy *et al.* (46) examined the Systemic Immune-Inflammation Index (SII) as a prognostic indicator for resected PDAC after NAT. The SII is calculated using platelet, neutrophil, and lymphocyte counts. This was a retrospective analysis from a single institution. They noted no significant correlation between pre-NAT SII and clinical outcomes; however, an elevated post NAT SII was an independent predictor of overall survival (P=0.006). Additionally, they noted an 80% reduction in SII was associated with a CA 19-9 response after NAT (P=0.024) (46). Clinical assessment and patient reported outcomes need further investigation into

their impact on OS, disease free survival, post-operative complications and morbidity and mortality following NAT for PDAC.

Conclusions

NAT has become a key strategy for localized pancreatic cancer. There are multiple promising methods to evaluate response to NAT. CA19-9 shows potential as a clinically available indicator of response to NAT and may be utilized as a guide for the need for further therapy. However, its use may be limited in patients who either are non-secretors or for whom their baseline CA19-9 is normal. ctDNA may also prove useful as an assessment of response to NAT as well as possible recurrence. This biomarker, in combination with CA 19-9, could be valuable in determining response to therapy as well as prognosis. More work is necessary to evaluate its efficacy in this role. Further investigation into the use and standardization of CT and MRI radiomics and imaging modalities such as FDG PET and EUS elastography to predict response to NAT is also needed. These modalities are widely available yet require consensus on which modalities to use and how they should be evaluated to reduce interobserver variability. Finally, an improved understanding of differential effect of chemotherapy versus chemoradiation on histologic grading will aid in enhancing the prognostic capability of pathologic response assessment after NAT. Taken together, improved assessment of the key modalities described in this review may be used not only to predict survival, but to guide multiple aspects of cancer care, including length of NAT, need for radiotherapy, need for a change in neoadjuvant regimen, as well as surgical planning and adjuvant therapy.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://cco.amegroups.com/article/view/10.21037/cco-22-49/rc

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